Management of Inpatient Hyponatraemia:

Past, Present, and Future

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I, Dr Ploutarchos Tzoulis, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

This research work includes 5 studies evaluating mortality, investigation, and treatment of inpatient hyponatraemia. The first, a case–control study showed that hyponatraemic patients had 17.3% inpatient mortality rate and were 12 times more likely to die during admission than normonatraemic controls, concluding that hyponatraemia is an independent predictor of mortality. The second study in the same cohort confirmed that hyponatraemia is frequently underinvestigated with 5% of patients without endocrine input having complete work-up compared to 80% of those receiving endocrine input. The third, multicentre observational study found that only 23% of participants had measurement of paired serum / urine osmolality and sodium, while 37% did not have any treatment for hyponatraemia and 63% had persistent hyponatraemia at discharge. The fourth study, a case series of 61 tolvaptan-treated SIADH patients over a 3-year period, demonstrated the great efficacy of tolvaptan, evidenced by a mean 24-hour serum sodium rise of 9 mmol/l with 96.7% of patients having increased serum sodium by ≥ 5 mmol/l within 48 hours. However, tolvaptan carried a significant risk of overly rapid sodium correction with 23% of patients with starting serum Na < 125 mmol/l exceeding correction limits. The fifth, a prospective-controlled intervention study showed, for the first time, that endocrine input is superior to routine care in correcting hyponatraemia since the intervention group achieved ≥ 5 mmol/l sodium rise in 3.5 vs. 7.1 days in controls. The endocrine input shortened hospitalisation by a mean of 3.6 days. The likely contribution of hyponatraemia by itself to excess mortality, in combination with underinvestigation and undertreatment of hyponatraemia characterising real-life clinical practice, highlight the need to improve clinical care. A key finding of these

studies is that widespread provision of endocrine input can result in more effective hyponatraemia treatment and shorter hospitalisation.

Impact Statement

These five research studies, described in my thesis, can have a significant impact both inside and outside academia. The first study informs clinicians about the adverse prognostic significance of low serum sodium in hospitalised patients. Also, by raising the possibility that hyponatraemia by itself may contribute to high mortality rates, this case-control study shows the need to undertake further reseach into the mechanistic aspects of hyponatraemia. Our data prompt other research groups to conduct in vitro and in vivo studies to explore the mechanisms, whereby hyponatraemic stress may cause maladaptive responses, leading to excess mortality, such as the effects of acute osmotic stress in the immune system.

The second and third study are of paramount importance to clinical service providers since they provide contemporary real-world data from several UK hospital sites into the management of hyponatraemia. Our studies, by allowing different institutions and healthcare professionals to compare their performance in the field of hyponatraemia against our data, can be a driving force behind better clinical care. These studies, not only confirm that hyponatraemia is often underinvestigated and underdiagnosed, but also identify for the first time the key determinants of the adequacy of investigation. Therefore, they can help policy makers and clinicians to design and implement initiatives which may improve standards of day-to-day clinical practice.

The fourth study has filled a distinct gap in the literature concerning the efficacy and safety of tolvaptan for the treatment of severe hyponatraemia. Our study, reporting unprecedentedly high effectiveness and great rate of overly rapid sodium correction, informs clinical decision-making in the context of severe biochemical hyponatraemia. Finally, our data highlight the urgent need for high quality evidence supporting the

use of tolvaptan in order to answer the unresolved question of whether the potential improvement in hard outcomes outweighs the risk of overly rapid sodium correction. Thus, this study could benefit public health by prompting regulatory authorities across the globe to reinforce a transformation of drug studies in the field of hyponatraemia, with pharmaceutical industry conducting studies with primary endpoints being patient-relevant outcomes instead of surrogate markers, like increase in serum sodium.

Finally, the fifth study, showing superiority of intensive endocrine input to routine care in correcting hyponatraemia and reducing length of hospitalisation, challenges the current approach to inpatients with hyponatraemia. If these findings are reproducible in other cohorts, they could improve clinical outcomes of patients with hyponatraemia and potentially reduce the utilisation of hospital resources. Also, they may change radically the model of care delivery by widespread provision of endocrine input to inpatients with SIADH.

By disseminating my research findings through five original research articles in peer-reviewed journals, eight poster presentations at major national and international conferences and more than 20 lectures to various audiences, I have promoted best clinical practice in hyponatraemia. In summary, this work has the potential to deliver a range of benefits, including influencing the direction of future research in the field, informing clinical decision-making and altering the future mode of care for inpatient hyponatraemia.

Dedication

I would like to dedicate this work to my family, especially…

…to my beloved father who sadly died towards the end of writing this thesis. He was, has always been and will continue being the greatest teacher for me. Whenever we worked together, we could make everything happen.

…to my lovely wife, Peny, for her, much needed, patience, support and understanding throughout our amazing journey together for the last 2 decades. Without her, all my accomplishments, first and foremost our wonderful family, would not be possible.

…to my daughter, Nicole, whom I keep telling that this thesis is the largest book in the world and she has been a great source of inspiration for me. She keeps reminding me what the true purpose of my life is;

…to my baby boy, Evangelos, who was born just before I started writing this thesis and has offered me extra energy and inspiration to finish it. He has never stopped smiling from the first day of his life up to this time, showing me why I should always persevere;

…to my mother for her continuing support throughout all these years. She has been motivating me and reminding me that there is no limit to what I can achieve;

…to my brother for his constant encouragement and motivation.

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Chapter 1

Introduction

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1.1 Physiology of water balance

1.1.1 Introduction

Normal human cellular function depends on constant tonicity of the extracellular fluid. Water homeostasis is very accurately controlled in order to maintain plasma osmolality within a remarkably narrow range of 282-298 mOsm/kg[1] [2]. Sodium, being impermeable to cell membranes and restricted to the extracellular fluid (ECF) compartment, is an effective solute since it can create osmotic pressure gradients across cell membranes leading to osmotic movement of water from the ICF (intracellular fluid) to the ECF[2] [3]. Sodium, the most important osmotically active cation, is the key determinant of plasma osmolality. Plasma sodium concentration is maintained within a tight physiological range of 135-145 mmol/l over time, despite wide variation in both sodium and water intake[4]. The main determinants of serum sodium are sodium intake / output and water balance. In view of the rarity of disorders of sodium balance, hyponatraemia is usually caused by a defect in water homeostasis which is maintained through arginine vasopressin (AVP) and thirst[5].

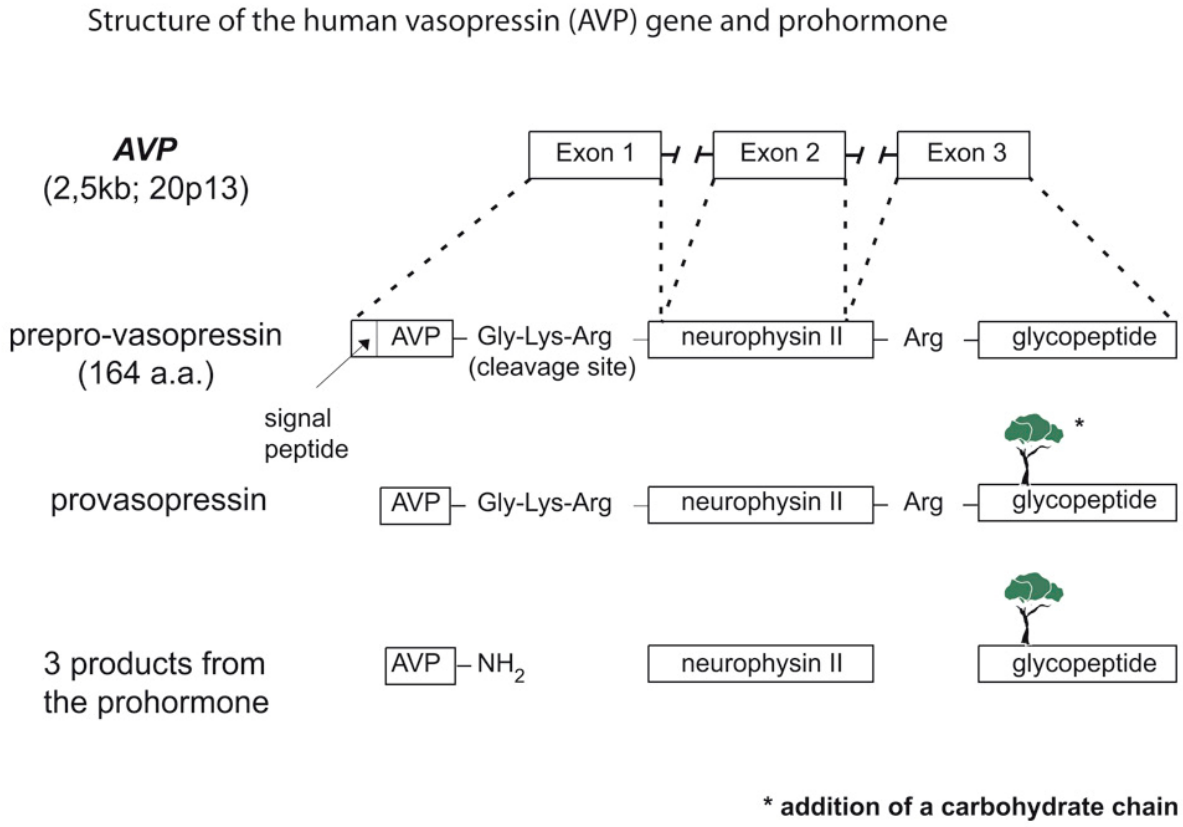
1.1.2 Arginine vasopressin and aquaporins

The AVP (arginine vasopressin) gene, coding for AVP and neurophysin II (NPII), and the OXT (oxytocin) gene, coding for OXT and neurophysin I, are located within the same chromosomal locus on chromosome 20 at a very short distance from each other in a head-to-head orientation[6]. Of note, AVP and OXT, called nonapeptides for their nine-amino acid composition, are closely related in primary structure, differing in only two amino acids at position 3 and 8. This structural similarity in combination with the strong conservation of the neurophysin domain in AVP- and OXT- related prohormones provide evidence in favour of the general belief that the mammalian AVP / OXT family have developed from a common ancestral molecule by gene duplication about 450 million years ago[6].

Prepro–vasopressin which has 164 amino acids with its corresponding carrier, neurophysin II, are synthesised as a composite precursor by the magnocellular neurons located in the paraventricular and supraoptic nuclei of the hypothalamus. Exon 1 of the AVP gene encodes the signal peptide, AVP, and the NH2-terminal region of neurophysin II. Exon 2 encodes the central region of neurophysin II, and exon 3 encodes the COOH-terminal region of neurophysin II and the glycopeptide. The precursor is packaged into neurosecretory granules and transported in the pituitary stalk[7]. Prepro-vasopressin is transformed to pro-vasopressin following removal of the signal peptide and addition of a carbohydrate chain to the glycopeptide, as illustrated in Figure 1. Additional post-translational processing of prepro-AVP occurs within neurosecretory granules during their transport to the posterior pituitary gland, yielding the active hormone AVP which is a nine-amino acid peptide as well as neurophysin II and the glycopeptide[7]. The AVP-neurophysin II complex forms tetramers that can self-associate to form higher oligomers. Finally,

vasopressin, neurophysin II and the glycoprotein are stored in neurosecretory granules in axon terminals of the posterior pituitary, and are released into the bloodstream in response to osmotic or nonosmotic stimulation[2].The full role of neurophysin II is not completely understood, but nowadays there is substantial evidence that it serves as chaperone-like molecule. Intact neurophysin II is necessary for the correct folding and self-association of the AVP-NPII precursor which is essential for its normal processing in the endoplasmic reticulum[8] and intracellular transport[6]. The key role of neurophysin II is also supported by the fact that the majority of the known mutations causing familial neurohypophyseal diabetes insipidus are located in the coding region of the NPII moiety[8 9], leading to structurally abnormal protein not being able to reach the Golgi apparatus and secretory vesicles for further processing and storage. As a result, retained misfolded protein in the magnocellular endoplasmic reticulum is accumulated and eventually either destroys the cell or undergoes degradation[8 9 10].

Figure 1. Structure of AVP gene and its prohormones. Structure of the human vasopressin (AVP) gene and cascade of vasopressin biosynthesis, signal peptide; AVP, arginine vasopressin; neurophysin; glycoprotein. Adapted from Bichet DG[7].



AVP has multiple actions which are primarily, but not exclusively, mediated by its interaction with three types of G protein-coupled receptors; AVPR1a (V1 receptor, mainly vascular), AVPR1b (V3 receptor, mainly central), and AVPR2 (V2 receptor, mainly renal) which is expressed on the basolateral membrane of the renal collecting duct cells and mediates the main action of AVP as antidiuretic hormone[7 11]. Also vasopressin stimulates oxytocin receptors and purinergic receptors[11]. AVPR1a is expressed on vascular smooth muscle, hepatocytes and platelets and its primary mediated effect is vasoconstriction. Stimulation of the AVPR1a receptor also induces production of the potent vasodilator nitric oxide in coronary vessels and pulmonary vessels[11]. In addition, AVPR1a activation induces platelet aggregation via thromboxane release[12]. AVPR1b, or V3 receptor, is expressed in the anterior pituitary gland and hippocampus. Stimulation of AVPR1b by vasopressin releases adrenocorticotropic hormone (ACTH) because vasopressin flows from the posterior pituitary through pituitary portal capillaries to bind to the AVPR1b on corticotroph cells of the anterior pituitary. Vasopressin and corticotrophin-releasing hormone (CRH) are both physiological mediators of ACTH secretion induced by hypoglycaemic stress and have synergistic effects on release of ACTH, as shown in AVP response to hypoglycaemia with threefold rise in its concentration observed 30-45 minutes post insulin injection[13 14]. On the one hand, animal studies including AVPR1b knockout mice have found that intact AVPR1b is required for normal pituitary and adrenal response to some acute stressful stimuli such as hypoglycaemia[15]. On the other hand, AVPR1b has been found to be markedly overexpressed in corticotropinomas with AVPR1b expression being positively correlated with elevated plasma ACTH levels[16]. Besides its effect on water reabsorption, stimulation of AVPR2 (V2 receptor) increases release of von

Willebrand factor, von Willebrand factor multimers, and risk of clotting[11]. AVP also binds to oxytocin receptors (OTRs) which exist in high density on vascular endothelium, mediating nitric oxide-dependent vasodilation[17] and activates OTRs in the heart, stimulating the release of atrial natriuretic peptide[18]. Finally, vasopressin acts on the P2 class of purinergic receptors (P2Rs) that mediate endothelial vasodilation[17], but this effect is reversed when vasopressin, at high levels, stimulates the AVPR1a receptor to mediate vasoconstriction[11].

It is worth mentioning that very recent data showed that vasopressin is expressed in a subpopulation of retinal ganglion cells that project to the suprachiasmatic nucleus (SCN) of the hypothalamus, the circadian pacemaker of the mammalian brain which is responsible for aligning our internal body states with the external day and night cycle[19]. This study revealed for the first time that light-induced vasopressin release enhances the responses of SCN neurons to light as well as the expression of genes involved in photo-entrainment of biological rhythms, demonstrating a key role of vasopressin as a time-dependent mediator of light information from the retina to the SCN. These exciting results showed a potentially new pharmacological route to manipulate our internal biological clocks, highlighting the need for future studies to assess whether alteration of vasopressin signalling through the eye could lead to developing eye drops as a treatment for jet lag[19].

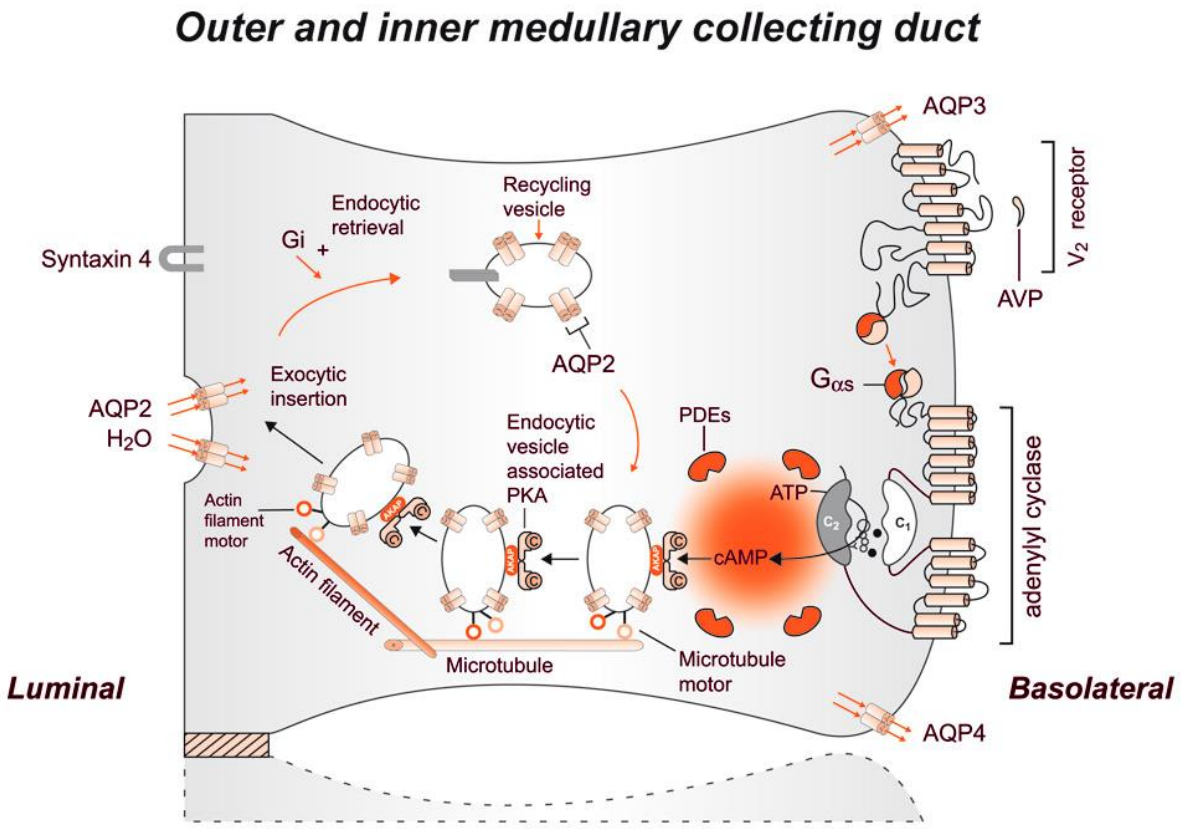
There is also growing interest in the potential role of vasopressin as a modulator of complex social cognition and interaction through its two centrally expressed receptor subtypes AVPR1a and AVPR1b, with AVPR1a (V1 receptor) having been the focus of most research examining vasopressin's role in regulating social behaviour. This concept emerged from data about oxytocin, one of the most studied peptides in behavioural sciences over the last 3 decades, which seems to play a

role in social attachment and bonding since human studies have found that intranasally administered oxytocin can substantially increase trust[20], for example by not changing trust behaviour despite their trust had been breached several times[21]. A number of recent molecular genetic association studies suggest that variation in four polymorphic microsatellites of the AVPR1a locus, three within the 5′ flanking region and one within the intron of the gene, may also contribute to sociobehavioural diversity in humans[22]. For example, the length of AVPR1a RS3 promoter-region repeat was associated with the degree of altruism, assessed by individual differences in the allocation of funds in an established economic game, called the 'dictator game'[23]. Another line of research reported an association between one of the human *AVPR1a* repeat polymorphisms (RS3) and traits reflecting pair-bonding behavior in men, including partner bonding, perceived marital problems, and marital status, and show that the RS3 genotype of the males also affects marital quality as perceived by their spouses[24]. Interestingly, the same allele RS3 334 was implicated in autism in another study[25]. In addition, human double-blind placebo-controlled trials have found that intranasally administered AVP strongly increases cooperation in response to a cooperative gesture by a partner[26] and also increased willingness to engage in risk taking to cooperate for mutual benefit[27]. In total, there is still limited evidence with respect to the potential contribution of variation in AVPR1a and its potential manipulation to human sociobehavioural traits.

AVP binding to the G-protein-coupled V2-receptor (V2R) in the basolateral membrane of the principal cells of collecting ducts of the kidney initiates a cascade of events leading to increase of water permeability[2]. Occupancy with AVP of V2 receptor, which has seven transmembrane domains in its structure, leads to a conformational change of the receptor with replacement of guanosine diphosphate

(GDP) with guanosine triphosphate (GTP) in the alpha-subunit of Gs[28 2].This activated $G_{\alpha s}$ allows the stimulation of adenylate cyclase, increasing the intracellular concentration of cyclic adenosine monophosphate (cAMP)[2 28]. Generated cAMP is the cellular second messenger that targets and activates protein kinase A (PKA) which phosphorylates aquaporin-2 (AQP2)[28]. In addition to increasing cAMP levels in the cytoplasm of the principal cells of the collecting duct, AVP also evokes a rise in intracellular calcium concentration in collecting duct cells which is followed by sustained temporal oscillations of calcium levels. This process of AVP-mediated calcium mobilisation seems to play a key role in AQP2 exocytosis[28 29]. AQP2 phosphorylation leads to increased AQP2 mRNA expression and translocation of storage vesicles containing AQP2 water channels from the cytoplasm of principal cells to the luminal cell surface membranes (also called the apical membranes)[7 28], as illustrated in Figure 2. This relocation of phosphorylated AQP2 to the cell membrane renders the water cell permeable, resulting in water reabsorption[28].

Figure 2. Schematic representation of the cascade of events following AVP binding to V2 receptor through which vasopressin increases water permeability in the principal cells of the collecting duct by regulating of aquaporin-2. Adapted from Bichet DG[7].

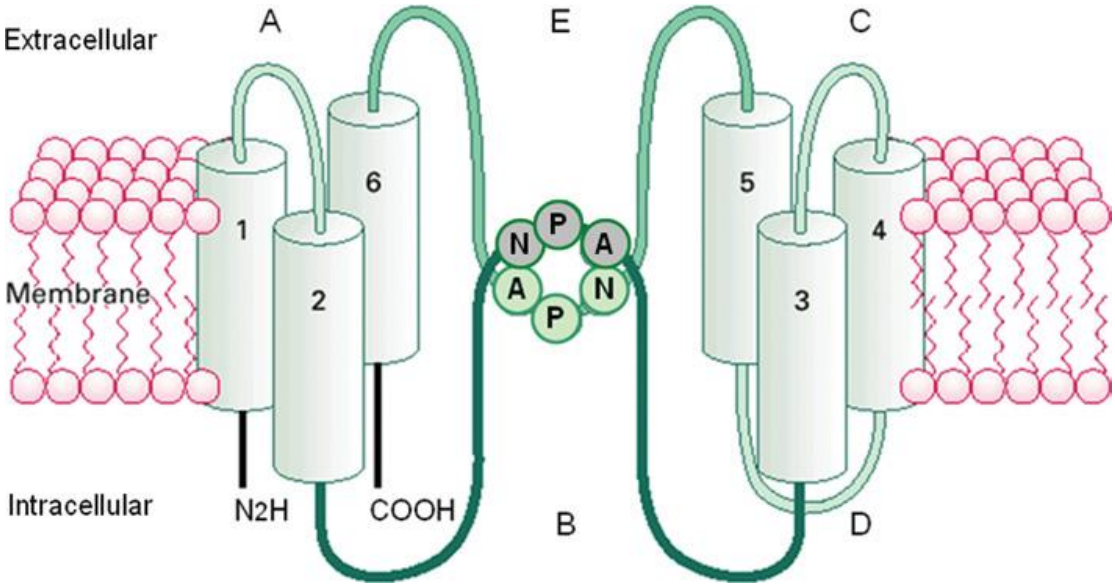


AQP2 is the predominant vasopressin-regulated water channel in the kidney and plays a key role in the control of collecting duct water permeability. There are short-term and long-term regulatory systems of water permeability and AQP2 by AVP. Short-term regulation occurs within few minutes and involves trafficking of AQP2 from intracellular cytoplasmic storage vesicles to the apical plasma membrane, allowing reabsorption of water from lumen to the cell [30]. The trafficking of AQP-2 is very prompt, as apical membrane labelling of AQP-2 has been shown to appear within 15 min of AVP administration, inducing very high water permeability of the luminal membrane. With suppression of AVP, these apical AQP2 water channels undergo rapid endocytosis into the cytoplasm with the AQP-2 being diffusely translocated into the cytoplasm 1 hour after forced water administration[31]. The vasopressin-induced redistribution of AQP2 to the apical plasma membrane takes place through two general processes; speeding up of the rate of exocytic insertion of AQP2 into the plasma membrane and slowing down the rate of the endocytic removal of AQP2 from the apical plasma membrane. Therefore, the amount of AQP2 in the plasma membrane is a result of a balance between continuing endocytosis and exocytosis of AQP2, with the majority of AQP2 regulated by the shuttle recycling in the collecting duct cells[29]. In total, vasopressin can increase the water permeability in the collecting duct by a factor of 10-100, inducing a steep increase in water reabsorption[28]. The long-term regulation of water permeability of the collecting duct occurs within hours to days by alteration of the number of the water channels in the cell. This response is mainly induced by an increase in AQP2 abundance due to increased transcription of the gene as it is well known that long-term administration of vasopressin markedly increases AQP2 abundance in the renal collecting duct[28]. The long-term regulation involves cAMP-mediated increased phosphorylation of

transcription factors, such as CREB-P [(cAMP-Response Element)-binding protein], which bind to CRE in the promoter of the AQP2 gene to increase gene transcription[32] and increased abundance of AQP2 m-RNA and protein in collecting duct cells[33 34]. The amount of AQP2 in a given collecting duct cell at a steady state represents a balance between production of AQP2 by translation and removal from the cell by either degradation or exosomal secretion[29]. The combination of these AVP-regulated short-term and long-term regulatory processes greatly increase water reabsorption through increase of collecting duct water permeability.

The discovery of the first water channel, aquaporin 1 (AQP1)[35], led to the awarding of Nobel Prize in Chemistry in 2003 to Peter Agre and elucidated the mechanism by which water crosses biological membranes [35]. The aquaporins (AQPs) are a family of “water channels”, with 13 mammalian aquaporins having been identified to date. Aquaporins are specialised membrane transport proteins with their primary function to facilitate water transport across cell plasma membranes and are widely distributed in specific cell types in many organs and tissues[36 29]. All AQPs form tetramers in membranes in which monomers contain six transmembrane-spanning domains (cylinders) joined by connecting loops, which form a pore (P, proline; N, asparagine; A, alanine) to allow water transport across biological membranes and they are organised as shown in Figure 3[30].

Figure 3. Schematic representation of the structure of aquaporin. Aquaporin consists of six transmembrane-spanning domains (cylinders) joined by connecting loops, two intramembrane loops (B and E) and three extramembrane loops (A, C and D). An NPA (Asparagine-Proline-Alanine) motif is contained in each of the highly conserved B and E loops. These loops fold into the lipid bilayer in an 'hourglass' fashion, which forms a pore[30]. Adapted from Chen et al[30].



In the kidney, at least seven aquaporins are expressed at distinct sites. AQP1 is extremely abundant in the proximal tubule and descending thin limb and is essential for urinary concentration, while AQP2 is exclusively expressed in the principal cells of the collecting tubule and collecting duct and is the predominant vasopressin-regulated water channel. AQP3 and AQP4 are both present in the basolateral plasma membrane of collecting duct principal cells and represent exit pathways for water reabsorbed apically via AQP2[36 37]. Three additional aquaporins are present in the kidney with AQP6 being present in intracellular vesicles in collecting duct intercalated cells and AQP8 being present intracellularly at low abundance in

proximal tubules and collecting duct principal cells. AQP7 is abundant in the brush border of proximal tubule cells and is likely to be involved in proximal tubule water reabsorption[37]. AQPs are also expressed in various secretory epithelia including exocrine glands, choroid plexus, ocular ciliary epithelium, airway submucosal glands, sweat and lacrimal glands, and several gastrointestinal organs[36]. However their physiological importance in these epithelia seems limited, as suggested by animal studies, probably because the rate of transepithelial fluid transport in these epithelia is much lower than in kidney proximal tubule and salivary gland[38]. Recent evidence suggest various emerging roles of AQPs with AQP4 being expressed in astrocytes throughout the CNS, particularly at interfaces between brain parenchyma and cerebrospinal fluid in the ventricular and subarachnoid compartments, and playing a central role in brain and spinal cord water balance. In addition, AQP4 is expressed in neural tissues in supportive cells adjacent to excitable cells, including glia in brain, Müller cells in retina, supportive cells in inner ear, and support cells in olfactory epithelium and is involved in neuroexcitatory phenomena and determination of seizure threshold[36]. The strong expression of AQPs in tumour cells of different origins in combination with their involvement in cell migration and proliferation suggests that AQPs may play key roles in tumour biology. AQP3 facilitates glycerol transport in skin and is an important determinant of epidermal hydration. Finally, aquaglyceroporin AQP7 is expressed in the plasma membrane of adipocytes and facilitates glycerol exit from adipocytes, preventing intracellular glycerol and triglyceride accumulation. This function of AQP7 suggests adipocyte glycerol permeability as a novel regulator of adipocyte metabolism and whole-body fat mass, raising the possibility of modulation of adipocyte AQP7 expression or function to alter fat mass[36].

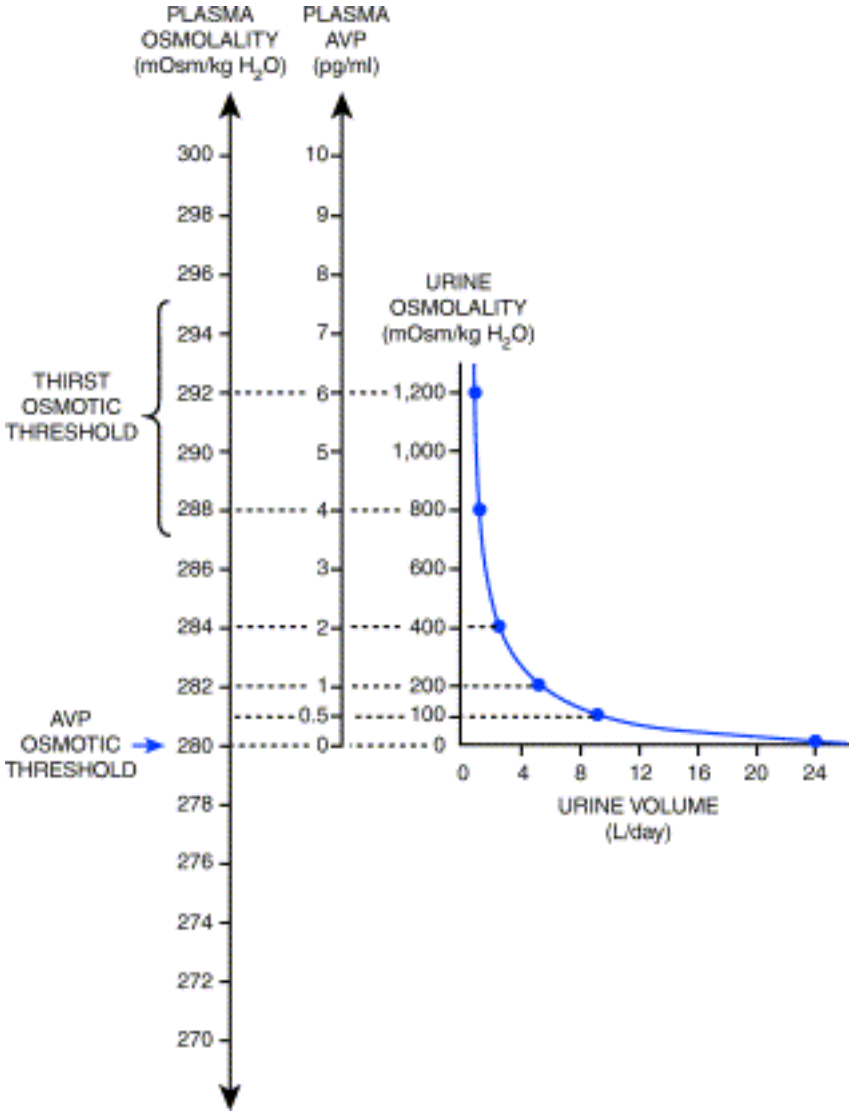
1.1.3 Regulation of AVP secretion

AVP secretion is primarily regulated by plasma osmolality. Changes in plasma tonicity are sensed by primary osmoreceptor neurons which are located within the circumventricular organs, specifically in the subfornical organ (SFO) and the organum vasculosum laminae terminalis (OVLT)[1]. The cellular osmosensing mechanism utilised by the OVLT cells is an intrinsic depolarising receptor potential, which these cells generate through a molecular transduction complex[39]. Several studies of the transient receptor potential vanilloid (TRPV) family of cation channel proteins provides evidence, supporting roles for TRPV1, TRPV2, and TRPV4 proteins in the transduction of osmotic stimuli in mammals[40]. Neural signals are transmitted from the osmoreceptors to the sites of AVP synthesis located in supraoptic and paraventricular nuclei. In addition to the well-described central osmoreceptors, recent studies identified also peripheral osmoreceptor neurons expressing TPRV4 sensing tonicity in the thoracic dorsal root ganglia that innervate hepatic blood vessels[41].

With regards to the osmoregulation of AVP secretion, several studies have supported the concept of a discrete osmotic threshold (mean 284.3 mOsm/kg in a healthy man) above which there is a linear and very close relationship between plasma osmolality and plasma vasopressin, as shown in Figure 4[1]. In general, each 1 mOsm/kg increase in plasma osmolality causes an increase in plasma AVP level of 0.4-0.8 pg/ml. The renal response to circulating AVP is similarly linear, with urine concentrations that are directly proportionate to AVP levels of 0.5-5.0 pg/ml, after which urine osmolality is maximal, as illustrated in Figure 1. As a result, increases in plasma osmolality of only 5-10 mOsm/kg H2O (2-4%) above the osmotic threshold lead to maximal antidiuresis[3]. This osmoregulatory system is very sensitive since

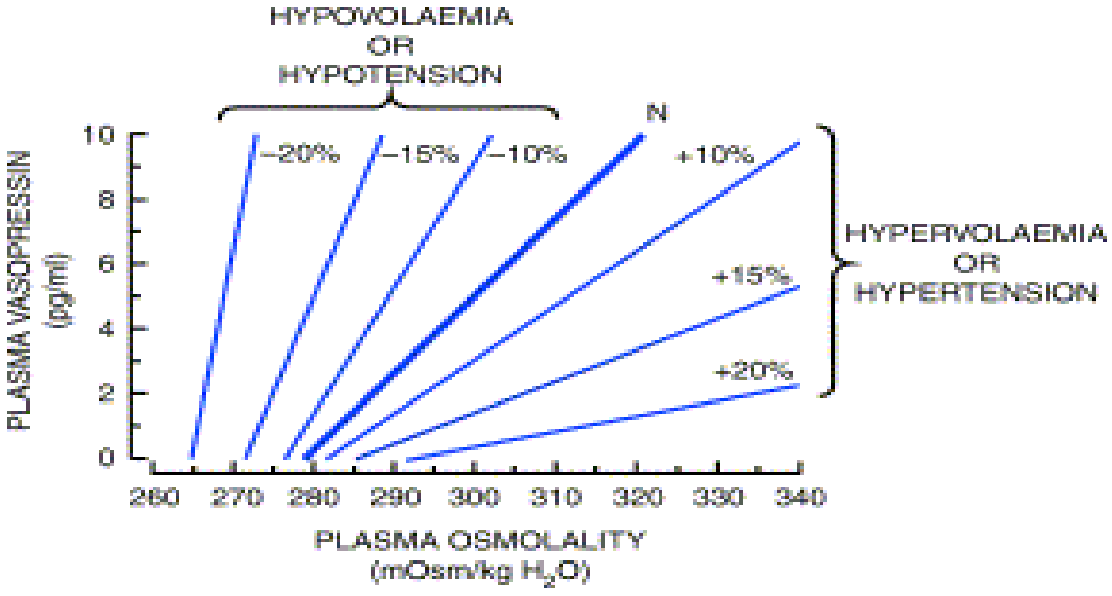
urine osmolality is directly proportional to plasma AVP concentrations, but also urine volume is inversely related to urine osmolality. Thus, an increase in plasma AVP concentration from 0.5 to 2 pg/ml has a much greater relative effect on decreasing urine flow than does a subsequent increase in AVP concentration from 2-5 pg/ml. In addition to its great sensitivity, this osmoregulatory system adjusts on a minute-to-minute basis since plasma AVP has a very short half-life of 10-20 minutes[3]. Finally the threshold and the slope of the regression line vary considerably between individuals due to genetic factors, but they are highly reproducible within an individual[42].

Figure 4. Representation of physiological relationships between plasma osmolality, plasma AVP levels, urine osmolality, and urine volume. Adapted from Verbalis et al[3].



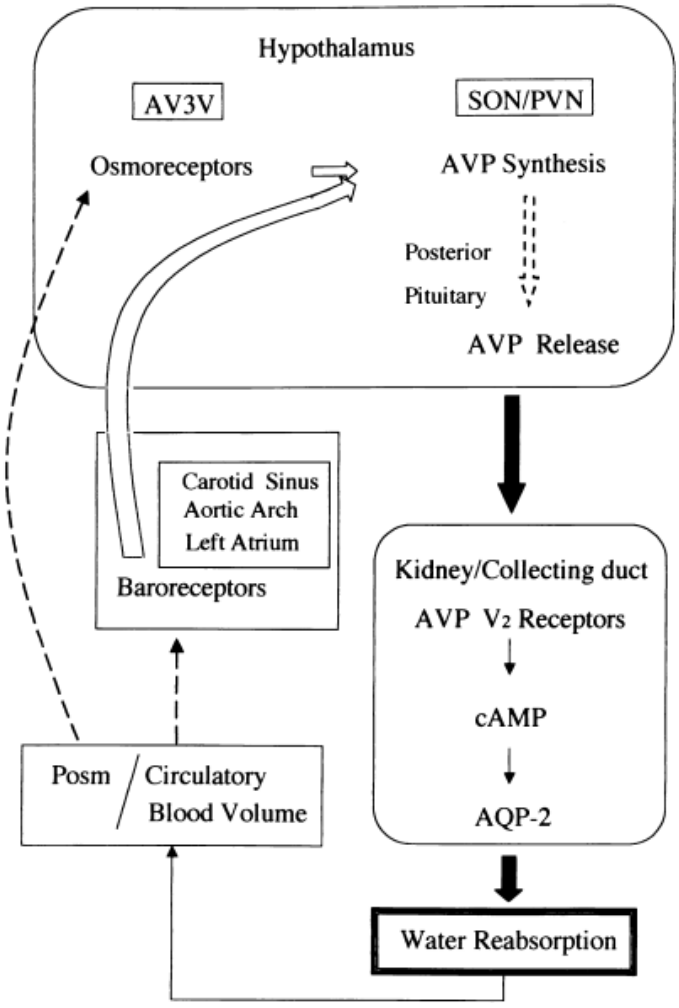
As a physiological response, hypovolaemia, sensed through baroreceptors located in the left atrium, aortic arch and carotid sinus, can result in urinary concentration and renal water conservation. However changes in volume status are a much weaker stimulus for AVP secretion than changes in plasma osmolality with modest reductions in effective arterial volume shifting the relationship between osmolality and AVP release to the left, as shown in Figure 5. Only severe plasma volume reductions of > 20-25% can override the osmoregulatory system[43].

Figure 5. Relationship between plasma AVP concentrations and plasma osmolality under conditions of varying blood volume and pressure. The line 'N' illustrates the linear regression line in euvolaemic normotensive adults. The lines to the left depict the changes in this regression line with progressive decreases in blood volume/pressure and the lines to the right depict the opposite changes with progressive increases in blood volume/pressure. Adapted from Verbalis et al[3].



An overview of mechanism underlying vasopressin-mediated water homeostasis is illustrated in Figure 6.

Figure 6. Overview of AVP-mediated water homeostasis, as adapted from Ishikawa et al[2]. Abbreviations: AV3V, anteroventral third ventricle region of hypothalamus; SON, supraoptic nuclei; PVN, paraventricular nuclei; AVP, arginine vasopressin; cAMP, cyclic AMP; AQP-2, aquaporin-2.

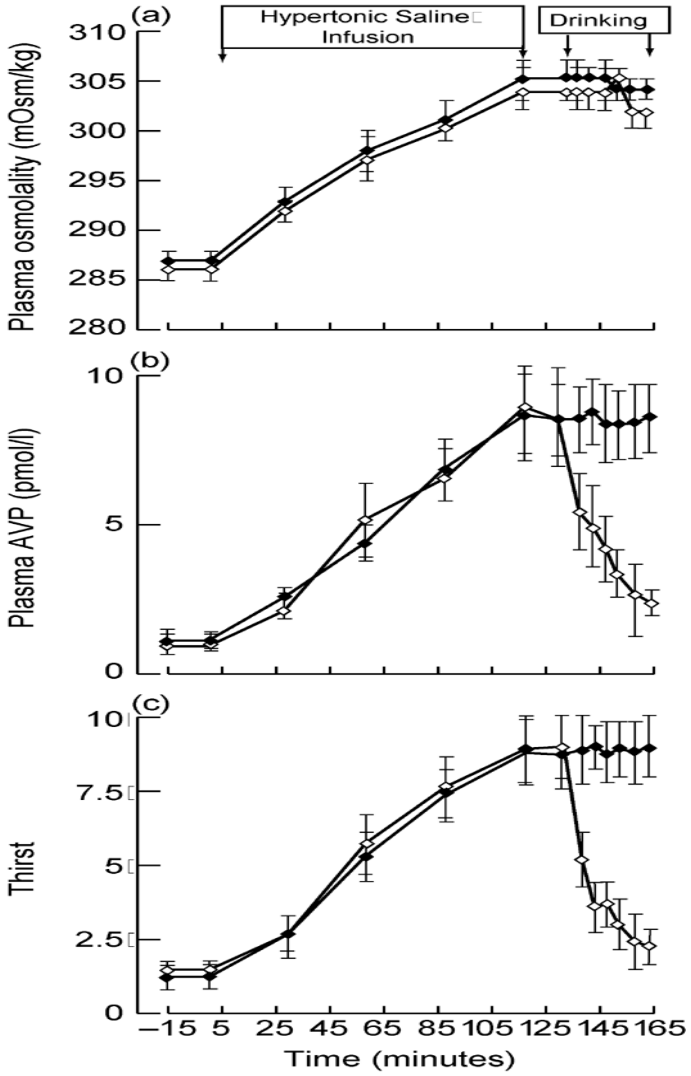


1.1.4 Regulation of thirst

Physiology of thirst is a challenging area since even its definition has been the subject of debate with thirst being defined as ‘a conscious sensation of a need for water and a desire to drink’[1]. Study of the thirst mechanism has been hampered by the subjective sensation of thirst and the concomitant lack of objective methods to quantify it[1 44]. In healthy humans, the osmotic threshold for the onset of thirst was thought to be around 294 mOsm/kg, appreciably higher by around 10 mOsm/kg than that for vasopressin release. This led to the belief that thirst mechanism was set so that it was stimulated only after hypertonic dehydration led to vasopressin release, sufficient to produce maximum antidiuresis. Thus, thirst was perceived as a back-up mechanism required only when dehydration began to surpass the protective renal capacity to preserve water, freeing the individual from the distraction which would otherwise result from constant thirst[44]. Also the normal, or only slightly increased, serum osmolality despite renal excretion of as much as 15-20 litres per day in patients with familial nephrogenic diabetes insipidus highlights the great capacity of thirst mechanism[44]. However, several studies, employing linear visual analogue scales to measure thirst perception, have found that the osmolar threshold for thirst onset is much lower (281 mOsm/kg) than previously suggested and similar to the theoretical osmolar threshold for vasopressin release (285 mOsm/kg)[45]. In a similar manner with osmoregulation of AVP release, there is a close linear relationship between plasma osmolality and thirst, highly reproducible within individuals on repeated testing[42]. Thus, thirst sensation is mild within the physiological range of plasma osmolality in order to replace insensible water loss, while a very intense thirst response is generated by plasma osmolality values at the upper end of normal range, prompting much larger fluid intake in order to replenish severe water deficits[1].

Another very interesting phenomenon is that the act of drinking inhibits rapidly thirst as well as vasopressin release[46] prior to any changes in plasma osmolality[47]. Studies in healthy volunteers have demonstrated that infusion of hypertonic saline caused linear increases in plasma osmolality (289 ± 1 to 306 ± 1 mOsm/kg), plasma vasopressin (0.6 ± 0.2 to 6.4 ± 1.9 pmol/l), and thirst (1.4 ± 0.4 to 7.4 ± 0.5 cm). After 20 minutes of drinking an average of 1,200 ml of water and despite no significant change in plasma osmolality, plasma vasopressin had dramatically fallen from 6.5 ± 0.9 to 1.3 ± 0.3 pmol/l and thirst from 7.7 ± 0.5 to 1.0 ± 0.2 cm[47], as shown in Figure 7. This observation highlights the importance of an early inhibitory signal in the control of water intake and suggest its basis: a neural input to the brain from the oropharynx, associated with rapid swallowing during the act of drinking[48]. This is a sophisticated defence mechanism to protect against overhydration[1]. This rapid but temporary inhibitory effect is followed by a more sustained termination of thirst and AVP secretion when ingested water is finally absorbed and lowers plasma osmolality.

Figure 7. Plasma osmolality, plasma AVP and thirst response to hypertonic saline infusion, followed by drinking (○) or water deprivation (•) in healthy controls. Adapted by Thompson et al[47].



Cerebral osmoreceptors for thirst are located in both the organum vasculosum of the lamina terminalis (OVLT) and the subfornical organ (SFO). The SFO and OVLT are two circumventricular organs that lack a blood-brain barrier and are situated in the lamina terminalis, the anterior wall of the third ventricle[49]. Thirst can also be stimulated by increased gastric sodium load detected by sodium receptors in the abdominal viscera, in specific hepatic sodium receptors, with vagal fibres projecting to the area postrema and adjacent nucleus of the solitary tract (AP/ NTS) in the brainstem[48]. Another thirst stimulant is reduction in blood volume detected by cardiac baroreceptors, even in the absence of changes in arterial blood pressure[48]. In addition, changes in arterial blood pressure provide two signals (one excitatory and one inhibitory) that are relevant to the control of thirst. On the one hand, arterial hypotension stimulates renin secretion via baroreceptors in carotid sinus-aortic arch and in the kidneys. The subsequent increase in plasma levels of angiotensin II which binds to receptors in the subfornical organ results in stimulation of thirst[49]. On the other hand, increased arterial blood pressure exerts an inhibitory effect on thirst, mediated by arterial baroreceptors[48].

Overall, a total of seven different stimuli have been identified in the control of thirst; two osmoregulatory signals (one excitatory and one inhibitory), two sodium-regulatory signals (one excitatory and one inhibitory), one excitatory volume-regulatory signal, and two signals associated with changes in arterial blood pressure (one excitatory and one inhibitory)[48].

1.2 Epidemiology and clinical presentation of hyponatraemia

1.2.1 Definition of hyponatraemia

Hyponatraemia, defined as serum sodium (sNa) concentration of below 135 mmol/l (normal range 135-145 mmol/l), is the most common electrolyte disorder encountered in clinical practice. Besides rare occasions when hyponatraemia is associated with hypertonicity or isotonicity, hyponatraemia usually reflects a state of hypotonicity. The two commonest mechanisms are by depletion of total body sodium in excess of water losses (hypovolaemic hyponatraemia) or by dilution of total body sodium through increases in total body water (euvolaemic or hypervolaemic hyponatraemia)[50].

The current literature review and original research undertaken have focused on hypotonic hyponatraemia which represents an excess of water in relation to total body sodium in hospitalised patients.

1.2.2 Incidence of hyponatraemia

Hyponatraemia is a common occurrence in hospitalised patients with incidence reported in studies varying between 5.5% and 42.6%, mainly due to differences in patient population, case mix and definition of hyponatraemia[51]. The largest multicentre study of its kind with a cohort of 198,000 patients across 39 US hospitals showed incidence of admission hyponatraemia (defined as serum Na < 135 mmol/l) of 5.5%, but it probably underestimated the frequency of hyponatraemia since subjects needed at least 2 values of serum Na < 135 mmol/l to qualify as having hyponatraemia, excluding patients whose hyponatraemia resolved rapidly following admission[52]. The second largest epidemiological study of hyponatraemia, conducted in a single acute care hospital in Singapore, reported a 42.6% prevalence of hyponatraemia (serum Na < 136 mmol/l), including 28.2% of patients having admission hyponatraemia and 14.4% developing hospital-acquired hyponatraemia[53]. In this large cohort, serum Na values < 126 mmol/l and < 116 mmol/l were documented in 6.2% and 1.2% of patients respectively[53]. Finally, a European study by Hoorn et al reported that, among 2907 hospitalised patients at a teaching hospital in the Netherlands, 30% had at least one episode of hyponatraemia (serum Na < 136 mmol/l), including 2.6% with serum Na < 126 mmol/l[54].

1.2.3 Effect of age and gender on water homeostasis and hyponatraemia

Increasing age is a strong independent risk factor for developing inpatient hyponatraemia, with the incidence of severe hyponatraemia increasing substantially after the age of 70 years[53]. Hyponatraemia is also common among older individuals in the community. Measurement of sodium levels in 5179 subjects aged 55 years or more from the population-based Rotterdam Study showed that the prevalence of hyponatraemia rose from 5.9% in the subgroup aged 65-74 years to 11.6% in the subgroup aged ≥ 75 years[55]. Elderly are susceptible to hyponatraemia because of an increased exposure to diseases and drugs associated with hyponatraemia as well as aging-related impaired water-excretory capacity[51]. Age-associated alterations to water homeostasis include aging-related decrease in total body water and plasma volume which means that an equivalent body water gain causes greater decrease in plasma osmolality in elderly than in younger individuals; reductions in glomerular filtration rate which decrease tubular delivery of free water to the distal diluting segments of the nephron and result in impaired ability to excrete a free water load; basal AVP secretion may be increased with normal aging; elderly have greater augmentation of AVP secretory response to osmolar stimuli than younger subjects[56]. All these changes in water homeostasis in the geriatric population may explain the unusually high incidence of idiopathic syndrome of inappropriate antidiuretic hormone secretion (SIADH) noted in elderly subjects[56].

In contrast to age, gender does not seem to be an important risk factor for development of hyponatraemia, in general[53 55], with the exception of female gender being an important risk factor for exercise-associated hyponatraemia[57]. However the relationship between gonadal steroids and AVP release has been a subject of research throughout the last few decades. Forsling et al monitored this relationship

in women undergoing prophylactic bilateral oophorectomy at the time of hysterectomy with subsequent hormone replacement therapy and compared it with that in women undergoing hysterectomy with conservation of their ovaries[58]. Bilateral oophorectomy was associated with significant fall in vasopressin levels, whereas hysterectomy with conservation of ovaries did not alter vasopressin concentrations. The post-oophorectomy fall in AVP levels was fully reversed with hormone replacement therapy[58]. The mechanisms through which gonadal steroids result in changes of AVP levels are unclear and could result either from altered release or clearance[58]. The modulatory effect of ovarian steroids on vasopressin release has also been confirmed in several studies of postmenopausal women. When administered alone, oral oestradiol valerate[59] and transdermal oestradiol[60] resulted in a significant increase in circulating levels of vasopressin. Medroxyprogesterone, in combination with oestrogens, counteracted the oestrogen-induced increase in vasopressin secretion[59 60]. With regards to the effect of medroxyprogesterone, given alone, studies have shown mixed results, suggesting that it either suppressed[59] or did not influence vasopressin levels[60].

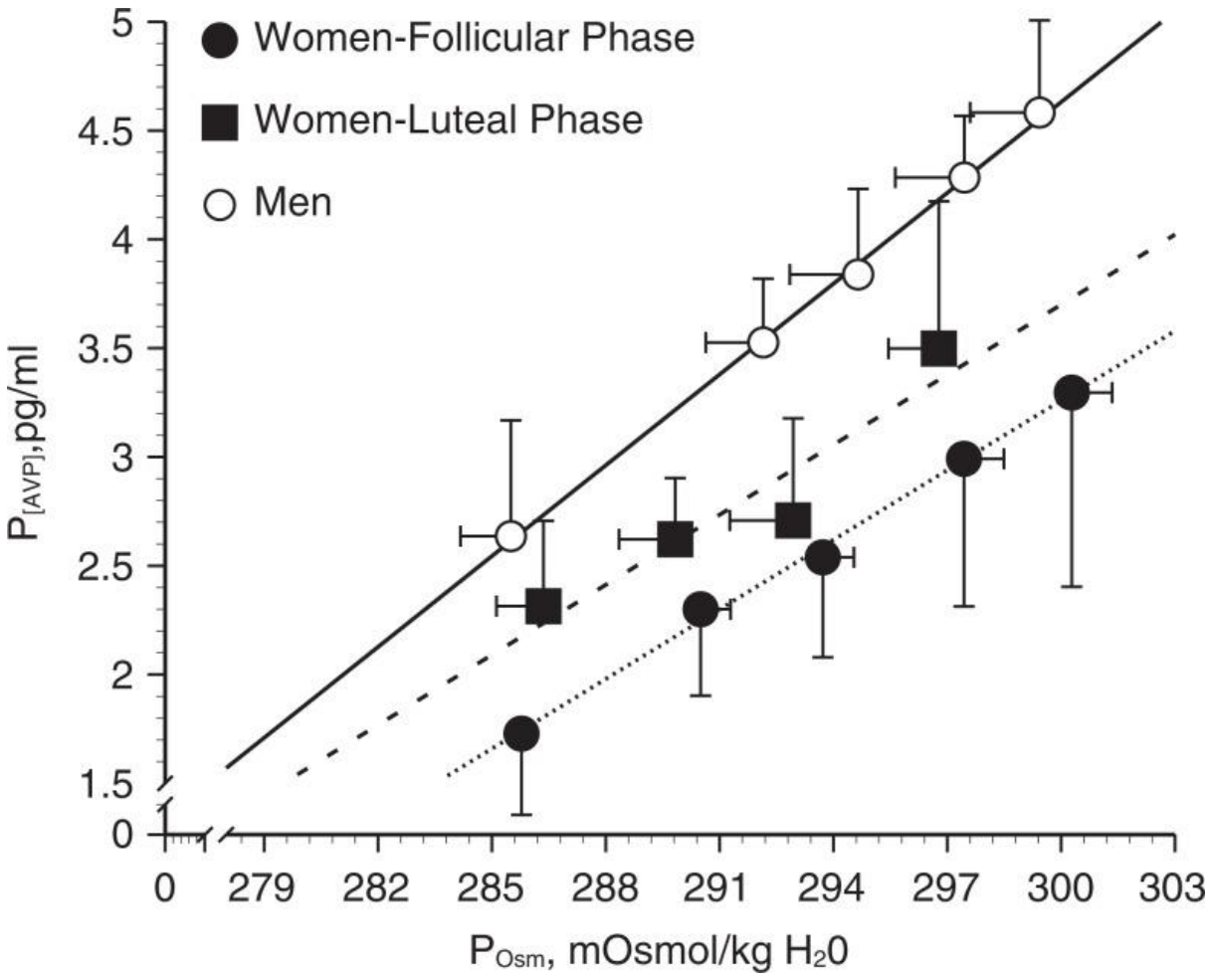
In postmenopausal women, oestrogens, besides their well-known association with increased basal levels of AVP[58 59 60], are associated with an earlier osmotic threshold for AVP secretion (280 vs 285 mOsm/kg for oestrogen vs placebo control treatments respectively)[61]. Taking into account that oestrogens do not seem to impact on thirst and fluid intake in postmenopausal women, reduced urine output results in greater water retention[62]. Oestrogens readily cross the blood–brain barrier and gain access to the hypothalamic nuclei that control AVP synthesis and release. The impact of oestrogens on the central regulation of AVP synthesis and release is probably mediated by ER (oestrogen receptors) with ER-α being expressed in the

OVLT and SFO (brain regions that connect with the PVN and SON) and ER-β being expressed in magnocellular neurons in the PVN and SON[62]. Oestrogens may also impact AVP regulation indirectly by acting on catecholaminergic neurons which have oestradiol-binding sites and project to the PVN and SON[62]. However, the primary explanation for water retention in postmenopausal women is via sodium rather than AVP-mediated free water retention, as a result of stimulation of the renin–angiotensin–aldosterone system. Oestradiol stimulates hepatic synthesis of angiotensinogen, a substrate to renin which is essential to form angiotensin I that is converted to angiotensin II. Angiotensin II stimulates release of aldosterone, leading to renal sodium retention and subsequent water retention[62].

With respect to women of reproductive age, plasma vasopressin concentrations throughout the menstrual cycle vary significantly with the highest values being recorded at the time of ovulation and the lowest at the onset of menstruation. These variations in plasma AVP levels probably reflect changes in the rate and pattern of AVP secretion, resulting from changes in the concentrations of oestrogens and progesterone in the circulation[63]. The osmotic thresholds for thirst and vasopressin release have been found to be lower by approximately 5 mOsm/kg in the luteal than in the follicular phase[64]. Nevertheless, women in the luteal phase do not exhbit a tendency for water retention. A series of studies has demonstrated an oestrogen-associated shift to an earlier threshold for the osmotic sensation of thirst and the release of AVP, with no change in the slope or sensitivity of this relationship, as shown in Figure 8[65]. The plasma osmolality threshold for AVP release was lowest in women studied in mid-luteal phase (263 ± 3 mOsm/kg) compared with women in follicular phase (273 ± 2 mOsm/kg) and men (270 ± 4 mOsm/kg)[65]. However, in these young women, the lower osmotic threshold for AVP release did not affect renal

free water clearance and was not associated with greater renal water retention, suggesting that oestrogen may alter renal sensitivity to AVP or even interfere with AVP action in the kidney. A landmark study, the first to isolate oestrogen effects on osmoregulation of AVP and water regulation in young women by suppressing reproductive function and administering oestrogen and progesterone in controlled doses, also found that oestrogen as well as oestrogen/progesterone combination treatment lower the osmotic threshold for the stimulation and release of AVP without affecting renal free water clearance[66]. However, oestrogen administration led to a greater sodium and fluid retention which was independent of AVP changes. Water retention was primarily associated with intrarenal sodium retention which was independent of the renin-angiontensin-aldosterone-system (RAAS)[66]. Finally, randomised crossover studies, comparing AVP and thirst responses to hypertonic saline infusion during administration of oral contraceptives containing progesterone and during treatment with oral contraceptives containing progesterone and oestrogen, found that progesterone does not alter osmotic threshold for onset of thirst or AVP release and does not affect osmotic fluid regulation[67].

Figure 8. Mean plasma AVP responses to increases in plasma osmolality during hypertonic saline infusion in the follicular and midluteal phases in women and in men. Data are expressed as means ± SE (standard error). Adapted from Stachenfeld et al[65].



A study evaluating the effect of gender on the regulation of urine osmolality in healthy humans confirmed that males have higher basal plasma AVP levels than females. However, after a period of water deprivation, urine osmolality was higher and more responsive to AVP levels in females, indicating greater sensitivity of the collecting duct to AVP in females[68]. A key animal study showing physiologically significant ramifications of sex differences in renal V2 receptor (V2R) expression has demonstrated the presence of marked sex differences in renal V2R expression with 2.6-fold greater V2R mRNA and 1.7-fold greater V2R protein levels in female compared to male rats[69]. A potential explanation for the marked sex difference in V2R expression is that V2R gene, located in X chromosome, may escape X inactivation in females, allowing expression from both X chromosomes in females compared with expression from a single X chromosome in males[69]. This difference was manifested physiologically by a higher urine osmolality in female rats compared with males, observed predominantly at higher doses of desmopressin administration more so than at lower doses, suggesting that the increased V2R receptor expression may be of greater functional significance during situations of high ligand concentrations[69]. The explanation may be that under basal conditions of submaximal AVP stimulation the limiting factor in urine concentration is not V2R receptor number, but rather circulating AVP levels. The result would be that female rats manifest greater maximal responses to high AVP concentrations. Taking into account that escape from AVP-induced antidiuresis is accompanied by a marked downregulation of V2R expression resulting in downregulation of AQP2 expression[70] and since females had higher basal levels of V2R expression, a hypothesis was formulated that females would undergo renal escape more slowly and to a lesser absolute degree relative to males. However, studies by the same group rejected this

hypothesis since both female and male rats reached the same level of escape by completion of the escape process[69]. Interestingly, female rats experienced a greater downregulation of V2R mRNA and protein compared with the males, resulting in complete abolition of profound sex differences in basal V2R expression[69]. It is still debatable whether increased V2R expression in females may cause greater sensitivity to nonosmotically stimulated AVP, thereby increasing the likelihood for development of hyponatraemia due to SIADH in females.

1.2.4 Clinical presentation

The symptoms and signs of hyponatraemia vary and depend on the severity of hyponatraemia, the rate of decline in serum sodium concentration, the patient's age and gender. Usually patients with mild hyponatraemia (serum Na 130-135 mmol/l) have subtle symptoms. Non-neurological symptoms, like nausea, vomiting, malaise, fatigue, cramps, thirst are more common in moderate hyponatraemia (serum Na 125-130 mmol/l). In cases of severe hyponatraemia (serum Na <125 mmol/l), central nervous system symptoms dominate with development of headache, muscle cramps, lethargy, restlessness, agitation, disorientation, confusion, apathy. In cases of severe or rapidly evolving hyponatraemia, seizures, coma, brainstem herniation, respiratory arrest and death can occur[5 50 71].

A prospective study by Nigro et al, including a thorough assessment of symptomatology in 298 consecutive inpatients with serum Na < 125 mmol/l, identified a wide spectrum of non-specific symptoms, with the commonest being nausea (44%), vomiting (30%), generalised weakness (69%), and fatigue (59%)[72]. Regarding neurological symptoms, the incidence for disturbance in memory was 36%, for disturbance in concentration 35%, for disturbed gait 31%, for disorientation 30%, and for headache 27%. The prevalence of acute falls was 20% and of recurrent falls was 16%, while 4% had newly detected fractures. Finally, more severe symptoms such as hyponatraemia-related seizures and focal neurological deficits were identified in 5% and 5% participants, respectively[72].

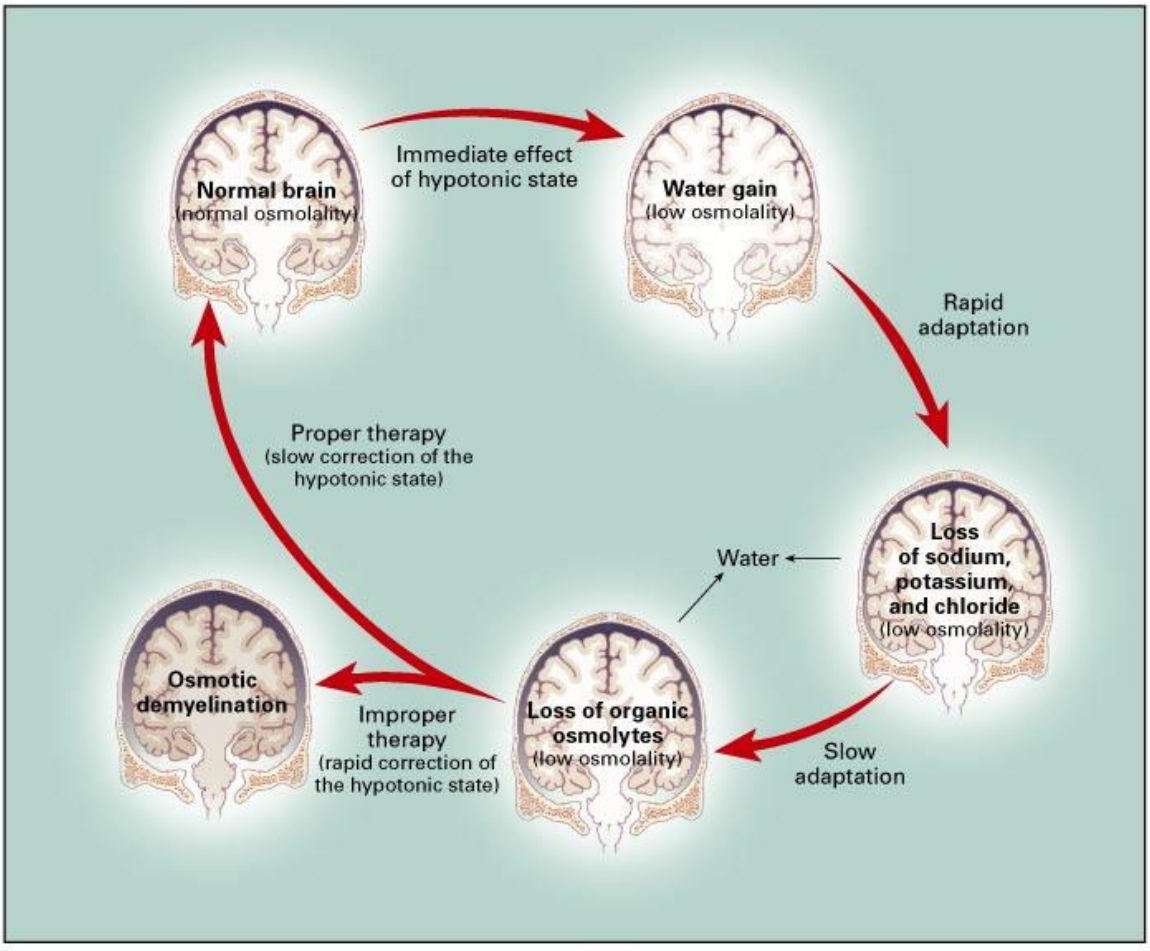
1.2.5 Hyponatraemic encephalopathy

The brain is the main target organ of changes in plasma osmolality. When plasma sodium and osmolality start to fall, water immediately starts to move into brain cells (both neurons and astroglia) to achieve osmotic equilibrium. In the face of a decrease in external osmolality, cells initially behave as nearly perfect osmometers and swell with a magnitude proportional to the osmolality reduction[73]. This water movement appears to be mediated by a specific type of water selective channel, aquaporin-4 (AQP4), located in the brain[74]. AQP4 is expressed prominently in the ependymal cells lining the aqueductal system and over the surface of the brain in contact with the subarachnoid space and facilitates transmembrane water movement, especially at the blood-brain barrier and blood-cerebrospinal fluid interfaces[75]. The action of ADH on AQP4 in the brain is mediated via V1 receptors [74]. Very soon thereafter, hypoosmolality-induced astroglial swelling activates a process known as volume regulatory decrease (VRD) in cell volume in order to minimise water shifts[76]. The first phase of this adaptive process is characterised by rapid loss of electrolytes from the brain through separate volume-sensitive channels. Na losses begin very rapidly within 30 minutes with the main pathway for sodium extrusion from brain being the Na-K ATPase pump[74]. Cl efflux occurs through volume-sensitive Cl channel (VSCC) which is activated by osmotic swelling and exhibits broad anion selectivity, being permeable to the majority of monovalent anions[73]. K losses occur more gradually over several hours, being detectable only at 3 hours after the onset of hyponatraemia[77]. Efflux of K takes place through two different types of K channels; volume-sensitive K^+ channels (VSKC) in epithelial cells which are calcium-dependent, large-conductance channels and require activation of calcium-mediated stretch receptors[78] and VSKC channels in other cell types which are calcium-

independent, small-conductance channels[76].

Taking into account the virtually complete normalisation of brain water content after long periods of sustained hyponatraemia and the fact that the decrease in electrolytes is clearly insufficient to account for this degree of cell volume regulation, it is evident that other intracellular osmotically active solutes, called organic osmolytes, play a key role in water regulation[77 76]. The electrolyte losses account only for 60-70% of the observed brain volume regulation, suggesting that the brain organic osmolyte losses account for approximately one third of the total brain solute losses during sustained hypoosmolality. This second phase of the adaptive process, characterised by loss of organic osmolytes, starts around 24 hours after changes in osmolality, as shown in Figure 9[50].

Figure 9. Schematic diagram of brain volume adaptation to hyponatraemia. Within minutes after the development of hypotonicity, water gain causes swelling of the brain and a decrease in osmolality of the brain. Partial restoration of brain volume occurs within a few hours as a result of cellular loss of electrolytes (rapid adaptation). The normalisation of brain volume is completed within several days through loss of organic osmolytes from brain cells (slow adaptation). Low osmolality in the brain persists despite the normalisation of brain volume. Proper correction of hypotonicity reestablishes normal osmolality without risking damage to the brain. Overly aggressive correction of hyponatraemia can lead to irreversible brain damage. Reproduced from Adrogue et al[50].



Besides myoinositol which is the most prevalent organic osmolyte in the brain with its concentrations being closely related with the levels of serum sodium[79], the main other organic osmolytes are glutamate, creatine, taurine, glutamine, and other amino acids (such as urea, GPC; glycerophosphocholine, GABA; gamma-aminobutyric acid, glycine, aspartate)[76]. Efflux of myoinositol and taurine takes place through bidirectional ''leak pathways'' with net solute movement depending on concentration gradient direction and without significant contribution from energy-dependent carriers[73]. Most other organic osmolyte pathways exhibit a biological profile similar to that of the volume-sensitive Cl channel (VSCC), suggestive of a common pathway with Cl efflux or of a close connection between the two pathways[76]. However, the mechanisms of glutamate and GABA release are different and not clearly characterised yet, possibly via calcium-independent PKC (Protein Kinase C)-modulated, actin-dependent exocytotic release[80]. Animal studies have demonstrated that, after 24 hours of severe hyponatraemia, brain tissue levels fell by 33-45% for glutamate, 21-60% for myoinositol and 39-71% for taurine[81 82]. Interestingly, while decreases of brain electrolytes reverse with time, decreases of organic osmolytes are sustained as long as hyponatraemia persists[81]. It is increasingly recognised that the large reduction in brain organic osmolyte contents has several potentially important effects. During volume regulation, significant effluxes of intracellular osmolytes from brain cells could result in transiently increased local brain extracellular fluid concentrations of osmolytes. For example, high concentrations of glutamate, an excitatory neurotransmitter, in the extracellular fluid could change neuronal membrane potential and account for the increased incidence of seizure activity[76].

As explained above, the volume-adaptation process takes a finite period of time to

complete. As a result, the more rapid the fall in serum Na, the more water influx into the brain will occur before the brain will be able to extrude solutes and along them part of the increased water content. Thus, in acute hyponatraemia, arbitrarily defined as developing over less than 48 hours, when hypoosmolality develops at a rate that exceeds the brain's ability to regulate its volume by losing solutes, severe brain oedema may occur with the potential to lead to neurological dysfunction and sometimes even death[76]. In contrast to acute, chronic hyponatraemia is characterised by near normalisation of brain volume, resulting in less severe neurological symptomatology[74]. For these reasons, the severity of neurological sequelae of hyponatraemia is often more strongly associated with the rate of developing serum sodium decrease than the actual magnitude of decrease.

1.2.6 Influence of gender, age and hypoxia on hyponatraemic encephalopathy

The key factors that substantially influence outcome in terms of brain damage in hyponatraemic patients are female sex and hypoxia. Reviewing the literature on patients with hyponatraemic encephalopathy, premenopausal women are at a substantially greater risk of dying or developing permanent brain damage from symptomatic hyponatraemia than either postmenopausal women or men[74 83]. While postoperative hyponatraemia occurs equally in both genders, premenopausal women are about 25 times more likely to die or have permanent brain damage compared with either men or postmenopausal women[84], with more than 80% of all patients with symptomatic hyponatraemia who die or experience brain damage being women[83 85]. This very clear female preponderance among patients dying or developing permanent brain damage in patients with hyponatraemic encephalopathy has a multifactorial aetiology. Firstly, both oestrogens and progesterone inhibit the function of the Na-K ATPase pump, the key pathway of sodium extrusion from cells, which has been found to be more effective in males than females[86 87]. Second, oestrogens increase circulating levels of AVP, resulting in higher plasma AVP levels and a lower osmotic threshold for AVP secretion (280 vs 285 mOsm/kg) in premenopausal compared to postmenopausal women[61]. This observation is important since there is evidence that AVP directly increases water movement into the brain[88]. Also studies in rats with mean serum Na 110 mmol/l showed that female rats had greatly reduced cerebral perfusion compared to male rats. This significant impairment in the brain blood flow and oxygen utilisation was observed only in female rats and was not reversed by testosterone administration[89]. Further studies in hyponatraemic rats by the same group confirmed that the effects of AVP on blood vessels is gender dependent, with AVP-induced hyponatraemia leading to a 36%

reduction in cerebral blood flow and a 60% reduction in cerebral oxygen consumption in female rats in contrast to no changes in male rats[90]. Thus, animal studies suggest a difference in vascular reactivity to vasopressin between females and males, resulting in increased vascular smooth muscle contractility, decreased cerebral blood flow and brain hypoxia in hyponatraemic females[83]. In total, female sex hormones prevent effective brain adaptation to hyponatraemia, stimulate water influx into the brain, and contribute to cerebral hypoperfusion and hypoxia[83]. Additionally, the ability of premenopausal females to appropriately adapt to hyponatraemia may depend in large part on the phase of the menstrual cycle at which hyponatraemia develops[74].

It is worth mentioning that elderly individuals, particularly men, tend to be resistant to the effects of hyponatraemic encephalopathy. A possible explanation might be related to changes in Na-K ATPase pump activity which is critical to the brain's adaptation to hyponatraemia. However, the fact that aging decreases, rather than increases, brain Na-K ATPase activity, does not support this hypothesis[91]. This highlights the significance of physical factors, in particular the relationship between brain size and skull size for different age groups. Men have larger skulls than women and, after the age of 25 years, brain size starts to shrink significantly, but much more so in men[83]. Therefore, by the age of 60 years, the male brain has shrunk substantially, whereas female brain size has not changed much; thus, elderly males have a lot more space, compared to women, in their skulls for their brain to expand[83]. On the other hand, children are at high risk of brain herniation in association with hyponatraemia due to a combination of fully developed brain and small skull size in view of the fact that a child's brain reaches adult size by 6 years of age, whereas the skull does not reach adult size until 16 years of age[92]. In addition,

the paediatric brain has much less Na^+-K^+-ATPase activity than the adult brain[93].

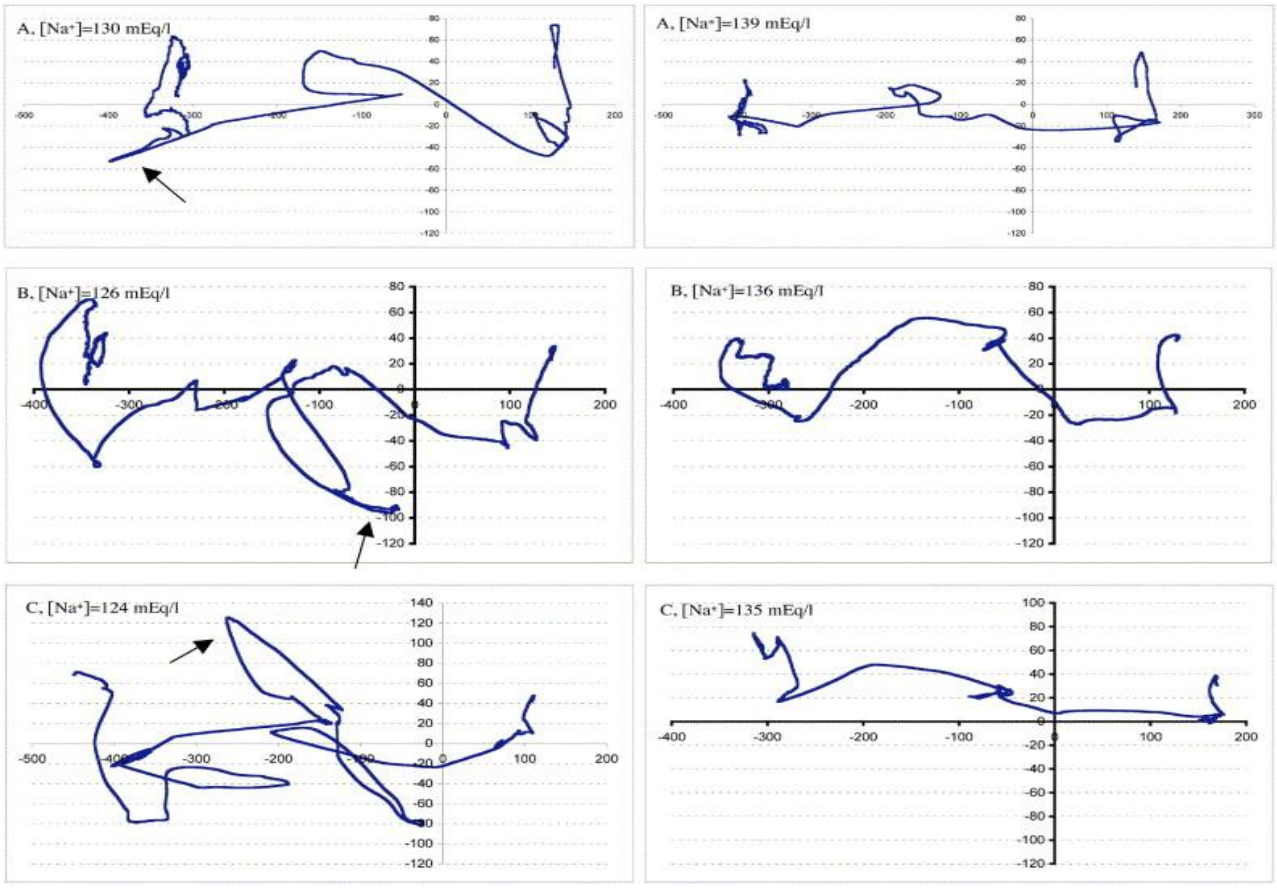
The implications of age and sex-based differences are that, at the same levels of hyponatraemia, young women exhibit more severe neurological symptoms than postmenopausal women and men. For example, the mean plasma sodium concentration in young females who developed permanent brain damage or respiratory failure was 117 mmol/l compared to 109 mmol/l in postmenopausal women[74].

Hypoxia is another major factor contributing to brain damage in patients with hyponatraemia. Hypoxia severely blunts the increase in Na-K ATPase transport activity, the primary mechanism for early brain adaptation, since it is an oxygen-requiring process[94]. Hypoxia is also a major stimulus for increased secretion of ADH which directly increases water movement into the brain and aggravates brain oedema. While hypoxia, under ordinary circumstances, leads to a compensatory increase of cerebral blood flow, hypoxia in the context of hyponatraemia decreases cerebral blood flow, further impairing brain adaptation[93]. All these effects of hypoxia explain why a recent retrospective study of 1,000 patients with hyponatraemic encephalopathy found that 96% of those who developed permanent brain damage or died had suffered a hypoxic episode[83 85].

1.2.7 Clinical significance of chronic hyponatraemia

The old concept that patients with chronic hyponatraemia are ‘’asymptomatic’’ is no longer valid in light of recent evidence suggesting that chronic hyponatraemia is not a benign condition[95 96]. Renneboog et al undertook a case-control study demonstrating that patients with chronic moderate hyponatraemia (mean serum Na 126 mmol/l) fall dramatically more frequently than normonatraemic controls with an adjusted odds ratio of 67[95]. This strong independent association between hyponatraemia, even mild, and high risk of falls has been confirmed in subsequent studies in older patients[97 98]. Renneboog et al firstly reported that hyponatraemic patients, considered to be clinically asymptomatic with normal neurological examination findings, were highly unstable in tandem gait with their eyes open. After correction of hyponatraemia, the ‘’total travelled way’’ by the centre of pressure significantly decreased, as shown in Figure 10[95].

Figure 10. Evolution of the “total traveled way” (TTW) of the center of pressure in the dynamic test to walk on the platform 3 stereotyped steps “in tandem” with eyes open, in 3 patients (A,B,C) with mild asymptomatic hyponatraemia and after correction. Patients are walking from right to left. Irregular paths of the centre of pressure observed in state of hyponatraemia. Reproduced from Renneboog et al[95].



The same group detected also attentional impairments in association with chronic hyponatraemia which consisted of significant increases in response latency and error rate. Chronic hyponatraemia was related with a global decrease of attentional capabilities and a defect in both visual and auditory tests[95 96]. Remarkably, patients with hyponatraemia exhibited more severe balance and attention impairments than normonatraemic individuals when tested 30 minutes after ingestion of 0.55 g of alcohol per kg of body weight[95]. Of note, the threshold for gait deficits associated with hyponatraemia was 134 mmol/l and for attention deficits was 132 mmol/l[96]. A recent study in community-dwelling older individuals with even milder degree of hyponatraemia (serum Na 130-135 mmol/l) showed a 5% decrease in a cognitive screening score in comparison with normonatraemic subjects, representing a cognitive deficit[97].

The first ‘before and after’ prospective study, assessing the impact of hyponatraemia on muscle strength and nerve conductivity in 11 subjects with mean serum Na 127.7 mmol/l, did not demonstrate a significant impact of mild hyponatraemia on muscle strength[99]. However, a statistically significant improvement was observed in ‘Timed up and go test’ (TUG) from a mean 14.9 seconds at baseline to 12.5 seconds following correction of hyponatraemia. Since TUG is a predictor of falls, this observation suggests that restoration of normonatraemia may lower the risk of falls. Also this study firstly reported that severe hyponatraemia (serum Na < 125 mmol/l) caused slowing of motor and sensory nerve conduction velocities (NCV) and increase in F-wave latencies, while correction of hyponatraemia significantly improved both NCV and F-wave latencies by 15-20%[99]. This impact on peripheral nervous system may contribute to gait disturbance, attention deficits and increased propensity for falls[99].

Fujisawa and colleagues published in 2016 an important study in a rat model showing that hyponatraemia caused ataxic gait, increased anxiety levels, and impaired recognition and associative memory, but these abnormalities were reversible after correction of hyponatraemia[100]. The authors of this study, addressing the mechanism of memory impairment in chronic hyponatraemia, showed an adverse effect on hippocampal long-term potentiation which is believed to be a main neural mechanism for memory storage. They also demonstrated that the main mechanism leading to impaired long-term potentiation is increased extracellular glutamate levels in the hippocampus because of decreased glutamate uptake by primary astrocytes[101].

In total, there is emerging evidence since 2006 supporting an association of chronic, even mild, hyponatraemia with gait impairment and attention deficits, contributing to high risk of falls[95 96]. Moreover, a recent study, published by Renneboog et al, showed that hyponatraemia-induced alterations in attention and gait tests are much more pronounced in older (mean age 73 years) than in younger adults (mean age 48 years)[102]. This increased sensitivity of older individuals in combination with their high incidence of falls suggests that, even mild, hyponatraemia can have significant physiological effects in this age group.

1.2.8 Hyponatraemia and bone

Since 2010, numerous observational studies have examined the relationship between serum sodium concentration and the incidence of fractures, demonstrating that, even mild, hyponatraemia is significantly associated with fracture occurrence[103 104 105 106 107 108 109 109]. Also several epidemiological studies have demonstrated a relationship between hyponatraemia and osteoporosis, mainly in the hip. A cross-sectional single-centre study by Afshinnia et al showed that, after multivariable adjustments, hyponatraemia was associated with 2.46-fold higher odds of total hip osteoporosis in age < 55 years, 1.96-fold in age 55-67 years, and 1.55-fold in age > 67 years, suggesting that age acts as a modifier of the independent association between hyponatraemia and osteoporosis[110]. In a novel observation, this study also showed that the longer the duration and the more severe the degree of hyponatraemia, the higher the risk of developing osteoporosis[110]. Data analysis from the Danish National Patient Registry (N=1575) found that hyponatraemic individuals have significantly increased odds ratio (OR) of osteoporosis at both total hip (OR = 2.17) and lumbar spine (OR = 1.83) in comparison to normonatraemic subjects[111]. Another retrospective cohort study using Danish data reported that mild hyponatraemia, defined as serum Na 130-135 mmol/l, was associated with lower bone mineral density (BMD) in the hip and neck of femur, but had limited effect on the lumbar spine[112]. Holm et al evaluated a historical cohort of 5610 women and found that, even after adjusting for several potential confounding factors in the multivariate analysis, hyponatraemic patients had a significantly lower T score at the total hip by a mean of 0.184, but not at the lumbar spine. In addition, hyponatraemic patients had a significantly increased hazard ratio of sustaining a major osteoporotic fracture with this association persisting after adjustment for BMD, indicating that

changes in BMD do not fully explain this association[105]. This significant association between hyponatraemia and increased risk of fractures which is independent of BMD was firstly found by Kinsella et al[103]. Similarly, a cross-sectional and longitudinal analysis of 5122 men aged ≥ 65 years enrolled in the Osteoporotic Fractures in Men (MrOS) study found that hyponatraemic men have a higher incidence of falls and a significantly lower T score at all sites compared to normonatraemic men. Nonetheless, the increased risk of hip fracture (HR = 3.04) and spine fracture (OR = 3.53) observed in hyponatraemic men was independent of bone mineral density (BMD) and falls[108]. Data analysis from the Third National Health and Nutrition Examination Survey (NHANES III) showed that, after multivariable adjustments, mild hyponatraemia was associated with higher odds of osteoporosis at the hip (OR = 2.85) and at the femoral neck (OR = 2.87). Among NHANES III hyponatraemic participants, a statistically significant positive linear association between serum Na and femoral neck BMD was observed[104]. The group by Verbalis et al undertook a case-control study in a US health population during which approximately 30,000 osteoporosis and 46,000 fragility fracture cases were matched on age, sex, and ethnicity with 30,000 controls without osteoporosis and 46,000 controls without fragility fractures[106]. They demonstrated that chronic hyponatraemia was associated with osteoporosis (OR = 3.97) and fragility fractures (OR = 4.61) with these odds increasing incrementally with a decrease in serum sodium[106]. This study provided further evidence that the association between hyponatraemia and osteoporosis is dose-dependent (more severe hyponatraemia results in higher elevated risk) and time-dependent (chronic hyponatraemia, defined as two serum Na measurements < 135 mmol/l at least one year apart, carries higher risk than an episode of hyponatraemia in the past which has now resolved)[106], as previously suggested by

Afshinnia et al[110]. Contrary to all those studies, Hoorn et al found in the prospective population-based Rotterdam Study (N = 5208) that hyponatraemic patients did not have significantly lower BMD than normonatraemic subjects[107]. The lack of significant difference in hip BMD and osteoporosis between hyponatraemic and normonatraemic patients observed in the Rotterdam study may be explained by the predominance of elderly patients in that cohort, with the attenuation of the risk in elderly patients reflecting aging being a competing risk factor offsetting the risk of hyponatraemia[110]. Additionally, Hoorn et al found that mild hyponatraemia in the elderly is associated with an increased risk of vertebral fractures and non-vertebral fractures, independent of BMD and falls, suggesting a possible detrimental effect of hyponatraemia on bone quality[107]. The first systematic review and meta-analysis, evaluating the association between hyponatraemia, fractures, and osteoporosis, was published in Spring 2016 and included 12, high quality, observational studies[113]. The results of the meta-analysis were robust with little heterogeneity, suggesting that hyponatraemia increases the risk of fracture and is associated with an increased prevalence of osteoporosis. Meta-analysis of BMD measured at all anatomical sites showed that hyponatraemic patients had significantly lower BMD only at the hip[113].

With regards to the pathophysiological basis of the effect of hyponatraemia on bone, Verbalis et al first demonstrated in 2010 that hyponatraemia can cause a substantial reduction of bone mass in a rat model of SIADH [104]. Analysis of excised femurs in rats using dual-energy X-ray absorptiometry (DXA) showed that severe hyponatraemia (mean serum Na 110 mmol/l) for 3 months reduced significantly BMD by 30% compared with normonatraemic rats. The most striking histologic finding was that hyponatraemia increased the number of osteoclasts per bone area. Micro-

computed tomography (mCT) and histomorphometric analyses indicated that hyponatraemia markedly reduced both trabecular and cortical bone via increased bone resorption. Also concentration of serum osteocalcin, a marker of bone formation, was significantly decreased in the sera from hyponatraemic rats compared with normonatraemic controls. In total, those results indicated that, at least prolonged severe, hyponatraemia increased bone resorption and decreased bone formation, leading to an uncoupling of these two processes[104]. The same research group revealed novel bone sodium signalling mechanisms in osteoclasts that may serve to mobilise sodium from bone stores during prolonged hyponatraemia. For example, hyponatraemia decreased in a dose-dependent manner cellular uptake of ascorbic acid with subsequent downstream effects, providing evidence for hyponatraemia-induced oxidative stress[114]. Key findings of in vitro[114] and in vivo[104] studies so far are that the increased osteoclastogenesis and osteoclast activity is a result of sodium sensing, and not osmolality sensing, and that hyponatraemia effects on bone occur independently of arginine vasopressin activity[115]. Moreover, a recent study provided evidence about the effect of chronically reduced extracellular sodium concentration, independently of osmotic stress, on human mesenchymal stromal cells (hMSC) from bone marrow, the common progenitor for osteoblasts and adipocytes[116]. There was a dose-dependent increase in the number of adipocytes as a function of hyponatraemia, suggesting a preferential commitment toward the adipogenic phenotype at the expense of osteogenesis. The analysis of cytoskeleton showed that low sodium was associated with disruption of tubulin organization in hMSC-derived osteoblasts, thus suggesting a negative effect on bone quality. These findings indicate for the first time that hyponatraemia may cause impaired osteogenesis[116].

Nonetheless, these data do not exclude a potential additive effect from elevated AVP levels per se. In vitro and in vivo studies in animal models have showed that two AVP receptors, AVPR1α and AVPR2, as well as oxytocin receptors are expressed in both osteoblasts and osteoclasts[117]. Stimulation of AVP receptors triggers extracellular signal regulated kinase (Erk) activation, which in turn suppresses bone formation and stimulates bone resorption[117]. For example AVP injected into wild-type mice enhanced and reduced, respectively, the formation of osteoclasts and osteoblasts. Conversely, the exposure of osteoblast precursors to AVPR1α increased osteoblastogenesis and reduced bone resorption, while AVPR1α$^{-/-}$ mice display a remarkable high bone mass phenotype[117]. Further studies by the same research group showed that Avpr1α and the oxytocin receptor (Oxtr) have opposing effects on bone mass: Oxtr$^{-/-}$ mice have osteopenia, AVPR1α$^{-/-}$ mice display a high bone mass phenotype, and, notably, this high bone mass phenotype is reversed by the deletion of *Oxtr* in *Oxtr*$^{-/-}$:*Avpr1α*$^{-/-}$ in double-mutant mice. Finally, a specific AVPR2 inhibitor, tolvaptan, does not affect bone formation or bone mass, suggesting that AVPR2 does not have a significant role in bone remodelling[118].

It has long been recognised that one-third of the total body sodium is stored in bone, some of which is readily exchangeable with serum sodium and is released from the bone during prolonged salt deprivation. Thus, it appears increasingly likely that sodium homeostasis is intrinsically related to bone physiology with osteoclast-mediated bone resorption during hyponatraemia occurring to preserve sodium homeostasis. Most experts in this evolving field agree that serum sodium concentration seems to be the signal by which osteoclasts sense extracellular fluid and total body sodium; therefore, osteoclasts ‘’misinterpret’’ conditions without absolute sodium deficiency like SIADH as total body sodium deficiency.

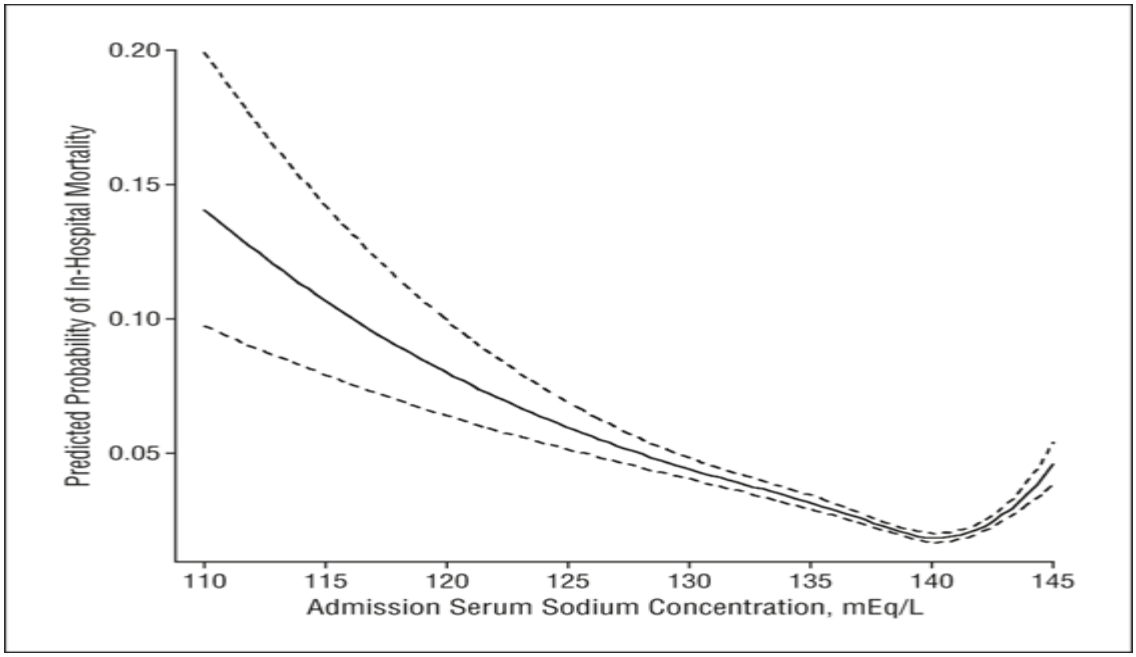
Consequently, there is ''no brake'' to the stimulated bone resorption, as the serum sodium remains low no matter how much bone is resorbed. This would lead to continued osteoclast-mediated bone resorption as long as hyponatraemia persists[119].

In conclusion, a considerable volume of recent epidemiological data support that hyponatraemia is an independent predictive risk factor for fractures. The aetiology of this relationship seems to be multifactorial. First, hyponatraemia has a negative impact on gait stability, resulting in an increased risk of falls. Second, hyponatraemia seems to directly contribute to osteoporosis by inducing increased bone resorption to mobilise sodium stores in bone. Low extracellular sodium directly stimulates osteoclastogenesis and bone resorptive activity through decreased cellular uptake of ascorbic acid and the induction of oxidative stress; these effects occur in a sodium level-dependent manner[120]. In addition, recent data suggest a primary role for AVP signalling in bone mass regulation acting on two receptors expressed in both osteoclasts and osteoblasts. Nonetheless, several studies, showing that neither osteoporosis nor falls are sufficient to fully explain the mechanisms by which hyponatraemia results in increased risk of fractures[103 105 108], indicate the likely presence of additional pathways through which hyponatraemia affects bone quality, for example direct effect of AVP on bone remodelling.

1.3 Hyponatraemia and mortality

The association between hyponatraemia and high inpatient mortality has been demonstrated in numerous studies. A large single-centre cohort study, including more than 50000 adult hospitalised patients, found that even mild hyponatraemia was independently associated with increased in-hospital mortality[121]. A classic U-shaped relationship was observed with lowest mortality documented for serum Na range of 138-142 mmol/l, as shown in Figure 11[121]. A similar U-shaped distribution has also been reported in other studies[122].

Figure 11. U-shaped relationship between hospital admission serum sodium concentrations and in-hospital mortality. Dashed lines represent the 95% confidence interval[121]. Adapted from Wald et al[121].



In contrast to studies supporting a U-shaped distribution[121 122], a large cohort study of more than 270000 medical inpatients challenged this hypothesis by reporting that 30-day and 1-year mortality increased for serum sodium levels from 139 mmol/l to 132 mmol/l, then reached a plateau and finally decreased for levels below 120 mmol/l[123]. Chawla et al also suggested that mortality rates increase as serum Na fell from 134 to 120 mmol/l, but the trend reversed below serum Na of 120 mmol/l with the mortality rate progressively decreasing[124]. This may be explained by the cause of profound hyponatraemia being often drug-induced rather than due to a severe underlying illness[124].The same paradoxical fall in mortality observed for very low serum Na values below 120 mmol/l was also recorded by Waikar et al[125]. In addition, the prognostic significance can differ across clinical settings[125] and underlying aetiology of hyponatraemia[126]. Several studies have also established the adverse prognostic significance of hyponatraemia in patients with specific illnesses, such as heart failure[127], myocardial infarction, cirrhosis, cancer[128] and chronic kidney disease[129].

Hyponatraemia in hospitalised individuals is a prognostic factor not only for short-term, but also for long-term mortality. A study, including more than 2900 unselected patients admitted to a general hospital, demonstrated hyponatraemia (defined as serum Na < 137 mmol/l) as an independent predictor of all-cause mortality after 1 year (hazard ratio 1.6) and 5 years (hazard ratio 1.4) with moderate-severe hyponatraemia having a higher risk of mortality than mild[130].

In addition to the adverse prognostic significance of hyponatraemia in hospitalised patients, three large contemporary population-based cohort studies have established the prognostic weight of hyponatraemia in the community. Hyponatraemia is an independent predictor of all-cause mortality and major cardiovascular events in men

older than 60 years[131], of deaths and myocardial infarctions in community female and male subjects aged 55 to 75 years[132], and of total mortality in the general population[133]. These studies have also provided evidence in favour of a U-shaped association between serum sodium, mortality and cardiovascular disease in the community[131 133].

While numerous cohort studies with large sample size have been conducted in this field, only 2 case-control studies had examined the association between hyponatraemia and in-hospital mortality prior to our own case-control study[134 135]. The first study of this kind was retrospective, comparing inpatients with serum Na < 130 mmol/l with controls matched for age, gender and date of admission, and recorded in-hospital mortality rate of 8.7% in hyponatraemic versus 1.1% in normonatraemic participants (odds ratio 7.33 with P value < 0.001)[134]. The second, published in 2006, is the only prospective case-control study up to date in this field and included cases with serum Na < 125 mmol/l. Gill et al showed a significantly increased mortality of the hyponatraemic patients compared with the controls (27% vs 9%, P value 0.009) who were matched only for date of admission[135]. However, hyponatraemic patients were older, had much more comorbidities such as poor renal function and were more frequently treated with cardiovascular medications. All these differences between cases and controls made difficult to conclude if the excess mortality of hyponatraemic patients should be attributed to the severity of underlying illness or to their electrolyte abnormality[135].

In total, a strong association between hyponatraemia and excess mortality in hospitalised patients has been demonstrated in numerous studies[121 122 123 124 125 126 130 134 135], but causality has not been proved yet. However, whether hyponatraemia by itself can contribute to mortality or merely represents a surrogate marker for the

severity of the underlying diseases remains a contentious issue. Some authors have suggested that hyponatraemia is merely an epiphenomenon of illness reflecting its severity and patients die ‘’with’’ rather than ‘’from’’ hyponatraemia[124 126]. Other authors have argued that hyponatraemia per se contributes directly or indirectly to death through unclear mechanisms and is probably causally linked to excess mortality[125 136 137].

1.4 Economic burden of hyponatraemia

Several studies have demonstrated that hyponatraemia is associated with an increased length of hospital stay and of hospital resource utilisation. The first large study finding these associations was a retrospective cohort study of hospitalised patients which was published in 2008 and represented 198,281 discharges from 39 US hospitals[52]. After adjusting for confounders such as age and Deyo - Charlson Comorbidity Index score, patients with hyponatraemia (serum Na < 135 mmol/l) at admission had a significantly greater mean (± SD) length of stay (8.6 ± 8.0 vs 7.2 ± 8.2 days, P < 0.001) and cost of hospitalisation ($16,502 ± $28,984 vs $13,558 ± $24,640, P < 0.001) than normonatraemic individuals. This study concluded that hyponatraemia contributed an average increase in length of stay of 1.0 day and total hospital costs of $2,289[52]. A very recent meta-analysis by Corona et al, based on all 45 published studies reporting data on duration of hospitalisation and including in total 3,940,042 patients with 757,763 of those being hyponatraemic, showed that hyponatraemia is associated with a significantly longer duration of hospitalisation (3.3 days, 95% CI 2.9-3.7 days; *P* < .000)[138]. Similar results were obtained when series of hospitalised hyponatraemic patients due to various aetiologies were analysed as well as when patients with specific diseases (for example heart failure[139], liver disease[140] and cancer[128 141]) were analysed separately. In addition, hyponatraemic patients had a higher risk of readmission (odds ratio 1.32, 95% CI 1.18-1.48; *P* < .000) after a mean follow-up of 72 days following first hospital discharge when compared with normonatraemic ones at the first hospital admission[138]. Another large-scale, real-world hospital database study evaluated the incremental burden of 558,815 hospitalised hyponatraemic patients versus 558,815 normonatraemic patients matched for age, gender and severity of illness[142]. It

showed that, after multivariate adjustment, hyponatraemia was associated with an incremental increase ranging between 14% and 17% for hospital readmission rate 30 days post discharge for any cause ($P < 0.001$) as well as an increase of 11% for length of stay ($P < 0.001$)[142].

The same meta-analysis by Corona et al took into account 8 studies, all performed in the US, to estimate the difference in mean hospital cost between subjects with and without hyponatraemia. Hyponatraemia was associated with an increase of hospital costs of up to $3000 when compared with normonatraemia[138]. In 2006, a consensus panel estimated the direct costs of treating hyponatraemia in the U.S. on an annual basis to range between $1.6 billion and $3.6 billion[143]. The main cost driver was hospitalisation costs (due to longer hospital stay and increased risk of readmission) accounting for approximately 70% of the total cost of illness with follow-up treatment being the second largest cost driver accounting for 15%–20% of total costs. This study calculated the annual cost per hospitalised hyponatraemic patient directly linked to hyponatraemia between $1528 and $3441[143]. However more recent longitudinal data from the Integrated HealthCare Information Services National Managed Care Benchmark Database suggested that the 1-year mean inpatient cost related to a hyponatraemic patient was approximately $10,636[144], more than 3 times higher than the previous estimate by Boscoe et al[143]. After controlling for demographic variables and other clinical predictors of poor outcomes, hyponatraemia was found to be a significant independent predictor of total medical costs at 6 and 12 months with their medical costs being more than double those incurred by normonatraemic patients, mainly because of cost related to inpatient care[144]. While several studies have quantified the contribution of hyponatraemia to hospitalisation costs in the US, there are very little data available in European

healthcare settings. A data analysis from the Minimum Basic Data Set of a total of 2,134,363 discharged patients from all medical departments of the Spanish National Health System between 2007 and 2010, including 31,933 (1.5%) with a diagnostic code of hyponatraemia, demonstrated that the mean cost per admission in the presence of hyponatraemia was €4023 compared to €3537 in normonatraemic individuals ($p < 0.001$)[145]. Hyponatraemic subjects also required longer hospitalisation (mean of 11.7 days) compared to 9.8 days among the general population ($p < 0.001$) and had a higher risk of readmission (OR 1.33, CI 95% 1.29-1.38)[145].

Overall, there is substantial evidence nowadays that hyponatraemia is associated with prolonged hospital length of stay and higher risk of readmission and may represent one important determinant of the hospitalisation costs. However, it is still not known if correction of hyponatraemia can reduce length of stay, readmission rate and use of healthcare resources.

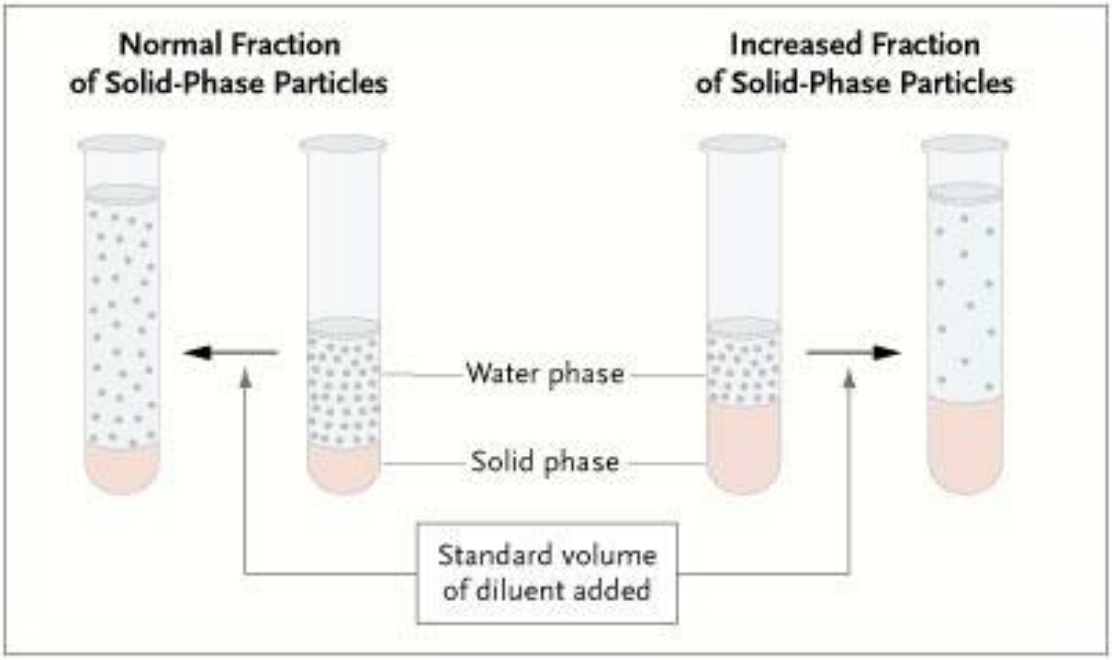
1.5 Classification and causes of hyponatraemia

1.5.1 Non-hypotonic hyponatraemia

Hyponatraemia and hypo-osmolality are usually synonymous. However, there are 2 situations when hyponatraemia and hypo-osmolality are discordant; pseudohyponatraemia and isotonic / hypertonic hyponatraemia.

Pseudohyponatraemia is defined as spuriously decreased serum sodium concentration because larger relative proportion of plasma volume is occupied by excess proteins or lipids[146]. There are two methods using ion-selective electrodes (ISE), direct ISE and indirect ISE, for the measurement of serum electrolytes. In direct potentiometry, a predilution step is not involved and, therefore, the measurement is not dependent on the water content of the sample, minimising the likelihood for pseudohyponatraemia. However, more than two thirds of the currently used instruments for sodium measurement use the technique of indirect ion potentiometry which is prone to pseudohyponatraemia, because it involves the dilution of the serum sample with a predetermined volume of ionic solution before the actual measurement is obtained[147]. The concentration of the electrolyte is then adjusted by a fixed factor of 0.93 (the average volume water in serum) to obtain the actual ion concentration in serum. This calculation is based on the fact that, in normal individuals, serum is composed of approximately 93% water with fats and proteins (nonaqueous or solid phase) accounting for the remaining 7%[146]. Of note, sodium is located in the serum water phase only. Therefore, if more than 7% consists of proteins or lipids, the degree of dilution is underestimated, resulting in artificially low sodium levels[147], as illustrated in Figure 12.

Figure 12. Artificially Low Sodium Levels as Determined by Dilution-Based Methods. Normally, serum contains 7% solids by volume. In order to reduce the volume of blood needed for analysis, serum is diluted before the actual measurement is obtained. The same volume of diluent is always used; the degree of dilution is estimated under the assumption that the serum contains 7% solid-phase particles. When the fraction of solid-phase particles is increased, the same amount of diluent results in a greater dilution, unbeknownst to the laboratory personnel (right side of figure). Consequently, the calculation of sodium concentration with the use of a degree of dilution that is based on the incorrect fraction of solid-phase particles will lead to an underestimate. Adapted by Turchin et al[147].



The common causes of pseudohyponatraemia are marked hyperproteinaemia (due to paraproteinaemia, hypergammaglobulinaemia or intravenous immunoglobulin administration) or hyperlipidaemia (due to severe hypertriglyceridaemia or marked hypercholesterolaemia due to the presence of lipoprotein X-like particles[147])[146]. In contrast to the rarity of indirect ISE sodium underestimation, the opposite phenomenon of pseudonormonatraemia or pseudohypernatraemia in association with indirect ISE estimation is a regular occurrence, as a result of severe hypoproteinaemia[146]. A study, comparing plasma sodium measurements on 346 samples, suggested that indirect ISE measurements overestimated direct ISE by at least 4 mmol/l in 8% of hospital specimens and 25% of specimens from ICU patients, with discrepancies approaching in some cases 10 mmol/l[148]. Another study of 300 ICU samples reported the proportions of indirect ISE misclassifications due to pseudonormonatraemia and pseudohypernatraemia being 13% and 7% respectively, reflecting the prevalence of hypoproteinaemia in critical illness[149].

Isotonic or hypertonic hyponatraemia occurs when effective solutes other than sodium are present in the plasma. By far the commonest cause is severe hyperglycaemia induced by the extracellular shift of water due to the restriction of glucose to the extracellular space, resulting in an equilibrium state of mild hyperosmolality in both intracellular and extracellular spaces[150]. Noteworthy, hyperglycaemia rapidly decreases serum sodium concentration due to immediate extracellular flux of water. The most commonly used correction factor, proposed by Katz et al, used to be a 1.6 mmol/l decrease in serum sodium concentration for every 5.5 mmol/l increase in glucose concentration[151]. However, Hillier et al demonstrated in 1999 that, especially in markedly hyperglycaemic patients with serum glucose > 22 mmol/l, the magnitude of osmotic shift is more accurately predicted, by a

correction factor of a decrease of 2.4 mmol/l in sodium concentration per 5.5 mmol/l increase in glucose concentration[150]. Besides severe hyperglycaemia, non-hypotonic hyponatraemia can also happen with significant amounts of other osmotically active substances such as mannitol, glycine or hyperosmolar contrast media[152].

The focus of this section will be hypotonic hyponatraemia which usually indicates excess water relative to solute in the extracellular fluid (ECF). Based on ECF volume status, hypotonic hyponatraemia is classified into: hypovolaemic, euvolaemic and hypervolaemic hyponatraemia.

1.5.2 Hypovolaemic hyponatraemia

Hypovolaemic hyponatraemia is characterised by extracellular volume depletion with sodium loss. As a result, there is appropriate baroreceptor-mediated AVP release in response to volume depletion[153]. Hypovolaemic hyponatraemia is caused by non-renal or renal sodium losses.

Non-renal sodium losses, characterised by low urine Na < 20 mmol/l, include gastrointestinal (for example severe diarrhoea or vomiting), transdermal (for example heavy sweating due to vigorous endurance exercise), and losses in third space (for example bowel obstruction or pancreatitis).

Renal sodium losses, characterised by urine Na > 20 mmol/l, occur due to diuretics, mineralocorticoid deficiency, cerebral salt wasting and salt-wasting nephropathy[154]. Most cases of diuretic-induced hyponatraemia are associated with thiazides alone or in combination with potassium-sparing diuretics such as amiloride, while only a small minority is related to loop diuretics. Mineralocorticoid deficiency most often occurs as part of primary adrenal insufficiency with renal salt wasting leading to hypovolaemia, followed by non-osmotic stimulation of AVP release. Cerebral salt wasting (CSW), a syndrome of marked natriuresis in the context of intracranial disease, is much less common than thought in the past[155]. Hannon et al did not report a single case of CSW in a cohort study of 100 patients with acute non-traumatic aneurysmal subarachnoid haemorrhage[156], while the same group recorded an incidence of 6.5% for CSW in a retrospective series of 187 consecutive neurosurgical patients[157]. Finally, examples of salt-wasting nephropathy are cisplatin-induced tubulopathy and analgesic nephropathy[154].

1.5.3 Euvolaemic hyponatraemia

Euvolaemic hyponatraemia usually occurs as a result of excess of body water. The four major disorders associated with euvolaemic hyponatraemia are: syndrome of inappropriate antidiuretic hormone (SIADH), including nephrogenic syndrome of inappropriate antidiuresis (NSIAD); low solute intake; glucocorticoid deficiency; hypothyroidism. The latter 2 will be covered separately in the section of endocrine causes of euvolaemic hyponatraemia.

SIADH, by far the commonest cause of euvolaemic hyponatraemia, is the syndrome when AVP is not appropriately suppressed despite serum sodium levels falling below the osmotic threshold for physiological AVP secretion[158]. SIADH is characterised by slight extracellular volume expansion that is not clinically detectable. In addition to abnormalities in AVP secretion, studies of osmotically stimulated thirst have shown a downward resetting of the osmotic threshold for thirst in SIADH patients (mean 264 mOsm/kg) vs healthy controls (mean 286 mOsm/kg)[159]. Also, while drinking causes suppression of thirst in SIADH similar to that in healthy controls, drinking leads to a much slower fall in plasma AVP concentrations in SIADH than in healthy subjects[159]. SIADH was initially described in 1957 by Schwartz and Bartter in 2 patients with lung cancer[160]. Interestingly, the diagnostic criteria for SIADH remain largely the same as originally proposed by Bartter & Schwartz in 1967[161]. SIADH remains a diagnosis of exclusion, and the absence of other causes of euvolaemic hyponatraemia needs to be verified. The essential and supporting criteria for the diagnosis of hyponatraemia secondary to SIADH are listed in Table 1.

Table 1. Essential and supplemental criteria for the diagnosis of hyponatraemia due to SIADH. Adapted from Ellison DH et al[162] and Thompson C et al[163].

Essential criteria
Serum Na < 135 mmol/l
Effective serum osmolality < 275 mOsm/kg of water
Urine osmolality > 100 mOsm/kg of water at some level of plasma hypo-osmolality
Urinary sodium concentration > 30 mmol/l with normal dietary salt and water intake
Clinical euvolaemia
Absence of hypothyroidism and hypocortisolism
No use of diuretic agents within last week
Supplemental criteria
Serum uric acid < 0.24 mmol/l
Serum urea < 3.57 mmol/l
Fractional sodium excretion* > 1%
Fractional urea excretion¥ > 55%
No significant improvement of hyponatraemia after 0.9% saline infusion
Improvement of hyponatraemia through fluid restriction

* Fractional sodium excretion = (urinary sodium excretion/serum sodium) / (urinary creatinine/serum creatinine) × 100

¥ Fractional urea excretion = (urinary urea/serum urea) / (urinary creatinine/serum creatinine) × 100

The commonest causes of SIADH include malignancies, drugs, pulmonary disorders, and central nervous system (CNS) disorders, as listed in Table 2. However, the relative frequencies of each vary according to the population of different published series. The multicentre Hyponatraemia Registry in a large European and US cohort found that, following SIADH of unknown aetiology being recorded in as many as 36% of cases, the commonest known causes were malignancy (24%), drugs (18%), pulmonary disease (11%), and CNS disease (9%)[164]. A recent single-centre retrospective study which described the distribution of SIADH aetiologies amongst 555 hospitalised patients showed that malignancies and medication-induced SIADH were the most common aetiologies, followed by idiopathic SIADH, pulmonary infections, pain and nausea, and CNS disorders[165]. A single-centre study form a general hospital in Taiwan reported idiopathic SIADH as the most common diagnosis (39.8%), followed by pulmonary disorders (34.2%), medications (10%), CNS aetiologies (8.4%), and malignancies (7.3%)[166]. In contrast to the results of these studies, a prospective single-centre observational study of 353 patients in a hospital, which was also the site of the Irish National Neurosurgical service, reported CNS disease as the commonest cause of SIADH, followed by pulmonary diseases and malignancies[167].

Table 2. Causes of SIADH. Adapted from Hannon et al[158], Janicic et al[168], and Liamis et al[169].

Malignancy	Lung cancer (especially small cell)
	Mesothelioma
	GI tract malignancy (stomach, duodenum)
	Pancreatic malignancy
	GU tract malignancy (ureter, bladder, prostate)
	Lymphoma
	Sarcoma
	Nasopharyngeal cancer, olfactory neurobastoma
Drugs	Selective serotonin reuptake inhibitors
	Tricyclic antidepressants
	Monoamine oxidase inhibitors
	Venlafaxine
	Phenothiazines
	Butyrophenones (haloperidol)
	Antiepileptic drugs (carbamazepine, oxcarbazepine, sodium valproate)
	Vinca alkaloids (vincristine, vinblastine)
	Alkylating agents (cyclophosphamide, melphalan)
	Oxytocin

	DDAVP
	3,4-Methylenedioxymethamphetamine (MDMA)
	Opioids
	Proton pump inhibitors
	ACE-inhibitors
Pulmonary	Pneumonia, especially *Legionella* and *Mycoplasma*
	Tuberculosis
	Abscess
	Aspergillosis
	Empyema
	Acute respiratory failure
	COPD
	Positive pressure ventilation
CNS disorders	CNS tumour
	Meningitis
	Encephalitis
	Abscess
	Hypophysectomy
	Cerebrovascular event
	Subarachnoid haemorrhage
	Subdural haemorrhage

	Traumatic brain injury
	Guillain Barre syndrome
Miscellaneous	Pain
	Nausea
	Prolonged strenuous exercise (marathon, ultra-marathon, triathlon)
	HIV
	Idiopathic

SIADH has been traditionally classified into four distinct types according to the pattern of AVP secretion, as firstly suggested by Zerbe et al in 1980[170] and illustrated in Figure 13.

1. Type A is regarded as the commonest, found in 30-60% of patients with SIADH, and is characterised by erratic, excessive secretion of AVP and loss of the close linear relationship between plasma osmolality and AVP secretion. The secretion of AVP in this subtype appears to be completely uncoupled from osmoreceptor control[171]. In type A SIADH, the large fluctuations in AVP levels tend to occur in a range consistently above that required to produce maximum antidiuresis. For this reason, they do not usually lead to significant changes in urine osmolality because urine osmolality tends to be fixed at the highest possible level[172]. Grossly elevated AVP concentrations independent of serum osmolality suggest an ectopic tumour-associated AVP secretion[173], with type A having been typically reported in small cell

lung cancer and nasopharyngeal tumours. The combination of markedly elevated AVP and non-suppressed thirst often lead to development of severe hyponatraemia.

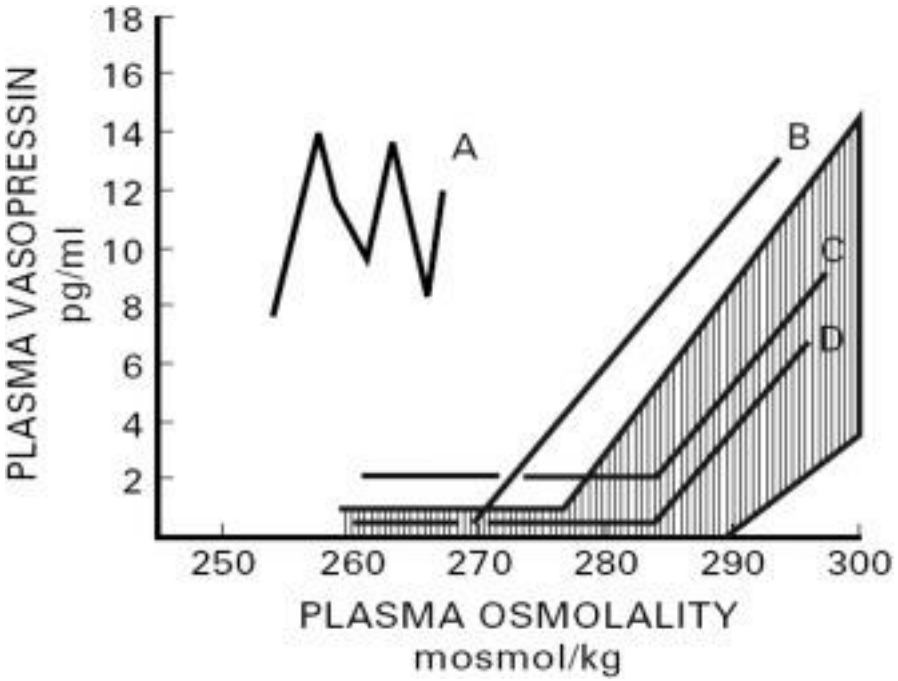
2. Type B, well known as ‘’reset osmostat’’, where the linear relationship between plasma osmolality and AVP secretion is preserved, but the osmotic threshold for AVP release is reset to a lower level than normal. Because patients are able to fully suppress AVP below their reset threshold, subsequent development of hypotonic diuresis protects them against the progression to severe hyponatraemia[174]. Plasma sodium remains relatively stable, typically between 125 and 135 mmol/l[174]. Type B osmoregulatory defect is considered common with reported prevalence of 20-40%[172] [158] [170], including some patients with malignant SIADH.

3. Type C is a rare condition[158] [174], characterised by a slow, constant ‘’leak’’ of AVP at levels below normal osmotic threshold. The failure to suppress AVP secretion at plasma osmolalities below the osmotic threshold should be probably attributed to dysfunction of inhibitory neurons in the hypothalamus[174]. However, at plasma osmolalities above the osmotic threshold, the linear relationship between plasma osmolality and AVP secretion is preserved. The levels of urine osmolality tend to be fixed at a lower level than in type A.

4. Type D is a rare clinical phenomenon characterised by undetectable AVP levels and cannot be attributed to a demonstrable defect in the osmoregulation of AVP[172] [158]. Despite the consistent lack of detectable AVP in plasma under hyponatraemic conditions, patients with type D defect cannot dilute their urine or even produce a water diuresis as a response to an oral water load[174]. The aetiology is not completely clear, but potential mechanisms include secretion of an unidentified antidiuretic compound other than AVP, a gain-of-function mutation in which V2 receptor is constituently activated, and a postreceptor defect in trafficking of AQP2 water

channels[172 174]. The first two cases of gain-of-function mutations of the AVP V2 receptor leading to a chronic SIADH-like clinical picture with undetectable AVP levels were reported by Feldman et al in 2005[175]. These novel activating mutations cause constitutive activation of V2 receptor and antidiuresis in the absence of AVP – V2R ligand binding[175]. This relatively new entity has been termed “nephrogenic syndrome of inappropriate antidiuresis” (NSIAD)[175] and several cases have been described during the last decade[176 177]. Therefore, NSIAD should be considered in young patients with unexplained hyponatraemia. A water load test with AVP measurement is a potentially informative investigation, while AVPR2 sequencing provides a definitive molecular genetic diagnosis[177].

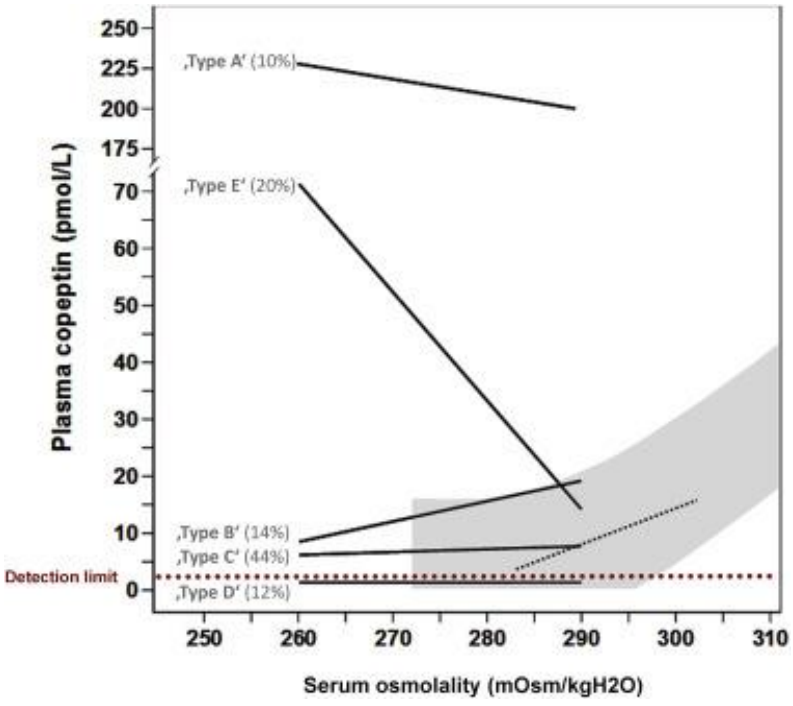
Figure 13. Summary of different patterns of AVP secretion observed in patients with SIADH (A-D). Each line represents the relation between plasma AVP and plasma osmolality of individual subjects in whom osmolality was increased via hypertonic saline infusions. The shaded area represents AVP levels in normal subjects over physiological ranges of plasma osmolality. The lines A-D refer to the different types of vasopressin secretion. Adapted from Smith et al[153].



A recent study by Fenske et al used the hypertonic saline infusion test in 50 patients with the syndrome of inappropriate antidiuresis (SIAD), including predominantly patients with malignancy-associated SIAD, to examine different osmoregulatory defects based on serial measurements of copeptin, a stable and easily measurable glycopeptide which is derived from the same precursor peptide as AVP and is released in equimolar amounts together with AVP[173]. This study revealed major deviations from previous studies as to both subtype prevalence and phenotype. This series showed a prevalence of 10%, much lower than previously recorded, for type A SIAD. Also it found that AVP fluctuations were more moderate than substantial, indicating a predominantly continuous release of AVP[173]. Moreover, this study reported 14% prevalence for type B and 44% for type C SIAD which contradict the high frequency for type B and rarity of type C recorded in past studies. This series found also 12% prevalence for type D SIAD, characterised by suppressed copeptin concentrations independent of osmolality. Surprisingly, none of these patients was found to have mutations in the AVP V2 receptor gene[173]. Thus, it seemed that type D in these cases should be attributed to other phenomena, such as secretion of AVP with some bioactivity but altered immunoreactivity, the presence of other circulating antidiuretic factors, increased renal sensitivity to undetectably low circulating levels of AVP or possibly to a downstream receptor defect[171]. Additionally, Fenske et al observed a novel SIAD subtype, termed type E or ‘’barostat reset’’ and found in 20% of patients, which was characterised by a linear decrease in copeptin response to increasing serum osmolality (a negative copeptin slope below −0.25 pmol/l per mOsm/kg). The pathophysiology of this reverse pattern of physiological copeptin response is not fully understood. This ‘’barostat reset’’ defect may be explained by a model of combined osmotic and non-osmotic dysregulation of AVP release.

According to this model, on the one hand, the altered baroreceptor signalling mimics volume depletion despite normovolaemia, shifting the copeptin response to the right, while volume expansion through hypertonic saline infusion may compensate for the reduced baroreceptor sensitivity resulting in suppression of nonosmotic AVP release. On the other hand, there is an attenuated gain of the osmoregulatory AVP reponse leading to overriding importance of the nonosmotic AVP regulation[171]. In conclusion, Fenske et al proposed a different classification of SIAD patients into five different groups of disturbed osmoregulation (types A-E), as illustrated in Figure 14.

Figure 14. Schematic illustration of the copeptin-based quantitative classification of five distinct subtypes of osmoregulatory defect (types A to E) in SIAD subjects. Adapted by Fenske et al[171].



Low solute intake can be the aetiology in some cases of euvolaemic hyponatraemia. Classic examples are beer potomania (ingestion of large volumes of beer with little food intake for prolonged periods) and ‘’tea and toast’’ diets. The amount of water that the kidneys can remove on a daily basis depends on solute excretion and solute intake. Depending on the kidney's ability to dilute urine, at least 50-100 mmol of solutes are required to remove 1 litre of fluid. Then very low urine solute excretion limits solute-free water excretion; as a result, hyponatraemia will occur when fluid intake exceeds the maximum volume of urine than can be excreted based on the available urine solute[152]. For example, if daily protein and solute intake is very poor daily leading to solute excretion below 250 mOsmol/kg and maximal urine diluting ability is 70 mOsm/kg, the maximum urine output will fall below 4 liters day. In this case, hyponatraemia develops if oral fluid intake exceeds 4 liters per day.

1.5.4 Secondary adrenal insufficiency as cause of hyponatraemia

Secondary adrenal insufficiency, characterised by impairment in ACTH secretion leading to glucocorticoid deficiency, may be a frequently overlooked cause of hyponatraemia[178]. Up to the time of undertaking our study measuring the prevalence of endocrine causes in hyponatraemic inpatients, the frequency of adrenal insufficiency amongst hospitalised hyponatraemic patients was largely unknown. Small sample size was the main limitation of all studies which had evaluated the adrenal reserve in patients with hyponatraemia. For example, a case-control study reporting a 3% rate of adrenal insufficiency as a cause of hyponatraemia in a hospitalised geriatric population included only 30 hyponatraemic individuals aged ≥ 65 years and 30 age-matched controls[179]. Interestingly, the same study found that the mean cortisol levels were significantly higher in the hyponatraemic compared with control subjects, both in the basal state (585 vs 381 nmol/l) and after stimulation with 1 mcg tetracosactide (933 vs 781 nmol/l). The association of hyponatraemia with hypercortisolaemia may be explained by increased AVP levels stimulating ACTH release or, alternatively, by a direct non-ACTH-mediated stimulatory effect of hyponatraemia on the adrenal cortex[179]. Contrary to the lack of data on the rate of glucocorticoid deficiency in unselected hyponatraemic patients, several recent studies have examined the role of hypocortisolism in neurosurgical patients with hyponatraemia. A recent prospective study of patients with acute non-traumatic aneurysmal subarachnoid haemorrhage (SAH) found that, amongst 100 SAH patients, 49% developed hyponatraemia and 14% acute ACTH deficiency. Acute glucocorticoid insufficiency, defined in this context as 09:00 am plasma cortisol concentration < 300 nmol/l, was the cause of hyponatraemia in 8.2% of cases[156]. The same group studied prospectively the pituitary function, including daily plasma

cortisol measurements, in a large cohort of 100 patients with traumatic brain injury (TBI) and reported a very high incidence (78%) of hypocortisolaemia. Hannon et al used a 9 am plasma cortisol concentration < 300 nmol/l as a cut-off to indicate inappropriately low cortisol secretion for this degree of physiological stress. The appropriateness of this threshold was confirmed by the fact that all participants in a comparison group of previously healthy patients after major vascular surgery had plasma cortisol > 300 nmol/l at all times during their intensive care stay[180]. Another novel finding of this study was that 13 out of 15 patients who became hyponatraemic following TBI had evidence of cortisol deficiency[180]. These data suggest that many cases of hyponatraemia following TBI, attributed in the past to SIADH, may be due to acute adrenal insufficiency[174].

In the context of neurosurgical patients or any other acutely ill individuals, corticotropin stimulation test is a reliable test for primary or chronic secondary adrenal insufficiency, but not for acute ACTH deficiency, while the insulin tolerance test cannot be employed safely. For these reasons, the approach of measurement of 09:00 am cortisol levels and empirically replacing patients with glucocorticoids below critical levels of cortisol < 300 nmol/l is a sound approach until further evaluation with dynamic testing at a later date[155 156]. In patients with intermediate early morning cortisol levels of 300-439 nmol/l, a decision should be made on a case-by-case basis, based on the presence of symptoms or signs suspicious for acute glucocorticoid deficiency, such as hypoglycaemia, hypotension or slow clinical progression, and a trial of glucocorticoid therapy should be considered[181]. Early morning serum cortisol ≥ 440 nmol/l can exclude adrenal insufficiency, as demonstrated in a study of patients with hyponatraemia due to ACTH deficiency, confirmed in a stimulation test, whose highest baseline cortisol concentration was

439 nmol/l[182]. Finally, it is worth mentioning that a new immunoassay Roche GenII method, aligned with ID-GCMS (isotope dilution-gas chromatography mass spectrometry) as a reference method for cortisol measurement, has been introduced in most London hospitals since 2016. With the new assay, the values of serum cortisol tend to be lower in the range above 300 nmol/l with a value of 380 nmol/l being equivalent to 450 nmol/l using the old assays. Therefore, the local cut-offs need to be adapted, depending on the assay used in each laboratory.

A study of 28 hospitalised patients with severe hyponatraemia due to secondary adrenal insufficiency showed that hypopituitarism was undiagnosed in almost all those subjects prior to presentation with symptomatic hyponatraemia[182]. Noteworthy, half of those subjects had recurrent admissions with hyponatraemia, suggesting that hypopituitarism as a cause of hyponatraemia is frequently overlooked[182]. Recent data from a large, prospective multicentre cohort from both Europe and the USA, showed that the proportion of patients who had cortisol dynamics measured was low with 33% having measurement of morning cortisol levels and only 9% undergoing a dynamic test[164]. In light of this evidence, the true contribution of cortisol deficiency to euvolaemic hyponatraemia remains unknown. In view of most symptoms and signs of secondary adrenal insufficiency being non-specific and insidious in onset, especially in older individuals, formal biochemical exclusion of ACTH deficiency is mandatory in the evaluation of euvolaemic hyponatraemia[174].

Hyponatraemia in secondary adrenal insufficiency is attributed mainly to inappropriate AVP release despite plasma hypoosmolality[183]. Cortisol is a physiological tonic inhibitor of AVP secretion with studies showing that AVP expression in hypothalamic neurons is strongly suppressed by glucocorticoids[184 185]. Studies in animal model of glucocorticoid-deficient rats showed that the impaired

water excretion is closely linked to the non-suppressible levels of plasma AVP and the upregulation of AQP-2 messenger RNA, with hydrocortisone replacement normalising AVP secretion, urinary excretion of AQP-2, and water diuresis[186] [184]. Also, patients with secondary adrenal insufficiency may have alterations in cardiac output and mean arterial pressure which cause non-osmotic AVP release[178]. Another key factor is that glucocorticoid deficiency seems to alter renal sensitivity to AVP[178] [155]. As a result, for a given level of AVP, free water excretion by the kidney is further reduced in the state of hypocortisolism due to upregulation of AQP2 water channels[183]. Animal studies of adrenalectomised rats comparing those who were administered aldosterone alone (glucocorticoid-deficient rats) vs those administered both aldosterone and dexamethasone showed that plasma AVP levels were not sufficiently suppressed by an acute oral water load in the glucocorticoid-deficient rats. The expressions of AQP2 mRNA and protein in kidney of the glucocorticoid-deficient rats were increased by 1.6- and 1.4-fold compared with the control rats, respectively, while the AVP V_2-receptor antagonist totally abolished the increases in their expression. These findings strongly indicated that the augmentation in AQP2 mRNA expression is dependent on plasma AVP and that the upregulation of AQP2 plays a crucial role in impaired water excretion, dependent on AVP, in glucocorticoid deficiency[187].

1.5.5 Hypothyroidism as cause of hyponatraemia

Traditionally textbooks, clinical guidelines and review articles state hypothyroidism as one of the causes of euvolaemic hyponatraemia and recommend exclusion of hypothyroidism as one of the prerequisites for the diagnosis of SIADH[188]. On the one hand, multiple studies have demonstrated an association between hypothyroidism and hyponatraemia. Warner et al, examining a cohort of 999 newly diagnosed hypothyroid patients, reported a statistically significant association between serum sodium concentration and thyroid status with sodium concentration decreased by 0.14 mmol/l for every 10 mU/l rise in thyroid stimulating hormone (TSH)[189]. Amongst 999 hypothyroid subjects, there was not even a single case of a patient with serum Na < 120 mmol/l. Taking into account that a severely hypothyroid individual with serum TSH of 100 mU/l might be expected to have serum Na lowered only by 1.4 mmol/l compared to a euthyroid individual, this association is unlikely to be of clinical significance[189]. Schwarz et al, studying the relationship between thyroid hormones levels and serum sodium in 9,012 patients, demonstrated that serum sodium was significantly lower in patients with high than normal TSH (serum Na 138 vs 139 mmol/l), but the effect of thyroid status on serum sodium was minute[190]. A study of 212 consecutive patients with thyroid cancer who were admitted for radioiodine therapy prospectively evaluated serum sodium before and after withdrawal of thyroid hormone replacement[191]. A statistically significant, but small, difference was observed in mean Na concentration pre- (139.5 mmol/l) and post- (137.8 mmol/l) induction of severe hypothyroidism (defined as the combination of TSH > 30 mU/l and fT4 < 6 pmol/l). Also the incidence of mild hyponatraemia (Na 130-134 mmol/l) was 1.4% pre- compared to 8.5% post- development of hypothyroidism, while 1.9% of participants had moderate hyponatraemia (Na 120-129 mmol/l) post- vs none

before discontinuing thyroid hormone replacement[191]. Interestingly, hyponatraemia was relatively uncommon despite the severity of hypothyroidism with more than three quarters of hyponatraemic patients having serum TSH > 100 mU/l, the concomitant exposure to stress and nausea in relation with radioiodine treatment, and also the fact that patients followed low-salt diet with high fluid intake of about 10 litres over 3 days. Additionally, increased age and female gender were associated with lower serum sodium concentration in the setting of acute hypothyroidism[191]. A similar study assessed sodium levels in 101 differentiated thyroid cancer patients prior to total thyroidectomy and on the day of radioactive iodine therapy following thyroid hormone withdrawal. In this context of iatrogenic acute hypothyroidism, mean serum Na concentration fell from 140.7 mmol/l to 138.7 mmol/l with the observed frequency of hypothyroidism-associated hyponatraemia being 4%[192]. On the other hand, some authors have questioned the correlation between hypothyroidism and hyponatraemia. In 1997, Croal et al firstly questioned whether hypothyroidism is in fact causally linked to hyponatraemia since they did not find a difference in the prevalence of hyponatraemia between euthyroid and hypothyroid subjects in an unselected sample of 33,192 patients[193]. Another retrospective analysis comparing 132 patients with overt hypothyroidism (defined as TSH > 10 mU/l and fT4 < 2 pmol/l) with 1253 euthyroid controls revealed that the prevalence of hyponatraemia in the overt hypothyroidism group was not statistically significantly different from that in the euthyroid group[194]. Finally, Wolf et al published in May 2017 a retrospective analysis of 8053 hypothyroid patients with serum TSH > 4 mU/l and found that only 448 (5.6%) of those patients were hyponatraemic[195]. In all but 6/448 (98.9%) hypothyroid patients with decreased serum Na, a possible alternative cause for hyponatraemia was found with no case with serum Na < 130 mmol/l being assigned

to thyroid status. Additionally, among 138 patients with TSH > 100 mU/l, only 2 had hyponatraemia, both mild with Na 134 mmol/l and 132 mmol/l, and a potential alternative diagnosis for hyponatraemia could be identified for both of them. Wolf et al concluded that almost all hypothyroid patients have other explanations for their hyponatraemia than hypothyroidism with impaired thyroid function per se resulting rarely in, very mild, hyponatraemia[195]. Therefore, co-occurrence of hyponatraemia and hypothyroidism is relatively common, but it may suggest coincidence rather than causality[195]. Reviewing the literature, hypothyroidism-associated hyponatraemia is very rare and limited only to patients with profound hypothyroidism, especially in those who are elderly and have other comorbidities. Therefore, if a hypothyroid subject becomes hyponatraemic, their common occurrence does not necessarily equal causality, as the causal relationship probably applies only to elderly patients who meet the criteria for myxoedema coma[152] or at least very high TSH levels > 50 mU/l[196].

The proposed mechanism by which profound hypothyroidism leads to hyponatraemia involves an inability to maximally suppress AVP[197 188]. The key factor is the non-osmotic release of AVP, as evidenced by inappropriately high circulating levels of AVP in hypothyroid patients, not being suppressed after administration of an oral water load. Decreased heart rate and myocardial contractility contribute to reduced cardiac output which leads to non-osmotic release of AVP via carotid sinus baroreceptors[198]. In addition to reduced cardiac output, another contributing factor to increased AVP levels in patients with myxoedema may be the accumulation of interstitial mucopolysaccharides that results in fluid retention and decreased effective arterial blood volume leading to AVP-mediated water retention[188]. Chen et al, examining the molecular mechanisms contributing to impaired urinary dilution in

hypothyroid rats, showed that impaired urinary dilution in hypothyroidism is primarily compatible with the non-osmotic release of vasopressin and increased protein expression of renal AQP-2[199]. This conclusion was further supported by the reversal of the impaired urinary diluting ability, as assessed by minimal urinary osmolality, by administration of an AVP V2 receptor antagonist. However, the reversal was partial with maximal water excretion being still significantly less compared to euthyroid controls[199]. This finding suggests that reduced cardiac output is not the sole possible mechanism of hyponatraemia in hypothyroid state with diminished distal fluid delivery being the second key mechanism behind the association between hypothyroidism and hyponatraemia. Haemodynamic alterations (reduced cardiac output and increased peripheral vascular resistance) lead to reduction in plasma renal flow and in glomerular filtration rate (reduced GFR), which result in increased sodium reabsorption and diminished delivery of water to the distal diluting segment of the kidney and subsequently reduced capacity for water excretion[188]. It has been widely proposed that the greater the impairment in renal function, the more likely is the development of hyponatraemia[168]. However, studies of Chen et al in a model of advanced hypothyroidism found that renal function was not significantly impaired since creatinine clearance was similar in hypothyroid and euthyroid animals. The key difference was the association of hypothyroidism with a marked upregulation of renal cortex AQP-1, known for its role in proximal tubular reabsorption of water[199]. As a result, the upregulation in AQP1 expression led to increased proximal fluid reabsorption and diminished fluid delivery to the distal nephron diluting segments, limiting the amount of solute-free water available for excretion. Thus, diminished cardiac output resulting in arterial underfilling may stimulate enhanced renal cortex AQP-1 protein abundance[199].

1.5.6 Hypervolaemic hyponatraemia

Hypervolaemic hyponatraemia is characterised by expansion of extracellular volume with water retention exceeding sodium retention. The commonest disorders in association with hypervolaemic hyponatraemia are: heart failure, cirrhosis, nephrotic syndrome, and acute kidney injury/chronic kidney disease.

The main mechanism underlying the first three disorders (heart failure, cirrhosis, nephrotic syndrome) is non-osmotic release of AVP. Arterial baroreceptors sense arterial underfilling (either due to reduced cardiac output or due to arterial vasodilation) and activate the neurohumoral axis as a compensatory response to maintain arterial perfusion. The neurohumoral response has three components: baroreceptor-mediated AVP release to retain water, activation of the renin-angiotensin-aldosterone system to retain sodium and stimulation of the sympathetic nervous system to increase systemic and arterial vascular resistance.

In the context of acute kidney injury or chronic kidney disease, hyponatraemia occurs as a result of diminished glomerular filtration rate. Urine output is relatively fixed and determined by the number of osmoles excreted in the urine; as a result, hyponatraemia develops when water intake exceeds urinary free water excretion[152–154].

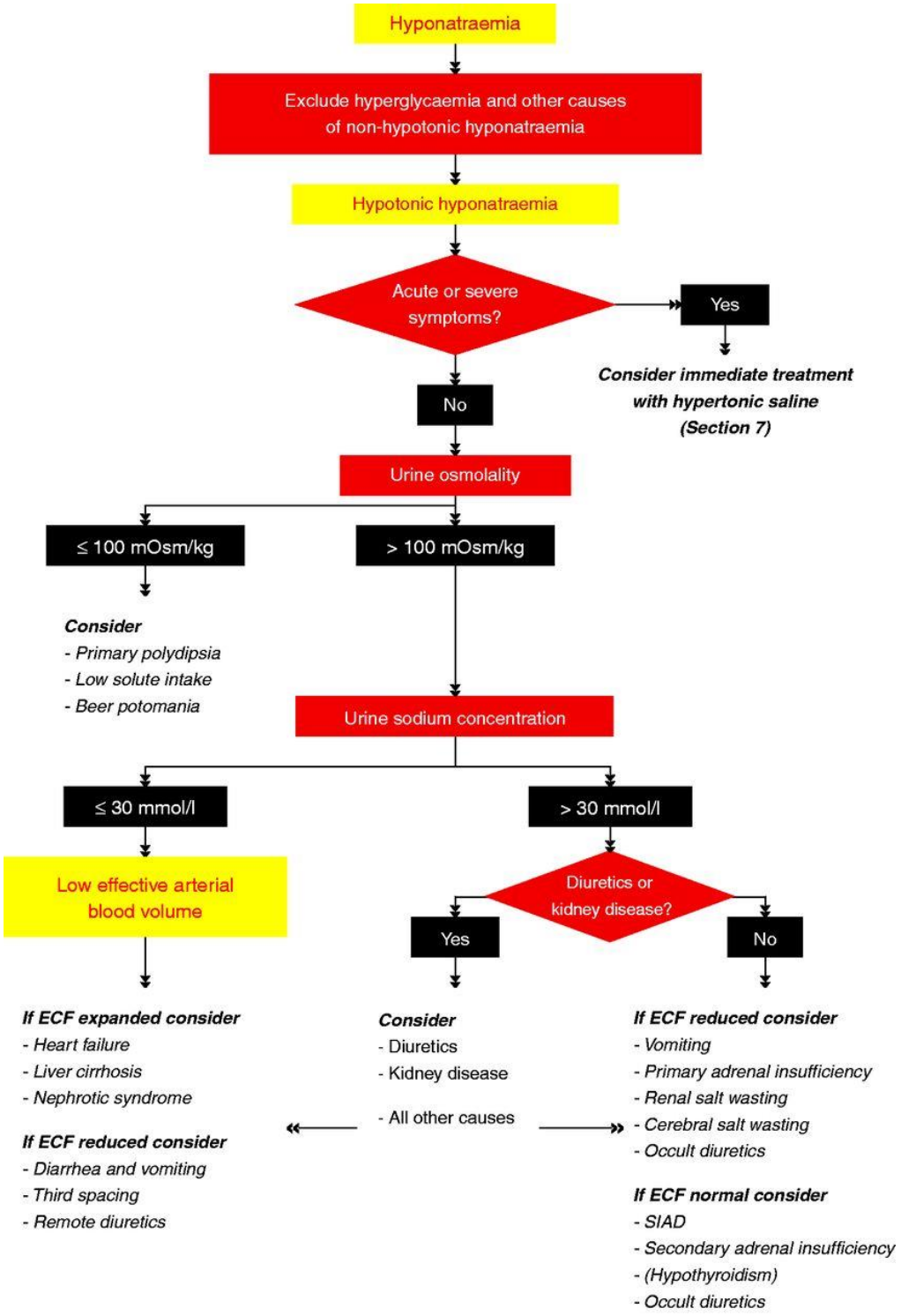
1.6 Investigation of hyponatraemia

1.6.1 Algorithms for assessment of hyponatraemia

Most reviews, guidelines and textbooks recommend that the first essential step in the approach to hyponatraemic patient is to classify the patient according to blood volume status into one of three categories (hypovolaemic / euvolaemic / hypervolaemic). Appropriate assessment of volume status is a key factor in the diagnosis of the underlying aetiology of hyponatraemia. Hypervolaemic status is usually easily recognised. However, the discrimination between hypovolaemia and euvolaemia, based on clinical parameters, can be very challenging in clinical practice. It is well known that the accuracy of clinical evaluation, even by experienced physicians, for predicting the state of extracellular fluid volume is low, with its sensitivity to diagnose hypovolaemic hyponatraemia on clinical grounds being reported as low as 41%[200] and 47%[201]. For example, a prospective evaluation of 35 non-oedematous hyponatraemic subjects found that clinical assessment of extracellular fluid (ECF) volume; by means of mucous membranes (dry or moist), skin turgor (decreased or not), jugular venous pressure (reduced or normal), orthostatic change in systolic blood pressure (a decrease of > 10% in supine compared to 2-minute upright systolic blood pressure), and orthostatic change in heart rate (an increase of > 10% in supine compared to 2-minute upright heart rate); had a sensitivity of 41.1%, specificity of 80%, positive predictive value of 70% and negative predictive value of 54.5% in diagnosing hypovolaemia compared to response to the ‘’gold standard’’ saline infusion test[200]. Saline responders were individuals who increased their plasma sodium by at least 5 mmol/l or increased their fractional excretion of sodium by < 0.5% following infusion of 2 liters 0.9% sodium chloride over 24 hours. This study suggested that clinical evaluation misjudged the

majority of responders to isotonic saline to be in a normovolaemic state[200]. Therefore, traditional algorithms, based on the belief that clinicians can detect mild to modest degree of ECF volume contraction by physical examination, often lead to misclassification of hyponatraemia[202]. Interestingly, Fenske et al demonstrated that the diagnostic accuracy of physicians in training, using an algorithm in which urine osmolality and sodium values were prioritised over clinical assessment of volume status, was clearly superior to that of senior physicians, not using the algorithm[203]. The agreement with reference standard (defined as judgement of senior Endocrinologist well versed in the field of hyponatraemia after complete diagnostic work-up) in diagnosing the cause of hyponatraemia was 71% for algorithm users compaed to only 32% for senior physicians[203]. This study also demonstrated that the use of clinical assessment of ECF volume as a decisive discriminating factor frequently resulted in misdiagnosis[203]. For this reason, ECF volume should be routinely assessed in hyponatraemic patients, but its low diagnostic accuracy should be taken into consideration[203 163]. In light of these findings, recently published European guidelines have put more weight on measurement of urine osmolality and, especially, urine Na, while the current position of clinical assessement of volume status is far down the algorithm, as a diagnostic aid rather than as the main discriminating factor[154], as shown in Figure 15.

Figure 15. Algorithm for the diagnosis of hyponatraemia. Adapted from Spasovski et al[154].



Spot urine Na < 20-30 mmol/l is strongly indicative of hypovolaemic hyponatraemia, unless there is renal solute loss[163] [152]. However, there are two important caveats in interpreting spot urine Na; firstly, diuretics can increase urine Na, and, second, reduced salt intake due to a low-salt diet or anorexia may lower urine Na in SIADH patients[200] [152]. Fenske et al studied 86 consecutive hyponatraemic patients in order to evaluate the diagnostic utility of various biochemical tests to differentiate SIADH from hyponatraemia with decreased ECF volume[204]. Urine sodium concentration > 30 mmol/l was shown to have sensitivity of 1.0 and specificity of 0.69 in diagnosing SIADH in patients not treated with diuretics[204]. However, diuretic use resulted in a pronounced loss of its diagnostic accuracy with urine Na > 30 mmol/l having sensitivity of 0.94 and specificity of only 0.24[204]. In addition, some volume depleted patients, especially elderly, have urine Na concentration > 30 mmol/l, and sometimes as high as 60 mmol/l, probably due to slower adaptive mechanisms to conserve renal sodium in response to hypovolaemia[200] [205].

For all these reasons, some authors have suggested the use of fractional excretion of different solutes which are estimated, taking into account plasma and spot urine values, calculated by the following formulae:

Fractional excretion of sodium (FENa)

FENa = (Urine Na × Plasma Creatinine / Urine Creatinine × Plasma Na) × 100 %

Fractional excretion of urea (FEUrea)

FEUrea = (Urine Urea × Plasma Creatinine / Urine Creatinine × Plasma Urea) × 100 %

Fractional excretion of urate (FEUrate)

FEUrate = (Urine Urate × Plasma Creatinine / Urine Creatinine × Plasma Urate) × 100 %

To overcome the effect of low salt intake on the diagnostic accuracy of urine sodium, Musch et al found that the combination of low fractional sodium excretion < 0.5% and fractional urea excretion < 55% is the best biochemical way to predict response to infusion of isotonic saline, indicative of volume depletion[200]. While most non-responders to saline have fractional excretion of sodium > 1%, there are some subjects with SIADH who have low fractional excretion of sodium, even < 0.5%, reflecting low salt intake. These individuals with SIADH and low salt intake are recognised by the combination of low fractional excretion of sodium and high fractional excretion of urea > 55%[200]. Noteworthy, the same group examined the effect of low diuresis (arbitrarily defined as high U/P creatinine value > 140) on the diagnostic utility of FENa and FEUrea[205]. While urine sodium concentration tends to increase with increasing U/P creatinine values because of the effect of urine concentration, a further increase in U/P creatinine values to levels above 140 does not lead to higher urine Na values. In fact, the influence of low diuresis on natriuresis acts as an opposite force to the urinary concentration effect on urine Na, resulting in lower urine Na. In SIADH, the mean urine Na and FENa fell from 96 mmol/l to 71 mmol/l and from 0.9% to 0.3% for U/P creatinine > 140 compared to < 140 respectively[205]. Thus, for patients with U/P creatinine > 140, FENa can still discriminate SIADH from volume depletion with (mean ± SD) FENa 0.3 ± 0.2% for SIADH compared to 0.1 ± 0.04% for hypovolaemia[205]. For the low diuresis patients, the thresholds should be adapted to 0.15% for FENa and 45% for FEUrea[206].

Other biochemical parameters, such as serum urea and urate concentration, can be used as supplemental criteria for SIADH diagnosis since they can aid discriminating hypovolaemia from euvolaemia. Serum urea levels and urea:creatinine ratio tend to rise in volume depletion and be low in euvolaemic state. Also urea levels are closely linked to dietary protein intake, as evidenced by Maroni's formula used to estimate protein intake can be estimated, regardless of renal function:
Protein intake [g/day] = 0.00625 x [urinary urea nitrogen level (g/dl) x 24-h urinary volume (ml/day)/100 + 31 x weight (kg)][207]

Kanno et al recently showed that urea nitrogen concentration determined from spot urine may be used for estimating daily protein intake[208]. Reduction in urea excretion in a state of low-protein intake is achieved not only by reduction in GFR and plasma urea, but also by a marked increase in net urea reabsorption along the distal parts of the nephron[209]. In addition, plasma urea tends to rise with age, as Musch et al found a more important decrease in urea clearance by 56% than urea production by 27% in older women leading to an average increase in plasma urea of 29%[209]. For this reason, SIADH patients < 40 years present with lower plasma urea (6.4 ± 2.8 mmol/l) and higher FEurea (58 ± 14%) compared with SIADH patients > 70 years (plasma urea 10.3 ± 2.8 mmol/l and FEurea 44 ± 15% respectively). These changes result in a significant overlap in values between SIADH and hypovolaemic hyponatraemia in elderly individuals[209]. In contrast to plasma urea, plasma creatinine remains stable with increasing age because of an age-related decrease of same magnitude in both creatinine production and creatinine clearance. The origin of a higher plasma urea and a lower FEurea in the elderly is not due to the age-related reduction in glomerular filtration rate. The exact mechanisms are not clear, but may involve age-

related increased urea reabsorption or decreased urea secretion along the renal tubule[209].

Serum urate levels can be of great value in differentiating between euvolaemia and volume depletion. A serum uric acid < 0.24 mmol/l has a positive predictive value of 73-100% for SIADH, while uric acid > 0.32 mmol/l is strongly suggestive of volume depletion. Fenske et al showed in a prospective study of 86 hyponatraemic patients that the sensitivity and specificity of serum urate < 0.24 mmol/l for SIADH diagnosis was 0.83 and 0.83 in patients without diuretics and 0.65 and 0.76 respectively in patients receiving diuretic therapy[204]. Urate is the end product of the catabolism of purines which perform many important functions in the cell, such as the formation of of the monomeric precursors of nucleic acids DNA and RNA. The exogenous pool of purines varies with diet and is derived mainly from animal proteins, while endogenous uric acid production is mainly from the liver and bowel with the conversion of adenosine monophosphate (AMP) and guanine monophosphate (GMP) to uric acid involving many enzymes[210]. Its excretion is primary renal with the transport mechanisms of urate being localised mainly in the proximal tubule, with the remaining 30% being excreted through the biliary and gastrointestinal tract[204 211]. Hypouricaemia in SIADH mainly results from volume expansion and associated decrease in proximal Na reabsorption which indirectly reduces urate reabsorption in the proximal tubule. As a result, there is increased Na delivery distal to the proximal tubule where further Na reabsorption takes place. In contrast to Na, clinically significant urate reabsorption does not take place distal to the proximal tubule, leading to high urate clearance[212 206]. The main limitation of serum uric acid in differentiating euvolaemia from hypovolaemia arises from other factors which can

either cause hypouricaemia (cirrhosis, patients on allopurinol) or hyperuricaemia (various malignancies due to high urate production, gout, chronic kidney disease)[211].

Diuretic-induced hyponatraemia can pose major challenges, with its misclassification being the commonest pitfall of hyponatraemia algorithms, as shown by Fenske et al[203]. In this context, urine sodium and fractional excretion of sodium have very limited diagnostic utility because most diuretics inhibit tubular sodium reabsorption, resulting in an increased renal sodium excretion. Fractional excretion of urate (FEUrate) performs best compared with all other biochemical parameters and has high diagnostic accuracy in the differential diagnosis of hyponatraemic patients on diuretics[204]. FEUrate > 12% has a sensitivity of 0.86, specificity 1.0, positive predictive value 1.0 and negative predictive value 0.95 in diagnosing SIADH in patients treated with diuretics[204].

In cases with equivocal clinical assessment or non-discriminatory laboratory results, a diagnostic trial of volume expansion with the intravenous administration of 2 litres isotonic saline over 24 hours can be a very useful diagnostic and, sometimes in case of volume depletion, therapeutic tool[152 167]. Musch et al has demonstrated that a test infusion with isotonic saline in patients with SIADH is safe and rarely causes significant serum sodium reduction, provided that urine osmolality is < 538 mOsm/kg and urine Na + K are below the Na concentration of the infused fluid (154 mmol/l)[213]. Increase in serum Na concentration by at least 5 mmol/l usually suggests hypovolaemic state, while increase by < 5 mmol/l indicates euvolaemia. However, studies have shown that this cut-off can be misleading in up to 30% of cases, either because some patients with SIADH and urine osmolality < 300 mOsm/kg respond very well to isotonic saline[213] or because some hypovolaemic patients with severe salt depletion do not respond well. In terms of using FENa criteria, an increase of

FENa by < 0.5% suggests hypovolaemia, while an increase of FENa by > 0.5% suggests euvolaemia[206]. Therefore, isotonic saline infusion test allows a reliable classification of hyponatremia, only if both these serum Na and FENa criteria are met.

Finally, a more sophisticated approach to hyponatraemia, involving copeptin measurement, has been suggested by some authors[214]. Plasma AVP measurement is not part of the routine diagnostic evaluation of hyponatraemia since its measurement is technically demanding and there is lack of reliable assays because of pre-analytical and analytical problems, such as its instability, very low plasma concentration, and its considerable association with platelets. To overcome these problems, copeptin, a highly stable 39-aminoacid glycopeptide, can be measured in the serum and is a reliable surrogate marker of AVP secretion. Copeptin, a C-terminal part of the precursor pre-provasopressin (pre-proAVP), may be a carrier protein of AVP and contribute to the correct structural formation of pre-proAVP as a prerequisite for its proteolysis[215]. Fenske et al found in a prospective study of 106 consecutive hyponatraemic patients that the copeptin:urine Na ratio was superior to the established criteria in discriminating volume-depleted from euvolaemic hyponatraemic patients. Specifically, copeptin/urine Na X 100 < 30 pmol/mmol had 85% sensitivity and 87% specificity in diagnosing SIADH and performed better than other tests with sensitivity and specificity of 82% and 53% respectively for urine Na > 30 mmol/l, 73% and 82% for serum uric acid < 0.24 mmol/l, and 71% and 60% for FENa > 0.5%[214]. However, copeptin is not routinely used in UK clinical practice with the interval period between its measurement and availability of results currently being, on average, 2 weeks.

The Co-MED Study, a prospective multicentre observational study, including the largest cohort for this kind of study so far of 298 hyponatraemic patients with Na < 125 mmol/l, compared the diagnostic utility of various laboratory parameters[216]. Urinary sodium > 30 mmol/l was shown to have a good sensitivity of 87%, but only a moderate specificity of 31% to diagnose SIADH. The sensitivity and specificity to identify patients with SIADH with a cut-off copeptin/urinary sodium ratio of 0.3 was 61% and 60%. After excluding patients taking diuretics, the specificity and sensitivity choosing the same cut-off value of 0.3 to diagnose SIADH was higher with 60% and 75% respectively[216]. FEUrate < 12% had a sensitivity of 66% and a specificity of 77% to detect patients with SIADH, while FEUrea value of > 55% showed a specificity of 96% and a sensitivity of 21% to identify patients with SIADH[216]. This landmark study concluded that FEUrea and FEUrate are superior to other parameters to discriminate between SIADH and other types of hyponatraemia, while copeptin measurement is of limited value[216].

A novel marker for discrimination between SIADH and hypovolaemic or hypervolaemic hyponatraemia has been recently reported in the form of mid-regional pro-atrial natriuretic peptide (MR-proANP)[217]. MR-proANP levels were lower in SIADH patients than those with hypovolaemic and hypervolaemic hyponatraemia with a cut-off value of 100.9 pmol/l predicting SIADH with a specificity of 91% and a sensitivity of 34%[217]. MR-proANP derives from the precursor hormone of ANP, is released in an equimolar ratio to ANP and is easily measurable. MR-proANP, is well known to correlate with excess effective circulating blood volume, especially in patients with congestive heart failure. Lower MR-proANP levels in SIADH may be explained by SIADH-related pronounced natriuresis promoting a negative feedback mechanism[217].

In the last decade, numerous studies have evaluated the use of multi-frequency bioimpedance spectroscopy (BIS) in the context of haemodialysis, peritoneal dialysis and chronic kidney disease, suggesting it as a useful method for the estimation of fluid status. Two recent small studies of using BIS in hyponatraemic patients concluded that it may perform better than physical examination in the evaluation of body fluid status[218] and could facilitate accurate patient ascertainment according to extracellular fluid volume status[219].

In patients with confirmed SIADH, every effort should be undertaken to reveal the underlying cause. In the absence of an obvious diagnosis, thorough history, including detailed drug history, and physical examination should be followed by consideration of CT thorax/abdomen/pelvis and CT or MRI brain. Despite the high prevalence of true idiopathic SIADH, especially in the elderly, a single-centre retrospective study recently reported for the first time that as many as 11.1% of patients with ‘idiopathic’ SIADH were later diagnosed with an underlying cause, in most cases cancer. Age younger than 70 years old, recent onset of hyponatraemia and suggestive clinical presentation could be predictive of an underlying cause[220]. Thus, thorough investigation is urged since SIADH can be an early, or even the first, sign of a serious disease such as cancer.

Hoorn et al has also suggested that, in selected cases and under careful monitoring, a water-loading test, during which an oral or intravenous water load of 20 ml/kg is administered in a 15- to 30-min period followed by a 4-hour observation period, can be informative to detect SIADH and NSIAD[221]. The test should not be performed in patients with a risk of fluid overload and may need to be discontinued when serum sodium falls considerably. If less than 80% of the water load is excreted in 4 hours, this suggests SIADH or NSIAD. In these cases, NSAID should be suspected if there

is a family history of hyponatraemia, if vasopressin levels are undetectable, or if there is no response to a vasopressin-receptor antagonist[221].

Despite being shown to improve diagnostic accuracy in clinical studies, complex approaches utilising fractional excretion or copeptin measurement have not been widely adopted in clinical practice. Also it is extremely important to emphasise that clinical acumen should be exercised in the application of any algorithm, bearing in mind that guidelines and laboratory tests provide only guidance. This becomes even more important, considering that the aetiology of hyponatraemia in real-life clinical cases can often be mixed, for example a combination of malignant SIADH and volume depletion due to gastrointestinal losses in a lung cancer patient with, poor oral intake, diarrhoea and vomiting.

1.6.2 Standards of hyponatraemia investigation in UK clinical practice

Numerous studies have shown that investigation of hyponatraemia is frequently inadequate with essential biochemical tests often underutilised and the underlying cause of hyponatraemia not ascertained in a large proportion of patients[222] [223] [224] . Huda et al found that, among 104 hospitalised patients with serum Na < 125 mmol/l, only 26% had serum osmolality measured, 27% urine osmolality, 10% urine Na, 8% serum cortisol, and 2% a short synacthen test[222]. Whyte et al studied a cohort of 113 hospitalised subjects with serum Na ≤ 120 mmol/l and found low frequency for performance of essential laboratory tests, evidenced by 56% for serum osmolality, 56% for urine osmolality, 51% for urine Na, 34% for serum cortisol and 61% for thyroid function tests[223]. The same authors also indicated for the first time that inadequate investigation, for example failure to measure serum and urine osmolality, was associated with excess mortality[223]. A report of 'real life' clinical practice in 2 UK hospitals found that, amongst 142 subjects with serum Na ≤ 125 mmol/l, serum osmolality was measured in 40% of cases, urine osmolality in 37%, urine Na in 25%, assessment of adrenal reserve in 19% and thyroid function tests in 59%, while the diagnosis of hyponatraemia was documented in 65% of patients[224]. Another study of investigation of 91 patients with serum Na ≤ 125 mmol/l in a UK hospital showed that serum osmolality was measured in 23% of patients, urine osmolality in 23%, urine Na in 19%, short synacthen test in 11% and thyroid function tests in 44%[225]. Clayton et al also studied a cohort of 108 patients with serum Na ≤ 125 mmol/l and found that 61% had serum osmolality measured, 47% urine osmolality, 40% urine Na, 15% basal cortisol or short synacthen test and 49% thyroid function tests[126]. Since then, another UK study in 2014 assessed the investigation of hyponatraemia in two teaching hospitals in Yorkshire and found that amongst 39 subjects with very low

serum Na ≤ 110 mmol/l, 77% of patients had serum osmolality checked, 77% urine osmolality, 49% urine Na, 33% serum cortisol and 59% thyroid function tests[226]. In total, all these studies have reviewed the clinical and biochemical assessment of hyponatraemic inpatients in various UK hospitals and have uniformly demonstrated suboptimal investigation and underdiagnosis of hyponatraemia[222 223 224 225 126].

1.7 Treatment of hyponatraemia

1.7.1 Rate of correction of hyponatraemia

Hyponatraemia treatment has two aims; on the one hand, to alleviate symptoms of hyponatraemic encephalopathy and prevent or treat brain oedema, and, on the other hand, to minimise the risk of osmotic demyelination syndrome in association with overzealous therapy.

Osmotic Demyelination Syndrome

Osmotic demyelination syndrome (ODS), firstly described in the 1970s, is characterised by neurological complications presenting in a stereotypical biphasic pattern[227]. This syndrome was initially named ‘central pontine myelinolysis’ (CPM), because the pons is the preferred site for myelinolysis. Pontine myelinolysis can cause classic neurological manifestations, such as spastic tetraparesis; pseudobulbar palsy leading to dysarthria, dysphagia and emotional lability; locked-in syndrome where the patient does not respond except by vertical gaze and blinking[228]. However, demyelination can also occur in areas outside the pons, such as the thalamus, internal capsule, cerebral cortex and cerebellum, and is termed extrapontine myelinolysis[229]. For this reason, nowadays the term ODS has fully replaced CPM. Of note, Magnetic Resonance Imaging (MRI) is the best imaging modality to detect demyelinating lesions, but radiological findings can often lag behind the onset of neurological symptoms by 3-4 weeks[230 231].

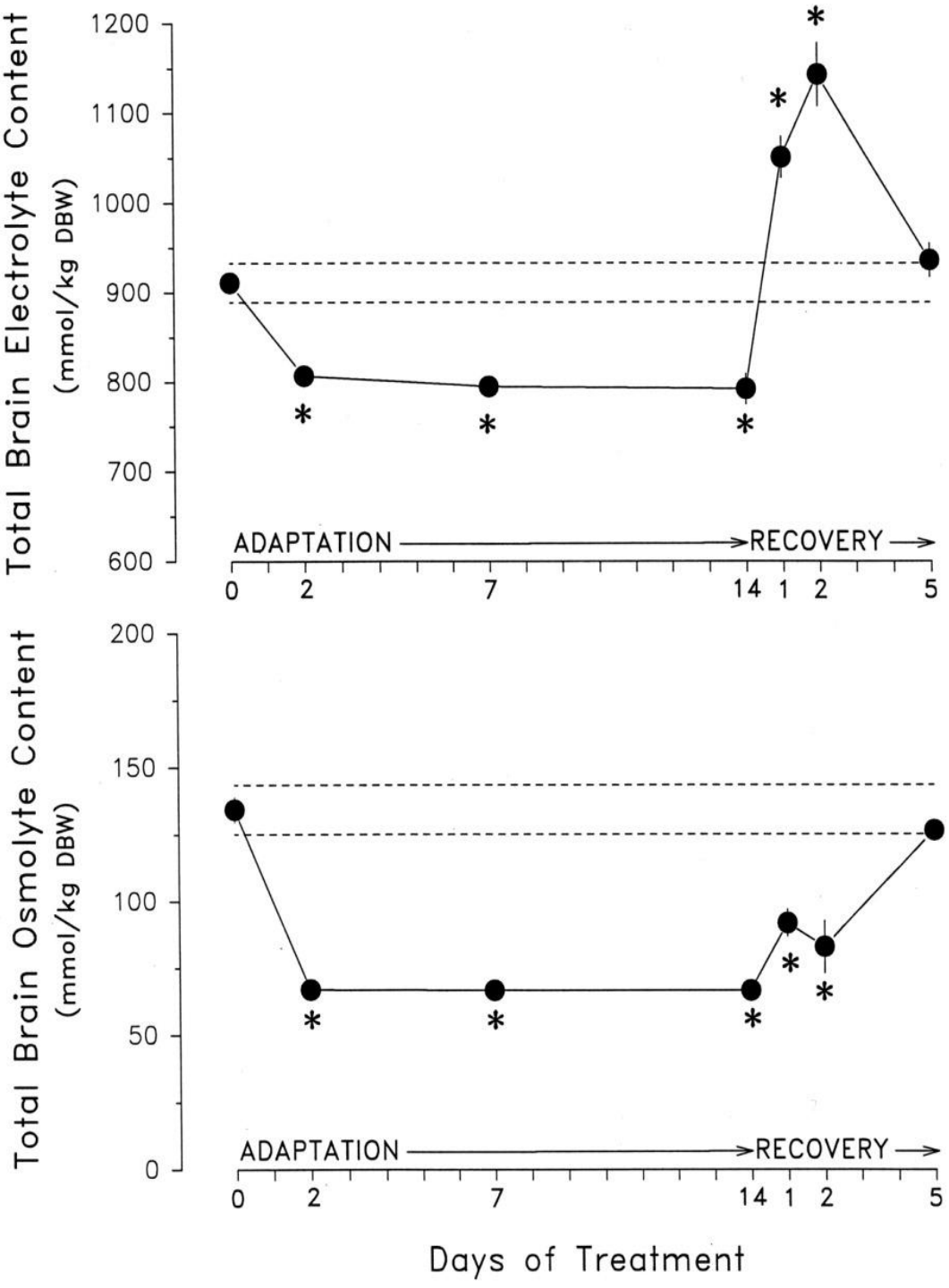
Landmark studies in this field by Sterns et al provided evidence that ODS is a preventable complication of overly rapid correction of chronic hyponatraemia, associated with correction of hyponatraemia by > 12 mmol/l/day or by > 18 mmol/l/48 hours[227 231]. A multicentre study by Sterns found that, amongst 56 patients with baseline serum Na ≤ 105 mmol/l, 14 out of 43 individuals (33.3%) with Na increase > 12 mmol/l in first 24 hours experienced neurological sequelae in contrast to none out of 13 cases with Na increase < 12 mmol/l in the first 24 hours[231]. These data confirmed observations made in animal models of chronic hyponatraemia. For example, a study by Verbalis et al, evaluating the effect of correction of chronic hyponatraemia at different rates in 91 rats with mean serum Na of 112 mmol/l, found that myelinolysis was observed only when magnitude of 24-hour correction

exceeded 16 mmol/l, with an incidence of myelinolysis as high as 64% in those rats with 24-hour correction > 25 mmol/l[232]. However, a prospective study of 184 patients with serum Na ≤ 120 mmol/l, confirming that neurological sequelae are associated with faster rates of correction, reported that, among 9 patients with ODS, 3 corrected by 12 mmol/l, 2 by 11 mmol/l and 1 by 10 mmol/l in the first 24 hours[233]. In agreement with this observation, recent case reports suggested that the limit of 12 mmol/l/day may be too high, particularly for patients with severe malnutrition, alcoholism, advanced liver disease or hypokalaemia who may be especially susceptible to ODS. Also it is well established that profound hyponatraemia with baseline serum sodium concentration ≤ 105 mmol/l is a significant risk factor for development of ODS[227 231 230]. In addition, the longer the duration of hyponatraemia, the greater the risk to develop myelinolysis in the context of hyponatraemia correction[152]. Spasovski et al reported that, amongst a total of 54 cases (63% females, median age 45 years) of ODS published between 1997 and 2012, the initial serum sodium concentration was < 120 mmol/l in 96% of cases, and < 115 mmol/l in 85%[154]. In 87% of cases, serum Na levels increased by ≥ 12 mmol/l during the first 24 hours or ≥ 20 mmol/l during the first 48 hours, while in 6% there were insufficient data to allow estimation of the sodium correction speed. Only 7% of cases, mainly individuals with history of alcohol abuse, developed osmotic demyelination syndrome at lower correction rates of 10-11 mmol/l in the first 24 hours[154].

The precise pathogenesis of ODS is unclear, but extensive evidence suggests that rapid correction of hyponatraemia results in significant water shifts from intracellular to extracellular compartment leading to cellular dehydration and shrinkage of brain endothelial cells. These water shifts occur because rapid correction does not allow adequate time for other homeostatic mechanisms, mainly the re-uptake of organic

osmolytes, for example myoinositol[79]. Following correction of hyponatraemia, electrolytes, mainly Na and Cl, rapidly reach supranormal levels in the brain within 24 hours with these changes being analogous to the rapid increases in brain Na and Cl that occur in response to acute hyperosmolality[76], as illustrated in Figure 16. However, with the exception of glutamate, organic osmolytes return to normal brain contents very slowly over a period of many days with restoration of brain contents taking around 5 days[76]. This slow reaccumulation of organic solutes is very analogous to the similarly slow increases in osmolytes that occur during chronic hypernatraemia, suggesting that, in general, the brain is much better able to lose organic solutes than to reaccumulate them[76]. It is worth mentioning that the recovery of organic osmolytes after hyponatraemia correction takes place at different rates in different brain regions. There is an inverse correlation between the regional efficiency to recover organic osmolytes and the severity of myelinolysis which occurs in this region[234]. Cell shrinkage disrupts their tight junctions and the blood-brain barrier, allowing circulating immune factors such as complement components, lymphocytes and cytokines to gain acces to central nervous system tissues where they can mediate oligodendroglial injury[76 229 235]. In addition, Kengne et al have shown in a rat model of ODS that, following rapid correction of hyponatraemia, massive astrocyte death occurs, causing a disruption in the trophic communication between astrocytes and oligodendrocytes, rapid upregulation of inflammatory cytokines genes, microglial activation, and finally myelin loss[236].

Figure 16. Time course of changes in brain electrolytes (top panel) and organic osmolytes (bottom panel) during adaptation to chronic hyponatraemia and after correction of hyponatraemia in rats. Adapted from Verbalis et al[76].



Based on these data regarding the pathophysiology of ODS, different manouevres to prevent ODS have been tested in animal models. Since glucocorticoids are known to reduce blood-brain barrier permeability and prevent its disruption, Sugimura et al tested the hypothesis whether dexamethasone could protect against osmotic demyelination in an animal model of CPM. This study showed that, following rapid correction of hyponatraemia, early treatment with dexamethasone prevented blood-brain barrier disruption with dexamethasone-treated rats not developing any demyelinating lesions and exhibiting minimal neurological impairment[237]. Kengne et al used a rat model of ODS to compare dexamethasone administration and re-lowering of serum Na as preventive treatment options for ODS and reached two conclusions[238]. First, re-induction of hyponatraemia was more efficient than dexamethasone in prevention of myelinolysis in a large series of hyponatraemic rats, with dexamethasone reducing neurological symptoms, but not altering mortality, while re-induction of hyponatraemia was effective in protecting from both adverse neurological sequelae and death. Based on these findings, early re-induction of hyponatraemia should be considered in patients submitted to rapid correction of hyponatraemia[238]. Second, the fact that animal models still died despite dexamethasone preventing the opening of the blood-brain barrier indicated that increased blood-brain barrier permeability may be a surrogate marker rather than the primary pathophysiological insult in ODS[238]. As a result, authors hypothesised that the increase in the permeability of blood-brain barrier in ODS might involve two components; one early reversible osmotic component mediated by rapid changes in plasma tonicity with the resultant mechanical shrinking of tight junctions of the barrier and a late inflammatory component mediated by the secretion of proinflammatory cytokines after propagation of the osmotic insult[238].

Myoinositol administration is another strategy which could be potentially protective against the neurological sequelae of too rapid correction of hyponatraemia, considering that hyponatraemic animals have brain myoinositol content about 50% of that in normonatraemic controls. Intravenous infusion of myoinositol in hyponatraemic animals was shown to increase markedly brain myoinositol content, but only when serum sodium increased rapidly[239]. The same group also showed that exogenous administration of myoinositol in rats reduced the severity of myelinolysis and improved survival after rapid correction of hyponatraemia[240].

Recently, the potential protective role of urea from development of myelinolysis has been explored. A study in hyponatraemic rats showed that, despite a large, on average 32 mmol/lday, correction of serum sodium, mortality rate was singificantly lower in the urea-treated rats (13%) compared to control rats treated by water diuresis (87%). However the brain organic osmolyte composition was similar in rats treated with urea and by water diuresis. These data suggested that urea per se may have a specific brain-protective effect against myelinolysis, independently of kinetics of major organic osmolyte reaccumulation[241]. The same group recently conducted an animal study, comparing urea administration to treatment with an AVP V2 receptor antagonist, lixivaptan, and hypertonic saline with respect to the risk of neurological complications in the event of a too rapid rise in serum sodium[242]. Despite a similar mean increase in serum sodium of 32 mmol/l/day obtained by the three drugs, treatment with urea resulted in significantly lower mortality rate (25%) than lixivaptan (71%) and hypertonic saline (93%) as well as much lower rate of demyelinative brain lesions[242]. Histological analysis showed that urea-treated rats had no evidence of microglial activation, another hallmark of ODS, while rats treated with hypertonic saline or vaptan displayed strong evidence of microglial activation. With regards to

breakdown of the blood-brain barrier, the same incremental rise in serum sodium resulted in a diffuse opening of the blood-brain barrier at 24 hours when achieved with hypertonic saline, but not when obtained with urea or lixivaptan. However, 6 days after rapid hyponatraemia correction, several large areas of broken blood-brain barrier were observed in animals treated with lixivaptan or hypertonic saline compared with urea-treated animals[242]. The same applies to astrocyte damage with the brain of animals treated with lixivaptan or hypertonic saline showing extensive areas of astrocyte death, whereas there was only minimal astrocyte loss in urea-treated animals[242]. In total, all these studies were undertaken in animal models and were set in extreme conditions of over rapid serum sodium correction that hardly reflect the daily clinical practice. Therefore, it remains to be seen whether all these therapeutic manouevres, such as dexamethasone, myoinositol and urea administration could have a protective effect in humans against myelinolysis.

Correction goals and limits

Both recently published European guidelines[154] and expert panel recommendations by Verbalis et al[152] distinguish between correction aims or goals and correction limits. A target is a goal the clinician is aiming for; it is the change in serum sodium concentration that clinician wishes and expects to achieve with a particular treatment. A limit is a change in serum sodium concentration the clinician does not want to exceed and, if surpassed, requires prompt counterregulating intervention. It is worth mentioning that the recommendations below apply to patients who have chronic hyponatraemia, defined as hyponatraemia for longer than 48 hours, and, as a result, are at risk of neurological sequelae if the correction of serum sodium occurs too rapidly due to the development of osmotic demyelination.

It is worth mentioning that over the years the recommended correction rates, as high as < 25 mmol/l/day in 1990s[243], have been gradually becoming more conservative[244]. The European guideline development group, after an extensive systematic review of ODS case reports, recommended restricting increases in serum sodium concentration to < 10 mmol/l in the first 24 hours and < 18 mmol/l in the first 48 hours[154]. Its authors also accepted that it is probably impossible to set absolutely 'safe' rate limits for correcting hyponatraemia, urging using correction targets and limits in the context of the individual patient[154]. The fact that the same limits were suggested for all hyponatraemic patients, regardless of the presence or absence of predisposing factors for ODS, was criticised by Adrogue and Madias, two well-known experts in the field[244]. They proposed even more conservative limits of 6-8 mmol/l for any 24-hour period, since, although the likelihood of demyelination caused by correction rate once thought to be safe is low, this magnitude of increase has been

proven to adequately treat the most severe manifestations of hyponatraemia with no evidence that clinical advantage will be derived from exceeding this cut-off[244]. Verbalis and co-authors in their expert panel recommendations proposed different goals and limits according to the presence or absence of risk factors for ODS[152]. For patients with high risk of developing ODS, such as individuals with baseline serum sodium ≤ 105 mmol/l, malnutrition, alcoholism, advanced liver disease or hypokalaemia, they proposed a correction goal of 4-6 mmol/l/day and limit of 8 mmol/l/day. Of note, the precise levels of serum K as well the the degree of alcoholism, malnourishment or liver disease that reduce the brain's tolerance to osmotic stress, increasing the susceptibility to ODS, have not been rigorously defined[152]. In the absence of risk factors for ODS, a goal of 4-8 mmol/l/day and a correction limit of 10-12 mmol/l in any 24-hour period and 18 mmol/l in any 48-hour period are recommended[152]. A group of senior UK clinicians with a special interest in the field of hyponatraemia proposed a safe limit for the treatment of hyponatraemia of < 10 mmol/l in the first 24 hours and < 18 mmol/l in 48 hours[245]. However, they proposed tighter correction limits with sodium increase not exceeding 8 mmol/l in 24 hours and 14 mmol/l in 48 hours for individuals most at risk for developing ODS, such as elderly individuals, children under 16 years of age, malnourished patients, patients with alcoholism, patients with central nervous system disease or hypoxia and patients in the postoperative setting[245].

Recommendations if correction exceeds limits

During the active correction phase of hyponatraemia, close monitoring of urine output and serum electrolytes are essential in order to promptly identify cases of overly rapid correction of hyponatraemia. However, an aspect overlooked by all guidelines is that the measurement of serum sodium may not offer the precision required for this monitoring because of analytical and biological variation. Tormey et al calculated the reference change value (RCV) for serum sodium measurement by indirect ISE with a common analyser and demonstrated that only changes in serum Na ≥ 4 mmol/l were certain to be real[246]. Taking the hyponatremia value of 121.2 mmol/l and 2 analytical standard deviations (SDs) above and below the mean revealed a 95% CI of 118.8-123.6 mmol/l, but the RCV was 117.3-125.1 mmol/l. As a result, a difference in 2 measurements of sodium at this concentration as large as the upper boundary minus the lower boundary of the 95% CI could occur by chance and not due to a true change in the severity of hyponatraemia[246].

European guidelines recommend prompt intervention for re-lowering serum sodium concentration if it exceeds safe correction limits[154]. First, ongoing active treatment should be discontinued. In addition, an expert should be consulted to consider if it is appropriate either to start an infusion of 10 ml/kg body weight of electrolyte-free water (glucose solutions) over 1 hour under strict monitoring of urine output and fluid balance or to add intravenous desmopressin 2 mcg, with the understanding that this should not be repeated more frequently than every 8 hours[154]. Of note, in established overly rapid correction, the benefits and harms of active treatments to re-lower serum sodium concentration have not been well studied. Nevertheless, the guideline development group felt that the dramatic consequences of ODS may warrant an attempt to re-lower serum sodium levels, but only after an expert is

consulted[154]. Verbalis et al recommends rigorous electrolyte monitoring at 4- to 6-hour intervals and close monitoring of urine output until serum Na concentration of ≥ 125 mmol/l is reached[152]. When the target for daily sodium increase is met, active measures, such as hypertonic saline or tolvaptan, should be temporarily withheld to prevent further correction. For the rest of the day, ongoing water losses should be replaced by oral water or intravenous infusion of 5% dextrose in water or alternatively by administering parenterally 2-4 mcg desmopressin. If overcorrection occurs, therapeutic re-lowering of serum sodium can be considered. There is lack of high quality evidence for this, but it was shown to prevent ODS in an animal study[238] and also a small case series showed that it could be used effectively in cases of inadvertent overly rapid correction of hyponatraemia[247]. It can be achieved by administering 2-4 mcg of desmopressin in combination with repeated 3 ml/kg infusions of 5% dextrose in water administered over 1 hour, following by measurement of serum sodium after each infusion to determine the need for more 5% dextrose in water, until serum sodium has returned to a level below the therapeutic limit for the patient[152].

Finally, a systematic review published in 2015 included 17 studies with 80 patients who were administered desmopressin according to three strategies; proactive, reactive or rescue[248]. The proactive strategy is DDAVP administration in combination with hypertonic saline infusion in patients at high risk of too rapid correction, based on low baseline serum Na < 120 mmol/l, while reactive strategy is characterised by DDAVP administration, often in combination with hypotonic fluids, based on high urine output or rapid change in serum Na, in order to halt further sodium rise. Patients at high risk of ODS who were managed with a proactive strategy had much lower likelihood (27.6%) to exceed safe correction limits compared with a reactive

strategy (87.9%). This systematic review contained 16 patients who were treated with rescue strategy of co-administration of DDAVP and hypotonic fluids after exceeding serum sodium correction limits or upon development of neurologic symptoms. Amongst these patients, there were no reported cases of ODS, while the rescue strategy effectively alleviated acute neurological symptoms in 4 patients, suggesting that DDAVP and re-lowering of serum Na may have prevented permanent neurologic injury[248]. The role of these three distinct strategies of DDAVP administration in order to control high rates of sodium correction is still unclear and warrants further research.

1.7.2 Treatment of hypovolaemic hyponatraemia

In cases of hypovolaemic hyponatraemia, restoring extracellular volume with intravenous infusion of 0.9% saline is recommended. In case of haemodynamic instability, the need for rapid fluid resuscitation overrides the risk of an overly rapid increase in serum sodium concentration. Volume depleted patients are particularly prone to overly rapid hyponatraemia correction because restoration of volume suppresses baroreceptor-mediated AVP secretion, leading to significant aquaresis. In view of this risk of prompt autocorrection following volume expansion, serum sodium levels should be monitored closely in order to ensure safe correction limits will not be exceeded.

1.7.3 Treatment of SIADH

The initial treatment of hyponatraemia due to SIADH will vary greatly depending on the presence of neurological symptoms which is the key factor in guiding the mode and urgency of treatment. The other important factor is the speed at which onset of hyponatraemia occurred. To a large extent, these two factors overlap, since most cases of acute (arbitrarily defined as ≤ 48 hours in duration) severe (serum Na < 125 mmol/l) hyponatraemia can cause severe symptoms. These patients with acute severe hyponatraemia are at greatest risk of neurological complications from the hyponatremia itself and should receive measures to promptly raise serum sodium levels. Since a lot of patients present with hyponatraemia of indeterminate duration, assessment of symptomatology and identification of individuals with severe symptoms are of paramount importance to prevent fatalities as a direct consequence of hyponatraemia.

Acute symptomatic hyponatraemia is best corrected with hypertonic (3%) saline given either via bolus or continuous intravenous infusion. The aim of initial therapy is to achieve a serum Na increase of 4-6 mmol/l which is sufficient to reverse clinical signs of herniation and reduces intracranial pressure by nearly 50% within an hour[249] [250]. Nowadays, all major guidelines recommend initial bolus therapy on the basis that fixed boluses obviate the need for complex calculations in the context of a medical emergency. They limit the risk for inadvertent overly rapid correction reported in association with use of formulae[251] since they mandate another measurement prior to each bolus and they can achieve rapid increase in serum sodium[252]. For these reasons, a regimen of 100 ml of 3% saline infused over 10 minutes[152] or 150 ml of 3% saline infused over 20 minutes[154] is recommended and, if needed, should be

repeated in order to reach the correction target[152]. Subsequently, initial treatment should be followed by infusion of 3% saline at a rate of 0.5-2 ml/kg/hour with the rate being serially adjusted based on frequent measurements of serum Na. Since there is often uncertainty about the chronicity of hyponatraemia, the rate of correction needs to be within the correction goals and below the correction limits. However, if it is known that the duration of hyponatraemia is less than 48 hours, the rate of hyponatraemia correction does not need to be restricted.

In most cases when SIADH does not cause severe symptoms, treatment entails choosing among several therapies. Treatment options include fluid restriction, demeclocycline, urea, combination of furosemide with NaCl tablets, and tolvaptan. Both the recently published recommendations by an expert panel led by Verbalis[152] and the guidelines endorsed by the European Society of Endocrinology and the European Renal Association[154] agree that fluid restriction is, in general, the first-line treatment for SIADH with mild to moderate symptoms. However, their recommendations differ with respect to the therapeutic utility of other treatment modalities. On the one hand, Verbalis et al suggests the use of vaptans as second-line agents, having been the only pharmacological agents widely approved by the regulatory authorities with well-established efficacy in correcting hyponatraemia and a good safety record[152]. Nonetheless, their recommendations do not exclude alternative therapies, such as urea and demeclocycline[152]. On the other hand, the European guidelines suggest that oral urea and a combination of low-dose loop diuretics with oral sodium chloride should be considered as equal second-line treatments[154]. The European guidelines recommend against the use of demeclocycline. With regards to the utility of vaptans, they do not recommend the use of vaptans in patients with serum Na of 125-135 mmol/l and, in fact, recommend

against the use of vaptans in patients with serum Na < 125 mmol[154]. Safety concerns about the use of vaptans, mainly the risk of too rapid correction of serum sodium as well as their potential for hepatotoxicity, are the reason for these negative recommendations. Reviewing the rationale stated in the European guidelines, it becomes apparent why they are much more ‘’conservative’’ in their recommendations about therapies effective in correcting hyponatraemia, such as vaptans. The European guideline development group judged that, in the absence of concrete evidence that treating hyponatraemia without severe symptoms improves clinical outcomes, their primary concerns were avoiding harm through treatment as well as preventing further deterioration of hyponatraemia with the potential to cause severe symptoms[154]. After reviewing latest evidence and taking into account their extensive clinical experience in this field, a group of senior UK clinicians with a special interest in hyponatraemia published in 2015 an algorithm for the assessment and management of hyponatraemia. They recommended fluid restriction as first-line treatment, while tolvaptan and demeclocycline were suggested as second-line treatment after consultation with an Endocrinologist[245]. Finally, the Spanish algorithm by Runkle et al supports the use of tolvaptan as second-line treatment, but it also highlights that concomitant adminstration of loop diuretics (oral or iv furosemide 40-80 mg/day) with salt tablets (oral NaCl 4-8 g/day) can have great therapeutic utility in selected cases[253].

Fluid restriction

Fluid restriction has traditionally been regarded as first-line therapy for SIADH, despite the lack of evidence base, such as systematic reviews or randomised controlled trials, to support its effectiveness[152 154]. Of note, there is also little to no evidence that fluid restriction is associated with important adverse events. Very few case reports of ODS in patients on fluid restriction do not support a causal relationship, because too rapid correction of hyponatraemia in these cases should be attributed to other factors such as discontinuation of SIADH-related drugs. The principal disadvantage of fluid restriction is poor adherence since a significant proportion of patients find it very difficult to comply due to thirst. The second drawback is that, even when it is effective, it usually takes several days to lead to significant increase in sodium levels. Fluid restriction should include not only water, but all fluid intake, not excluding intravenous fluids and enteral/parenteral nutrition. Sodium and protein intake should be liberal during fluid restriction.

There are predictors for the increased likelihood of failure of fluid restriction, such as high urine osmolality, high sum of urine Na and K, low 24-hour urine volume and limited increase in serum Na value after 48-hour fluid restriction[152]. High urine osmolality > 500 mOsm/kg H2O indicates little renal free water excretion and makes response to treatment unlikely, unless very strict water restriction is imposed. Patients with relatively low and fixed urine osmolality at 300-400 mOsm/kg H2O usually respond to water restriction[206]. Also urine output < 1500 ml/day predicts failure of fluid restriction since fluid should at least be limited to 500 ml/day below urine volume, making adherence to fluid restriction very difficult.

Both expert panel recommendations by Verbalis et al[152] and a treatment algorithm formulated by a group of UK endocrinologists[245] have recommended the use of Furst formula to predict likely failure of fluid restriction and guide volume of fluid restriction[254]. This formula was based on the concept that, in order to raise serum osmolality and sodium, water intake needs to be restricted to less than the amount of electrolyte-free water excretion. Therefore, the amount of electrolyte-free water cleared will determine the patient's response to fluid restriction[254]. As a result, Furst et al created a simplified formula for estimating free-water clearance, based on the urine/plasma electrolyte ratio (U/P) = $(U_{Na}+U_K) / (P_{Na}+P_K)$ measured in a spot urine sample[254]. For example, if U/P is < 0.5, then fluid restriction of 1000 ml/day should be imposed. If U/P is 0.5 – 1.0, then fluid should be restricted to 500 ml/day. If U/P > 1.0, then no electrolyte-free water is excreted and fluid restriction is unlikely to be beneficial[254].

In 2016, a large prospective observational study, evaluating predictors of fluid restriction failure in patients with SIADH, was published[255]. It included 82 SIADH patients with serum Na < 125 mmol/l treated with fluid restriction, defined as total fluid intake < 1000 ml/day. This study found that 59% of patients were responders, defined as having an increase in serum Na > 3 mmol/l within the first 24 hours, and 41% non-responders, as evidenced by ≤ 3 mmol/l serum Na increase within first 24 hours[255]. In line with current recommendations by Verbalis et al of alternative first-line therapy in case of urine osmolality > 500 mOsm/kg H2O[152], a significant association was found between urine osmolality and failure of fluid restriction with a cut-off level > 500 mOsm/kg H2O predicting nonresponse to fluid restriction with a specificity of 87%. Also urine osmolality < 300 mOsm/kg H2O had a sensitivity of 90.9% in predicting success of fluid restriction. Urine sodium at a cut-off level ≥ 130

mmol/l was found to be the best marker to predict failure to respond to fluid restriction with a specificity of 91.3%, whereas urine Na ≤ 50 mmol/l predicted success of fluid restriction with a sensitivity of 87.9%. U/P > 1.0 correlated significantly with failure to respond to fluid restriction with a specificity of 71.8%, but did not perform as well as urine Na alone[255]. Furthermore, high serum urea concentration ≥ 5.0 mmol/l predicted nonresponse to fluid restriction with a specificity of 84.1%, while low urea levels ≤ 2.5 mmol/l predicted response to fluid restriction with a sensitivity of 96.8%[255]. Finally, this study identified low serum mid-regional pro-atrial natriuretic peptide (MR-proANP) ≤ 80 pmol/l as a novel predictor of nonresponse to fluid restriction with specificity of 81.8%[255]. In conclusion, this study highlights the usefulness of predictors of response to fluid restriction such as urine osmolality, urine sodium, serum urea, and even serum MR-proANP, in order to individualise care of SIADH patients.

Demeclocycline

Demeclocycline is a tetracycline antibiotic which has a marketing authorisation in the UK and France for the treatment of hyponatraemia due to paraneoplastic SIADH[256]. In most other countries, it is occasionally used ‘’off-label’’ to treat fluid restriction-resistant hyponatraemia due to SIADH. It is thought that demeclocycline can induce nephrogenic diabetes insipidus, resulting in decreased urine concentration even in the presence of high plasma AVP levels. Its mechanism of action is poorly understood, but recent in vitro and in vivo animal data suggested that demeclocycline reduces cAMP generaration, AQP2 gene transcription and AQP2 abundance in the renal inner medulla[257]. Appropriate doses of demeclocycline range from 600 to 1200 mg/day administered in divided doses. Treatment must be continued for several days to achieve maximal diuretic effect since the onset of action for demeclocycline is unpredictable and ranges from 3 to 5 days[152]. The main shortcomings of demeclocycline are: firstly, it is effective in increasing serum sodium levels in only around 60% of patients with SIADH[256]; second, the individual response is unpredictable and, even when it is effective, the onset of action is usually delayed by at least 3 days; third, it is potentially nephrotoxic and can cause dose-dependent reversible uraemia due to a combination of the catabolic effect of demeclocycline leading to increased urea production and a mild specific drug-induced nephrotoxicity[152]; fourth, other adverse effects have been reported such as photosensitive skin rash and gastrointestinal intolerance, including nausea and vomiting.

A recent systematic literature review of all available evidence for the use of demeclocycline in SIADH highlighted the paucity of high quality data for the efficacy

and safety of demeclocycline[256]. In agreement with this review, the European guideline development group did not identify any systematic reviews or randomised controlled trials evaluating the benefits and harms of demeclocycline for the treatmenet of SIADH[154]. Our available data on the efficacy and safety of demeclocycline are based on observational cohort studies and case series which were primarily published between 1978 and 1985. For example, a series of 17 patients with malignant SIADH showed good efficacy with serum Na mean increase from 121 to 130 mmol/l after an average of 3.5 days following institution of demeclocycline[258]. However, half of patients, mostly individuals who were treated with high doses of demeclocycline 1200 mg per day or received concomitant nephrotoxic drugs such as aminoglycosides, developed serum urea levels in excess of 9 mmol/l with a mean maximum creatinine 168 umol/l[258]. Another case series of 14 patients with hyponatraemia (mean starting serum Na 118 mmol/l) due to malignant SIADH who were treated with demeclocycline 1200 mg per day demonstrated great efficacy with normonatraemia being restored in all cases after an average of 8.6 days[259]. Blood urea rose significantly from pre-treatment levels of 4.2 mmol/l to 10.1 mmol/l at 10 days, with urea concentration rising above 20 mmol/l in 4 individuals. Mean creatinine concentration rose from 78.5 umol/l to 106.5 umol/l[259]. Therefore, renal function should be monitored in patients treated with demeclocycline on a regular basis and the medication discontinued in case of significant uraemia.

In conlusion, most guidelines[152 245 260] state demeclocycline as a possible treatment option for SIADH without making specific recommendation in favour or against its use, with the exception of the European clinical practice guidelines which advise

against the use of demeclocycline in view of safety concerns associated with its use, such as uraemia and nephrotoxicity[154].

Urea

Urea leads to a rapid increase in plasma urea concentration and subsequent marked osmotic diuresis and elimination of free water. Urea is freely filtered by the glomerulus, and about half the filtered urea is excreted in the final urine along with electrolyte-free water[261]. If urine osmolality is 500 mOsm/kg, excretion of 500 mOsm of urea will promote excretion of 1 litre of electrolyte-free water. If the urine is more concentrated than 500 mOsm/kg, the amount of free water excretion and increase in serum sodium will be less, and if the urine is more dilute, the serum sodium will increase more. Besides its diuretic properties, urea has also osmotic properties with a rapid increase in plasma urea concentration creating an osmotic gradient across the blood-brain barrier that promotes water flow out of the brain. Because of its osmotic properties, urea became the standard of care for increased intracranial and intraocular pressure in the 1960s before being replaced by mannitol as the hyperosmolar agent of choice[261].

Urea is not widely available and its use to date has been limited in most countries with the exception of Belgium. The disadvantages associated with oral urea include poor palatability, the development of uraemia at higher doses, and the unavailability of an FDA- or EMA-approved pharmaceutical preparation. Data suggest that blood urea concentrations may double during treatment, but it is important to remember that this does not represent renal impairment[152]. With the bitter taste of urea being one of the barriers to its use, it is advisable to combine it with sweet-tasting substances, for example to dissolve the urea in orange juice or some other strongly flavoured liquid. For example, the European guideline development group suggests that the pharmacist could prepare the following as sachets: urea 10 g + $NaHCO_3$ 2 g + citric acid 1.5 g + sucrose 200 mg to be dissolved in 50 – 100 ml of water[154]. Doses

should be 15-60 g/day (0.25-0.50 g/kg urea) and can be titrated in increments of 15 g/day.

Decaux and co-workers reported the first use of oral urea for this purpose in 1980 and have continued to advocate its use for more than 30 years. Several retrospective, uncontrolled studies have demonstrated high efficacy of urea in correcting hyponatraemia due to SIADH. For example, a retrospective case series of 42 non-traumatic SIADH patients (mean baseline serum Na 127 mmol/l) treated with urea at doses of 15-30 g 3-4 times per day showed that hyponatraemia was fully corrected in all cases after a median treatment duration of 3 days[262]. A median serum Na rise of 3 mmol/l and 5 mmol/l was observed 24 hours and 48 hours respectively following initiation of urea, while the incidence of overly rapid hyponatraemia correction (defined as Na increase of ≥ 12 mmol/l/day) was 9.2% without any cases of ODS being observed. Three quarters of the patients received urea through a nasogastric tube and the remaining ingested it. Serum urea levels showed only a modest increase with no patients exceeding serum urea concentration of 13 mmol/l during treatment period because of significantly increased renal excretion of urea. Adverse gastrointestinal effects or renal dysfunction did not occur[262]. Another retrospective case series by Decaux et al reported high efficacy of urea in 50 SIADH patients with mild hyponatraemia (mean serum Na 128 mmol/l) in intensive care unit (ICU), as evidenced by a mean serum sodium increase of 7 mmol/l after 2 days of urea therapy[263]. Analysis of a cohort of 35 SIADH patients with severe hyponatraemia (mean serum Na 111 mmol/l) treated with urea and isotonic saline also found that urea is highly effective, leading to a mean serum sodium increase of 11 mmol/l in 24 hours. Of note, 29% of severely hyponatraemic patients treated with urea exceeded the safe rates for hyponatraemia correction[263]. A similar

series of 24 critically ill hyponatraemic patients (mean serum Na 124.8 mmol/l) with neurosurgical SIADH demonstrated a mean serum Na rise of 6.6 mmol/l on the second day of urea therapy and 11.4 mmol/l on the fourth day[264]. Pre-treatment mean serum urea was 4.9 mmol/l and increased to 12.1 mmol/l on the third day of urea therapy without nephrotoxicity or any side effects being noted[264]. A prospective long-term study by the same group compared urea with vaptans in the treatment of chronic SIADH[265]. Twelve SIADH patients with mean baseline serum Na 125 mmol/l were firstly treated with a vaptan, satavaptan or tolvaptan, then underwent an 8-day holiday period at the end of which hyponatraemia had recurred, and finally received oral urea for an additional 1-year. This study demonstrated that patients with chronic moderate hyponatraemia related to SIADH could be treated with the same efficacy, safety, and tolerance with oral vaptans or urea over a long-term period, with the mean serum Na being the same, 135 mmol/l, during therapy period with both drugs[265]. In 2015, Kengne et al found in hyponatraemic rats that rapid correction of hyponatremia with urea is less likely to cause osmotic demyelination than rapid correction with either hypertonic saline or a vasopressin antagonist[242]. These findings supported the hypothesis that urea protects astrocytes from injury due to hypertonic stress. In light of these data in animal models, studies are warranted to examine whether these findings would apply to humans.

The European guidelines recommended oral urea as second-line treatment for hyponatraemia due to SIADH[154]. Despite acknowledging the bitter taste of urea, it suggested that its acceptability could increase by combining urea with sweet-tasting substances. Also the European guideline development group did not consider availability of urea a problem as it is used in many other pharmacological preparations[154]. All other guidelines have a place of urea without making specific

recommendations. Noteworthy, all key studies about urea for treatment of SIADH have taken place in Belgium, whereas a standard preparation of urea has not been available in most other countries, including the UK and the US, limiting to a great extent its use in routine clinical practice and, subsequently, most clinicians' experience in using it.

1.7.4 Treatment of hypervolaemic hyponatraemia

Patients with hypervolaemic hyponatraemia due to heart failure should be managed with fluid restriction which, in case of fluid overload, should be combined with loop diuretics. For severely symptomatic patients with heart failure and very low serum sodium, the treatment should be hypertonic saline combined with loop diuretics to prevent or relieve fluid overload. Alternatively tolvaptan use could be considered, but it is worth mentioning that, while it is licensed for both euvolaemic and hypervolaemic hyponatraemia in the US, it is not licensed for hypervolaemic hyponatraemia in Europe. The utility of tolvaptan in this context has been tested in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST), a multi-centre, randomised, double-blind, placebo-controlled study which included 4133 patients hospitalised with heart failure[266]. Tolvaptan was effective in increasing serum sodium as well as in improving dyspnoea and reducing body weight, but it had no effect on long-term mortality and cardiovascular morbidity[266 267].

In patients with cirrhosis, treating hypervolaemic hyponatraemia can be even more challenging. First line-treatment is fluid restriction which needs usually to be imposed at < 750 ml/day in order to be less than the sum of urine output plus insensible losses. That means that it is very difficult to adhere to and, as a result, its effectiveness is quite limited. Tolvaptan seems to be effective in increasing serum sodium concentration, as shown in the subgroup of cirrhotic patients with hyponatraemia in SALT studies[268] and in the interim results from post-marketing surveillance (START sudy) in Japan[269]. In addition, a study of 14 hyponatraemic patients (mean baseline Na 126 mmol/l) with cirrhosis showed that 2-week tolvaptan therapy resulted in a mean Na increase of 5.5 mmol/l and significant improvement in

cognitive performance[270]. However, a recent retrospective case series of 9 patients with cirrhosis and severe hyponatraemia (median serum Na 121 mmol/l) reported low efficacy of tolvaptan, with only 2 out of 9 individuals responding to tolvaptan, as defined by increase of serum Na by ≥ 5 mmol/l and to a value ≥ 130 mmol/l throughout treatment[271]. In fact, Japan is the only country tolvaptan has been approved for the indication of volume overload in liver cirrhosis since 2013[272]. In light of recent FDA recommendations in relation with hepatotoxicity concerns, vaptans are not routinely used in patients cirrhosis, except for very selected cases when the potential clinical benefits outweigh the risk of worsened liver function, such as in patients with end-stage liver disease and severe hyponatraemia who are awaiting imminent liver transplantation[152].

1.8 Tolvaptan

Vaptans in general

Since plasma AVP levels are elevated in almost all SIADH cases, nonpeptide vasopressin receptor antagonists have been considered as potentially useful therapeutic agents for the treatment of hyponatraemia, by selectively increasing solute-free water excretion from the kidneys. Several of these pharmacological agents, known as vaptans, have been developed and tested in humans, including tolvaptan, conivaptan, mozavaptan, lixivaptan and satavaptan[273]. All vaptans are administered orally and are specific V2 receptor antagonists with the exception of conivaptan which is available only as an intravenous solution and has affinity for both V1 and V2 receptors[273]. Noticeably, the availability of vaptans and the approved indications for their use by different regulatory authorities varies significantly across the world[274]. For example, intravenous conivaptan is licensed, in the US only, for use in the treatment of both euvolaemic and hypervolaemic hyponatraemia, while mozavaptan has been approved, in Japan only, for the treatment of malignant SIADH[274]. Lixivaptan and satavaptan are not in clinical use anywhere in the world, following their applications for use in the treatment of hyponatraemia having been rejected by the FDA and the EMA respectively. We will focus on tolvaptan, the only vaptan licensed for use in Europe.

Mechanism of action

Tolvaptan, a selective V2 receptor AVP antagonist, competitively blocks the binding of vasopressin to V2 receptors located on renal collecting duct cells. As a consequence of V2 receptors inactivation, there is inhibition of the synthesis and transport of aquaporin-2 water channel proteins into the apical membrane of the collecting duct cells, resulting in a decrease of free water reabsorption[273]. Noteworthy, increased diuresis produced by tolvaptan is quantitatively similar to that induced by intravenous administration of 20 mg furosemide[275]. However it is qualitatively different because tolvaptan leads to increased water excretion without significant increase in the excretion of urine solutes, such as sodium and potassium. For this reason, tolvaptan has been termed aquaretic in contrast to classic diuretics, which are also natriuretic and kaliuretic[152].

Tolvaptan use was approved by the regulatory authorities in the US (FDA; Food and Drug Administration) and Europe (EMA; European Medicines Agency) in 2009. In the US, tolvaptan is approved for the treatment of both euvolaemic and hypervolaemic hyponatraemia, whereas in the European Union it is licensed only for use in the treatment of hyponatraemia due to SIADH.

In May 2015 the EMA approved the use of tolvaptan for Adult Polycystic Kidney Disease (ADPKD), while the regulatory authorities in Japan, Canada and Korea have recently granted marketing authorisation for this indication too. This approval was based on the results of TEMPO 3:4 trial (the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4 trial), a phase 3, multicentre, double-blind, placebo-controlled, 3-year trial, which randomly assigned 1445 ADPKD patients with eGFR ≥ 60 ml/min/1.73 m^2 in a 2:1

ratio to receive tolvaptan or placebo[276]. This landmark study demonstrated that tolvaptan slows the increase in total kidney volume and the decline in renal function over a 3-year period, leading to a significant 61% relative risk reduction in disease progression, defined as a 25% reduction in eGFR[276]. The results of its open-label extension study, TEMPO 4:4 study, were published in 2017, showing that the tolvaptan-related reduction in the decline of eGFR was maintained after 2 additional years of open-label treatment[277]. European guidelines have supported the use of tolvaptan in ADPKD patients who have documented rapid disease progression or are likely to have rapid disease progression, identified according to a hierarchical decision algorithm[278]. Therefore, tolvaptan is indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults with chronic kidney disease stages 1-3A (eGFR > 45 ml/min/1.73 m²) at initiation of treatment who also have evidence of rapidly progressing disease[278]. In contrast to these guidelines, the US FDA declined in 2014 to approve tolvaptan for ADPKD, expressing two main concerns; firstly, the dropout rate in the tolvaptan arm may have influenced the significance of efficacy data; second, tolvaptan-related liver damage may progress with longer use, causing liver failure in an estimated 1 of every 3000 patients. In addition, some FDA committee members commented on the small proportion of participants with advanced kidney disease and questioned the extent to which slower growth in kidney volume was clinically meaningful, requesting additional efficacy and safety data. In response to the FDA request, REPRISE trial (Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD), a phase 3, randomised, multi-centre, placebo-controlled, double-blind trial was undertaken and assigned 1370 ADPKD patients with more advanced kidney disease (eGFR 25-65 ml/min/1.73 m²) in a 1:1 ratio to receive tolvaptan or placebo

for 12 months[279]. The results of this study were published in November 2017, showing that tolvaptan also slowed the progressive loss of renal function in patients with later-stage ADPKD (mean eGFR 41 ml/min/1.73 m²)[279]. Further studies will be needed to conclude whether these results can translate into meaningful delays in the need for renal replacement therapy and whether the adverse events observed presage more substantial issues over time[280].

Japan is the only country where tolvaptan has been approved since 2013 for the indication of volume overload in liver cirrhosis[269]. The Evidence-based Clinical Practice Guidelines for Liver Cirrhosis, published in 2015 by the Japanese Society of Gastroenterology, recommend tolvaptan at a dose of 3.75-7.5 mg per day in combination with loop diuretics and aldosterone antagonists for the treatment of ascites and impaired water retention in cirrhotic patients[281]. Multicentre, randomised, placebo-controlled trials in liver cirrhosis patients with insufficient response to conventional diuretics have showed that tolvaptan as add-on therapy to conventional diuretics reduced body weight, abdominal circumference, and lower limb oedema compared to placebo[282 283]. A large-scale, prospective, multicentre, post-marketing surveillance study (START study) was undertaken in Japan, including safety data for 463 patients and effectiveness data for 340 patients with liver cirrhosis and fluid retention who have not sufficiently responded to conventional diuretics[269]. Patients were treated with a mean tolvaptan dose of 6.2 mg/day over a period of 57 days, resulting in improvement of symptoms, such as ascites and lower limb oedema. Tolvaptan led to a mean decrease in body weight of 3.5 kg in 14 days and 4.5 kg in the second month of therapy, with the effectiveness in reducing body weight being dependent on renal function[269].

Studies evaluating efficacy of tolvaptan

SALT-1 and SALT-2, two multicentre, randomised, double-blind, placebo-controlled trials, assessed the efficacy and safety of tolvaptan in patients with euvolaemic or hypervolaemic hyponatraemia. Patients were randomly assigned to oral tolvaptan at a dose of 15 mg daily (N=225) or oral placebo (N=223)[284]. Within 8 hours folowing tolvaptan administration, serum sodium concentration was significantly higher in the tolvaptan group than in the placebo group, and remained persistently higher for the 30-day study period. On day 4, there was a highly significant ($P < 0.001$) difference in the percentage of participants having achieved normonatraemia, with 40% of tolvaptan-treated patients having reached normal sodium levels compared to 13% of placebo-treated in SALT-1 and 55% vs 11% in SALT-2[284]. The urine ouput was significantly higher in the tolvaptan group (mean 3218 ml on day 1) compared to the placebo group (mean 2076 ml on day 1). Regarding clinical outcomes, scores on the Physical Component Summary did not differ significantly, but scores on the Mental Component Summary improved in the tolvaptan group in the combined analysis ($P = 0.02$) and in SALT-1 ($P = 0.04$), but not in SALT-2 ($P = 0.14$). Finally, the rate of serum sodium correction exceeded the safe limit of 12 mmol/l/day only in 4 out of 223 (1.8%) patients, with no cases of osmotic demyelination syndrome being recorded[284]. The results of these studies provided the basis for tolvaptan appproval by regulatory authorities across the world.

Verbalis et al undertook a subgroup analysis of SIADH patients recruited in SALT-1 and SALT-2 studies, comparing 58 patients randomised to tolvaptan and 52 cases randomised to placebo[285]. SIADH patients on tolvaptan exhibited a highly significant ($P < 0.001$) improvement in serum sodium value in comparison to placebo on day 4 (mean serum Na change 5.3 vs 0.5 mmol/l) and on day 30 (mean serum Na change

8.1 vs 1.9 mol/l). Also on day 4, restoration of normonatraemia was observed in 60% of tolvaptan-treated subjects vs 11.5% of placebo-treated patients. Of note, withdrawal of tolvaptan resulted in return of serum sodium to baseline levels within 7 days. Over the first 24 hours, the tolvaptan group had significantly larger mean urine output (3057 vs 1758 ml) and larger fluid intake (2016 vs 1563 ml) than placebo, contributing to net fluid losses almost 5 times greater than the placebo group (1109 vs 220 ml)[285]. The commonest side-effects of tolvaptan were thirst (18%) and dry mouth (16%). Only 5.9% of SIADH tolvaptan-treated patients exceeded recommended correction limits of serum Na increase > 12 mmol/l over the first 24 hours or > 18 mmol/l over the first 48 hours. Finally, over the 30-day study period, the tolvaptan group experienced significantly greater improvement in mean Physical Component Score than placebo, while a difference in Mental Component Score approached, but did not reach, statistical significance (P=0.051)[285].

SALTWATER was a multicentre, open-label extension of SALT-1 and SALT-2 studies, including a total of 111 hyponatraemic patients being treated with tolvaptan for a mean follow-up of 701 days[286]. The proportion of normonatraemic patients remained stable throughout the study, suggesting that tolvaptan retained its efficacy without associated significant toxicity for treatment duration as long as 4 years[286].

A recent multi-centre, randomised, double-blind, placebo-controlled trial evaluated the efficacy of tolvaptan in the treatment of Chinese patients with SIADH[287]. The sample size was much smaller than SALT-1 and SALT-2 studies, recruiting 19 patients on tolvaptan arm with a mean baseline Na of 127.1 mmol/l and 18 patients on placebo arm with a mean starting Na of 125.3 mmol/l. In line with the findings of other RCTs, the mean increase of serum sodium concentration from baseline to day 4 was 8.4 mmol/l in the tolvaptan group in comparison to 3.3 mmol/l in the placebo

group (P < 0.001), confirming that tolvaptan is superior to placebo in correcting hyponatraemia in SIADH patients[287].

In contrast to previous studies with very heterogeneous cohorts, a similar single-centre, randomised, double-blind, placebo-controlled trial assessed the efficacy and safety of tolvaptan in adult hyponatraemic patients (serum Na 125-130 mmol/l) and cancer[288]. This study demonstrated superiority of tolvaptan versus placebo since the primary endpoint of achieving normonatraemia was met by 16 of 17 patients who received tolvaptan and by 1 of 13 patients who received placebo (94% vs 8%; P < 0.001). In addition, no cases of overly rapid correction of serum sodium (defined by > 12 mmol/l/day) was noted in the tolvaptan group[288].

Jaber et al undertook a meta-analysis of 11 randomised controlled trials conducted until 2011, including 1,094 patients, that examined the efficacy and safety of vaptans in treating hyponatraemia[289]. Besides the SALT-1 and SALT-2 studies of tolvaptan, they included studies on conivaptan, lixivaptan and satavaptan. The meta-analysis concluded that use of vaptans resulted in a net increase of serum Na concentration by a mean of 3.3 mmol/l relative to the control group on day 1, 4.2 mmol/l on day 2 and 5.7 mol/l on day 5. Noteworthy, use of vaptans was associated with a 3-fold increase in the odds for overly rapid correction of serum Na compared to placebo[289].

A similar meta-analysis published in 2010 included 15 randomised controlled trials, comparing vaptans versus placebo with or without fluid restriction[290]. Vaptans significantly increased early response rate, defined as normalisation or increase of serum Na by ≥ 5 mmol/l after 5 days of treatment, and led to a significantly larger increase in serum Na levels with a mean difference of 5.3 mmol/l compared to the control group on day 5. Also the rate of overly rapid correction of hyponatraemia was

higher than in control group (relative risk of 2.5), but no cases of ODS were reported[290].

Another meta-analysis was published in 2017 with 18 randomised placebo-controlled trials meeting eligibility criteria, including 9 studies of tolvaptan and the remaining 9 assessing conivaptan, lixivaptan or satavaptan[291]. Patients randomised to vaptans were significantly more likely to experience a response, defined as an increase in serum Na ≥ 5 mmol/l or achievement of normonatraemia, compared to placebo, with tolvaptan showing the largest treatment effect (relative risk 3.3)[291].

There is a paucity of data about comparing the therapeutic effects of vaptans versus an alternative pharmacological agent. Soupart et al studied 12 hyponatraemic patients (mean serum sodium 125 mmol/l) with SIADH, who were initially treated with vaptans, 10 with satavaptan and 2 with tolvaptan, for 1 year[265]. Subsequently they had an 8-day drug holiday period which was followed by 1-year treatment with urea. This study demonstrated similar efficacy and comparable good tolerability for both medications, with vaptans and urea restoring normonatraemia in around 70% of participants[265].

Finally, the results of the first tolvaptan study with primary endpoint being patient-important outcomes were recently published. The Investigation of the Neurocognitive Impact of Sodium Improvement in Geriatric Hyponatraemia: Efficacy and Safety of Tolvaptan (INSIGHT) was a multicentre, randomised, double-blind, placebo-controlled, parallel group, titration-to-effect trial[292]. Among 56 patients with chronic euvolaemic or hypervolaemic hyponatraemia, 29 patients were randomised to tolvaptan and 27 patients to placebo. Mean serum sodium levels increased from 129 to 136 mmol/l in the tolvaptan group and from 130 to 132 mmol/l in the placebo

group (P < 0.001). No tolvaptan-treated patients exhibited overly rapid correction of hyponatraemia. This study did not detect statistically significant difference in the overall neurocognitive composite score of speed domains between two groups. In specific, reversal of hyponatraemia following tolvaptan therapy correlated with a statistically significant improvement in psychomotor speed domain, as assessed by the tapping test. The tolvaptan group showed a trend for improvement in reaction time (including choice reaction time, digital vigilance, simple reaction time) and processing speed domain (including numeric working memory, rapid visual information processing, word recognition), but it did not reach statistical significance[292]. The results for measures of gait and stability were divergent, since Romberg test and ‘’Timed Up and Go’’ test favoured tolvaptan, while Postural Stability score favoured the placebo group. With regards to the potential effect of tolvaptan on bone markers, concentration of osteocalcin (bone formation marker) increased and NTx-creatinine ratio (bone resorption marker) decreased to a greater extent in tolvaptan group than placebo, but these differences did not reach statistical significance. However, bone resorption index, defined as change from baseline in urine NTx-creatinine ratio divided by serum osteocalcin concentration, showed a highly significant decrease in the tolvaptan group compared to the placebo group. This striking improvement in resorptive index after only 22 days of hyponatraemia correction with tolvaptan indicates that long-term treatment of hyponatraemia could potentially reverse hyponatraemia-induced resorptive bone loss. In conclusion, this pilot study demonstrated that tolvaptan, by correcting hyponatraemia, may result in improvement of rapid motor movemements and reversal of resorptive bone loss[292]. However, it remains to be proved whether tolvaptan can reduce falls, increase bone mineral density or lower the fracture rate.

Hepatotoxicity of tolvaptan

In April 2013, the FDA issued a caution that tolvaptan-related hepatic injury had occurred in some patients being treated with tolvaptan in the TEMPO 3:4 trial, a multicentre, double-blind, placebo-controlled, 3-year trial, examining the effect of tolvaptan on ADPKD[276]. In the TEMPO 3:4 trial, 957 patients were randomly assigned to tolvaptan and 484 patients to placebo. The incidence of elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels greater than three times the upper limit of normal was significantly higher in tolvaptan-treated ADPKD patients (4.4% and 3.1% respectively) compared with 1.0% and 0.8%, respectively, in the placebo group[276]. More importantly, an external panel of liver experts reviewed all tolvaptan-treated participants in TEMPO 3:4 trial as well as in its open-label extension study and identified 3 cases of severe liver injury and jaundice which were probably or highly likely caused by tolvaptan and were reversed on discontinuation of tolvaptan. These 3 cases met criteria for Hy's Law (ALT > 3 times the upper end of normal range and serum bilirubin > 2 times the upper end of normal range), indicating that tolvaptan has the potential to cause hepatic injury capable of progressing to liver failure in patients with ADPKD. In total, there were no reports of liver failure and all subjects experiencing hepatic injury recovered[293]. Based on these adverse events reported in the TEMPO trial, the FDA recommended that tolvaptan treatment should be stopped if the patient develops signs of liver disease, while its treatment duration should be limited to 30 days or less with its use being avoided in patients with underlying liver disease, such as cirrhosis. The EMA also issued a warning about the possible occurrence of hepatic injury in patients treated with tolvaptan, but it did not recommend any restriction on the duration of treatment of SIADH patients with tolvaptan. The pathophysiology of

tolvaptan-induced hepatotoxicity is unclear, but a recent in vitro study using human hepatic cells suggested that the cytotoxicity of tolvaptan results from delayed cell cycle progression which was accompanied by decreased levels of several cyclins and cyclin-dependent kinases, the induction of DNA damage, and the execution of apoptosis[294].

Three important points should be noted with respect to the potential hepatotoxicity of tolvaptan. First, the average tolvaptan dose in the TEMPO study of 95 mg per day was much higher than the doses used for SIADH (15-30 mg per day). Second, the earliest case of serious liver damage was reported 3 months after starting tolvaptan treatment, indicating that liver toxicity is unlikely to occur with short-term use[276 293]. Third, cases of liver damage were not reported in clinical trials of tolvaptan treatment for euvolaemic or hypervolaemic hyponatremia, including long-term trials, such as SALTWATER[286] and EVEREST[266] trials. Also tolvaptan has been approved and is still used in Japan in cirrhotic patients with insufficient response to conventional diuretics with post-marketing surveillance data from 463 patients showing a good safety profile[269]. The absence of a liver safety signal in non-ADPKD patients treated with tolvaptan for hyponatraemia, including patients with heart failure or pre-existing cirrhosis, may suggest enhanced susceptibility of the ADPKD population to tolvaptan-associated liver injury[293]. Therefore, the rarity of hepatic injury observed with tolvaptan has all the characteristics of an idiosyncratic reaction, suggesting that the vast majority of patients should be able to receive long-term treatment without risk of liver injury.

The analysis of adverse events in the REPRISE trial was published in November 2017, including 681 tolvaptan-treated and 685 placebo-treated participants with

ADPKD and eGFR 25-65 ml/min/1.73 m²[279]. It found that ALT elevations that exceeded three times the upper limit of the normal range occurred in 5.6% of patients receiving tolvaptan, as compared with 1.2% of those receiving placebo. All these elevations started approximately 2-3 months after tolvaptan initiation, continued for the 12-month trial period and returned to normal after the interruption or discontinuation of treatment. No patients met Hy'w law criteria, possibly because of monthly monitoring of liver function tests and earlier interruption of tolvaptan, when indicated[279].

Verbalis et al suggest that appropriate caution should be exercised in patients treated with tolvaptan for hyponatremia for extended periods, longer than 30 days, but this decision should be based upon the clinical judgment of the treating physician[152]. Patients who are refractory to or unable to tolerate or obtain other therapies for hyponatraemia, and in whom the benefit of tolvaptan treatment outweighs the risks, remain candidates for long-term therapy with tolvaptan. In such cases, liver function tests should be monitored serially, probably every 4 weeks, and the drug should be discontinued in the event of significant changes in liver function tests, such as ALT elevation above two times the upper end of normal range[152]. With rare exceptions, tolvaptan should not be used in patients with underlying liver disease given the difficulty of attributing causation to any observed deterioration of hepatic function.

Low dose tolvaptan studies

In light of the high therapeutic potency of tolvaptan, concerns have been raised that the lowest formally approved dose of 15 mg/day may lead in some cases to overly rapid correction of hyponatraemia, thereby exposing patients at the risk of developing ODS. There is some evidence that low doses tolvaptan are effective when used for indications other than hyponatraemia, especially as an adjunct to standard treatment in symptomatic heart failure. For example, tolvaptan doses, as low as 3.75 mg/day, were added to conventional treatment in patients with heart failure and hypoalbuminaemia and led to significant increase in diuresis as well as improvement of heart failure symptoms[295]. Another prospective study of the effect of low tolvaptan dose on 22 patients with chronic heart failure and excess fluid retention demonstrated that short-term treatment with tolvaptan 7.5 mg/day increased daily urine output, reduced body weight by a mean of 2.7 kg and improved haemodynamic parameters[296].

By the time our real-world study on the efficacy and safety of tolvaptan for the treatment of severe SIADH was conducted, the only published data about the use of low dose tolvaptan for hyponatraemia treatment were derived from a small case series. Kenz et al examined the efficacy and safety of 7.5 mg, half the starting tolvaptan dose recommended by drug manufacturers, in 13 patients with paraneoplastic SIADH and baseline serum sodium concentration ranging from 110 to 126 mmol/l[297]. Apart from 2 patients requiring uptitration of tolvaptan dose, the remaining 11 out of 13 patients achieved normonatraemia under alternate day treatment with 7.5 mg tolvaptan. Of note, safe limits of sodium correction were not exceeded in any cases. These data provided the first evidence that lower than

suggested tolvaptan doses may be an effective and safe treatment for, at least paraneoplastic, SIADH[297].

Real-life tolvaptan studies

Although numerous studies have confirmed the efficacy of tolvaptan for the treatment of euvolaemic and hypervolaemic hyponatraemia, very little data existed about the effectiveness and safety of tolvaptan in a real-life clinical setting at the time we collected our real-world data in 2014. Rajendran et al published in 2012 the first consecutive retrospective clinical case series study which included 15 therapeutic episodes with tolvaptan for SIADH in a single centre from the United Kingdom[298]. Participants had a mean baseline serum Na of 120.1 mmol/l, including 5 subjects with serum Na ≤ 120 mmol/l (range 108-117 mmol/l) and 10 subjects with serum Na 121-126 mmol/l. Tolvaptan therapy led to a mean serum Na increase of 6.7 mmol/l in the first 24 hours and 9.6 mmol/l in the first 48 hours following tolvaptan administration. No patient exceeded the safe limit of 12 mmol/l in 24 hours or 18 mmol/l in 48 hours. These real-world data suggested that tolvaptan appears to be a safe and efficacious therapy for the treatment of hospitalised patients with hyponatraemia due to SIADH[298].

Cost-effectiveness of tolvaptan

Taking into account that the annual direct costs of treating hyponatraemia in the United States have been estimated to range between $1.6 and $3.6 billion, with hospitalisation accounting for approximately 70% of the total costs[143], it is essential to evaluate the impact of tolvaptan use on the costs associated with this condition. Findings from cost-effectiveness analysis will influence the extent of tolvaptan use for the treatment of SIADH in routine clinical practice. A post hoc analysis of SIADH patients enrolled in SALT-1 and SALT-2 trials revealed a trend towards a reduced length of stay in the tolvaptan group (mean 4.98 days) compared to the placebo group (mean 6.19 days)[285]. Based on these data and using the Healthcare Cost and Utilisation Project 2009 Nationwide Inpatient Sample database in order to estimate hospital cost and length of stay for hospitalisations of adults with SIADH, Dasta et al constructed a cost-offset model to evaluate the impact of tolvaptan on hospital cost and length of stay[299]. This cost-offset model demonstrated that, despite the incremental cost of tolvaptan therapy, tolvaptan use resulted in an estimated mean $694 cost savings per admission amongst SIADH patients in the US[299].

In 2014 a cost-effectiveness study evaluated the economic impact of tolvaptan treatment in South Korean patients who need to be hospitalised for treatment of euvolaemic or hypervolaemic hyponatraemia[300]. Data with respect to the efficacy of treatment were derived from SALT-1 and SALT-2 trials, while cost analysis was performed from the perspective of the South Korean health care setting in 2012 Korean won (KRW). The model outcome was the incremental cost per quality-adjusted life-year (QALY) gained per 1-month treatment period. The estimated total monthly cost per patient was equivalent to €1395 for tolvaptan treatment and €1743 for placebo, resulting in cost savings of €348. Also the quality-adjusted life-years

(QALY) for treatment with and without tolvaptan were 0.0481 and 0.0446, leading to a QALY gain per patient of 0.0035. This cost-effectiveness analysis found that the use of tolvaptan was less costly and more efficacious than treatment without tolvaptan in patients with euvolaemic or hypervolaemic hyponatraemia. In the subgroup analysis, this trend was more apparent in case of tolvaptan treatment only for patients with marked hyponatraemia (serum Na < 130 mmol/l)[300].

From the European perspective, the cost-effectiveness of tolvaptan for the treatment of hyponatraemia secondary to SIADH had never been studied prior to a publication in May 2016[301]. This study examined, from the societal perspective in Sweden, the cost-effectiveness of tolvaptan versus no active treatment in adult SIADH patients who either failed to respond to fluid restriction or for whom the use of fluid restriction was not suitable. The economic evaluation relied on evidence from the SALT-1 and SALT-2 trials[285], the Hyponatraemia Registry[302] and a population-based register study of the assessment of epidemiology, patient characteristics and outcomes related to patients with hyponatraemia/SIADH in Sweden. Noteworthy, this model assumed a reduction in length of stay of 20% derived from the overall reduction in length of hospitalisation observed in tolvaptan-treated patients versus placebo group in the SIADH population of the SALT studies[285]. In the general SIADH population, tolvaptan was associated with reduced costs (equivalent to €624 per patient) and increased quality-adjusted life-years (QALYs) (0.0019) compared with no active treatment and was therefore the dominant treatment strategy. This study provided evidence that tolvaptan represents a cost-effective treatment option in Sweden for hospitalised patients with hyponatraemia secondary to SIADH who have either failed to respond to or are unsuitable for fluid restriction[301].

Current therapeutic role of tolvaptan

The role of tolvaptan in the treatment of hyponatraemia due to SIADH has been the subject of great controversy, with tolvaptan having received different recommendations in recently published guidelines. On the one hand, an expert panel led by Verbalis recommends tolvaptan use as second-line therapy for SIADH patients with mild to moderate symptoms when patients do not respond to or cannot tolerate fluid restriction[152]. Verbalis et al also suggest that tolvaptan can be considered as first-line therapy for SIADH in selected cases with very little solute-free water excretion, when biochemical parameters, such as high urine osmolality > 500 mOsm/kg H2O or high urine / plasma electrolyte ratio > 1, predict high likelihood of failure of fluid restriction[152]. Of note, hypertonic saline, and not tolvaptan, remains the treatment of choice in hyponatraemic patients with severe symptoms, at least, until more evidence-based data are available. With regards to long-term treatment with tolvaptan on outpatient basis, factors, such as affordability and the high tolvaptan cost to the patient and healthcare system as well as the potential for liver damage, must be weighed against potential benefit and response to alternative treatment modalities[152].

On the other hand, recently published European guidelines do not recommend the use of tolvaptan for the treatment of SIADH[154]. The rationale is that, besides the well-recognised increase in serum sodium concentration, tolvaptan has no proven benefit with regards to important clinical outcomes, such as mortality, coma, seizures, cognitive function, quality of life and length of hospitalisation. With respect to safety concerns, tolvaptan is associated with increased risk for overly rapid correction of hyponatraemia and can rarely cause hepatotoxicity. Therefore, the European guideline development group considers the risk benefit ratio to be negative. In fact,

they recommend against tolvaptan use in individuals with serum sodium < 125 mmol/l, as the risk of too rapid correction is greater with lower baseline serum sodium values[154].

In the absence of high quality evidence on the optimal treatment strategy in the management of SIADH, the current place of vaptans in the therapeutic armamentarium for treating SIADH is heavily influenced by expert opinions. For example, Lehrich and Greenberg firstly stated in 2008 that vaptans are likely to offer an ideal treatment option for patients with chronic euvolaemic or hypervolaemic hyponatraemia because they specifically target the pathophysiologic derangement[303]. In the issue of the Journal of the American Society of Nephrology where the results of the SALTWATER study were published, an editorial by Greenberg and Lehrich titled ‘’Treatment of chronic hyponatraemia: Now we know how, but do we know when or if?’’ highlighted that, for now, clinicians must rely on good judgment rather than unequivocal evidence to decide which patients with chronic hyponatraemia should be given tolvaptan[304]. The reason is that landmark studies, including SALT and SALTWATER studies, have provided high quality evidence that tolvaptan is effective in correcting hyponatraemia. However, the success of these studies which were not designed or powered to assess improvement in symptoms or survival raises the key unanswered question whether treatment of hyponatraemia can improve hard end points[304]. In 2013, Alessandro Peri published an excellent review of the use of vaptans in clinical endocrinology, stating that vaptans are a valuable option either as second line agent, following failure of fluid restriction, in SIADH patients with mild to moderate symptoms or as first line agent, instead of fluid restriction, in SIADH patients with very limited renal excretion of solute-free water[273]. According to a review of vasopressin antagonists by

Tomas Berl published at the New England Journal of Medicine in 2015, vaptans are effective, safe, and simple to use for the short-term treatment of patients with mild to moderate symptoms due to euvolaemic or hypervolaemic hyponatraemia[305]. However, vaptans have no role in symptomatic patients with acute hyponatraemia[306]. Regarding long-term use of tolvaptan, Tomas Berl's expert opinion was that the risk-benefit balance favours the use of tolvaptan in patients with irreversible euvolaemic hyponatraemia who have a gait disturbance or a history of falls and who do not respond to water restriction[305]. In another review of vaptans by Gross, Wagner, and Decaux published in 2011, it was highlighted that there is considerable uncertainty as to which symptoms, which setting, and what degree of severity of hyponatraemia should be considered indications for vaptan treatment[307]. Also they concluded that vaptans cannot constitute, yet, the mainstay of therapy in hyponatraemia and emphasised the need for prospective studies assessing whether vaptans can save lives or, at least, money[307]. In the most recent review published in May 2017, Hoorn and Zietse expressed their view that an unresolved question with regards to the use of vaptans remains, of whether the potential symptomatic improvement outweighs the risk of overly rapid sodium correction, even considering that ODS is rare[252]. In conclusion, it still remains difficult to position vaptans in the therapeutic arsenal of hyponatraemia.

Finally, tolvaptan has attracted considerable interest from oncologists who have been increasingly using it in various contexts. A prospective case series of 10 tolvaptan-treated patients with small cell lung cancer and severe SIADH (serum Na < 125 mmol/l) showed that tolvaptan led to a rapid correction and stabilisation of serum sodium levels[308]. As a result, tolvaptan therapy significantly improved the ECOG (Eastern Cooperative Oncology Group) performance status, allowing prompt

initiation of platinum based chemotherapy[308]. Thus, tolvaptan is prescribed very often in patients where the treatment of malignancy causing SIADH requires an immediate start of chemotherapy that cannot be administered without concomitant infusion of large fluid volumes or in patients who need to start chemotherapy with drugs which can worsen hyponatraemia, such as platinum-based agents, cyclophosphamide, vincristine or etoposide. As a result, tolvaptan can facilitate the administration of chemotherapy cycles in a timely manner, which in turn can improve patient's prognosis and survival[309]. Other potential indications in the context of malignant SIADH are relief of hyponatraemic symptoms in the palliative setting as well as reduction of hospitalisation, decrease in the number of emergency visits and prevention of readmissions in the scenario of recurrent symptomatic hyponatraemia[309]. Interestingly, NHS England published in December 2016 its clinical commissioning policy regarding the use of tolvaptan, according to which routine commissioning of tolvaptan is restricted only to patients with malignant SIADH who have serum Na 125-135 mmol/l and whose hyponatraemia due to SIADH delays chemotherapy.

Safe use of tolvaptan

In order to minimise the risk of overly rapid hyponatraemia correction, the FDA and EMA have reinforced recommendations that tolvaptan should be initiated only in a hospital setting where fluid balance and electrolytes can be monitored closely. Also they have warned against concomitant use of other active treatments for hyponatraemia, such as fluid restriction, in order to avoid too rapid correction of serum sodium[273]. In addition, vaptans should not be used immediately after other treatments for hyponatraemia with high potency, especially hypertonic saline. Patients should be clearly advised to maintain ad libitum fluid intake, allowing their thirst to compensate for an overly vigorous aquaresis and helping to avoid overly rapid hyponatraemia correction[152]. As pre drug label, the starting dose of tolvaptan is 15 mg on the first day, and the dose can be titrated to 30 mg and 60 mg at 24-hour intervals if serum Na remains < 135 mmol/l or the increase in serum Na has been < 5 mmol/l in the previous 24 hours. It is essential to measure frequently, at a minimum of 6-hour intervals, serum Na concentration during the active phase of hyponatraemia correction, especially during the first 24-48 hours after initiating treatment. Fluid intake and urine output should also be monitored closely since brisk aquaresis can indicate too rapid correction of serum sodium levels, necessitating more vigilant electrolyte monitoring and prompting the clinician to consider replacing or stopping further water losses[152].

Once the targeted daily serum Na increase of 6-8 mmol/l has been achieved, appropriate measures should be taken in order to prevent overcorrection. In addition to withholding temporarily tolvaptan therapy, further correction from urinary free water losses for the rest of the day should be prevented either by replacing losses with 5% dextrose in water or, in case of very brisk aquaresis, by terminating further

urinary losses by administering 2-4 mcg of desmopressin parenterally. If serum sodium correction exceeds therapeutic limits, therapeutic re-lowering of serum sodium can be considered. It can be achieved by administering 2-4 mcg of desmopressin in combination with repeated infusions of 5% dextrose in water, under close electrolyte monitoring and until serum Na reaches the desired value within the safe correction limit[152].

Clinicians should be aware of and always take into account tolvaptan drug interactions, prior to initiating tolvaptan therapy. Since tolvaptan is metabolised by cytochrome CYP3A4, great caution should be exercised in case of co-administration of CYP3A4 inhibitors (such as ketoconazole, macrolide antibiotics, diltiazem) or inducers (such as rifampicin, barbiturates), which increase or reduce serum concentrations of vaptans, respectively[273]. For example, concomitant administration of 30 mg tolvaptan with ketoconazole, a potent CYP3A4 inhibitor, increased tolvaptan concentrations by approximately five-fold, while the increase in 24-hour urine volume was disproportionate, only 1.3-fold[310]. The reason for this discrepancy is the saturable nature of tolvaptan's effect on urine excretion rate, explaining why changes in the pharmacokinetic profile of tolvaptan do not produce proportional changes in urine output. The overall effect of tolvaptan and ketoconazole co-administration would be similar to the effects observed following high doses of tolvaptan, namely that as plasma concentrations remain elevated for longer periods of time, the duration that urine excretion rate will remain elevated is increased but the maximum urine excretion rate will not be increased[310]. Therefore, current labelling for tolvaptan contraindicates concomitant use with strong CYP3A4 inhibitors and recommends avoiding use with moderate inhibitors.

Chapter 2

A case-control study of mortality in hospitalised patients with hyponatraemia

2.1 Materials and methods

2.2 Results

2.3 Conclusions

2.4 Summary of main findings

2.1 Materials and methods

2.1.1 Study rationale

The rationale behind this study was that, by eliminating the influence of more confounders than previous case-control studies, it could shed further light on the possible independent contribution of hyponatraemia to excess mortality. In order to achieve this, we took the unprecedented step of recruiting for each case two controls matched for age, gender, nature of underlying illness, date of admission and provider of medical / nursing care. The hypothesis was that, if cases and controls did not differ in all these variables and hyponatraemic patients still had significantly higher mortality rate than controls, this would demonstrate an independent association of hyponatraemia with excess inpatient mortality.

2.1.2 Aims and objectives

The aim of this study was to compare the inpatient mortality rate of patients with serum Na ≤ 128 mmol/l vs controls matched by age, gender and residing hospital ward.

The secondary objectives were:

- To compare the in-hospital mortality rate between patients with hyponatraemia at admission and subjects with hospital-acquired hyponatraemia.

- To analyse the causes of death and the potential contribution of hyponatraemia in fatal hyponatraemic cases.

2.1.3 Study design

This was a single-centre, prospective, case-control study, examining patient outcomes in a real-life setting, which included all hospitalised patients with severe biochemical hyponatraemia at the Royal Free Hospital over a 3-month period (1st March 2013 to 31st May 2013). For the purpose of this study, severe hyponatraemia was defined as having at least 1 value of serum Na ≤ 128 mmol/l at any stage during hospitalisation.

The Royal Free Hospital, a major teaching hospital located in London, has around 900 beds. Besides all branches of medicine and surgery, our institution is a major centre for liver, kidney and bone marrow transplantation. It also has a large renal unit serving the whole of north London and provides specialist services including HIV, infectious diseases and plastic surgery.

The study was registered with the Clinical Governance & Clinical Audit Department of the Royal Free Hospital.

2.1.4 Sodium measurement

The instrument for sodium measurement at our laboratory used the technique of indirect ion potentiometry. Subjects with severe hyperglycaemia had their serum Na corrected for the degree of hyperglycaemia because of the phenomemon of translocational hyponatraemia and were included in the study only if their corrected serum Na was ≤ 128 mmol/l. If venous glucose was elevated, but did not exceed 22.2 mmol/l, serum Na was corrected by 1.6 mmol/l for every 5.6 mmol/l increase of glucose levels above 7 mmol/l[151]; if glucose was > 22.2 mmol/l, a correction factor of 2.4 mmol/l was used[150]. Noteworthy, serum protein concentration was not taken into consideration to correct Na results, regardless of hypoproteinaemia or hyperprotainaemia.

2.1.5 Cases

Cases were adult (> 18 years old) inpatients under any speciality with at least one value of serum Na ≤ 128 mmol/l during hospitalisation, regardless of whether they presented with hyponatraemia on admission or developed it during hospitalisation. The cut-off of 128 mmol/l was selected because preliminary data from this hospital cohort showed an upward inflection in inpatient mortality below that threshold. Subjects aged < 18 years old as well as outpatients or patients admitted for < 24 hours as day cases (for example individuals undergoing chemotherapy, haemodialysis, minor surgical procedures) were excluded. Patients having more than one hospital admission with serum Na ≤ 128 mmol/l over the study period were recorded only once and their data for the first episode of hospitalisation were analysed.

2.1.6 Controls

For each case recruited, we identified 2 control subjects of the same gender and similar age (within a range of ± 5 years) who stayed in the beds nearest to the case at the same hospital ward. This process of selection of controls was chosen in order to increase the probability that, apart from being matched by age, gender and hospitalisation date, cases and controls received care from the same medical and nursing team, were managed by the same speciality and had similar type of pathologies.

At the time of recruiting controls, the investigators were blinded to their serum Na concentration and gained access to these data only after hospital discharge in order to ensure that controls would accurately reflect hospital population with respect to serum Na levels. Amongst these subjects, some developed serum Na value ≤ 128 mmol/l, becoming ‘cases’ for the purpose of data analysis, and were no further considered ‘controls’. Controls were then classified into three subgroups: normonatraemic controls who remained constantly normonatraemic (all serum Na values 135–145 mmol/l) throughout admission, patients who developed mild to moderate hyponatraemia without reaching the cut-off value of 128 mmol/l for serum Na concentration (lowest serum Na value 129–134 mmol/l) and patients who developed hypernatraemia (serum Na > 145 mmol/l).

2.1.7 Data collection

The investigators were provided with a list of all patients with serum Na 128 ≤ mmol/l on daily basis through a computerised system developed by the Biochemistry Department. After cases and controls were discharged from the hospital, their case notes, prescription charts, discharge letters and laboratory results were reviewed.

Data were collected on age, gender, diagnosis and the speciality team responsible for patient care on the day of inclusion in the study. Data for all individuals were recorded for the presence / absence of 17 common comorbid conditions with significant health burden and for the use of 13 different classes of drugs within the last 5 days prior to the date of study inclusion. Those drugs, besides thyroxine and glucocorticoids, were chosen on the basis that they could cause hyponatraemia. For each patient, data were collected about: serum creatinine on admission; serum Na on admission; serum Na on discharge; lowest serum Na during hospital stay; median serum Na value during hospital stay; period in days of exposure to serum Na ≤ 128 mmol/l. The duration of hospital stay and admission in intensive care unit (ICU) were recorded. Data about the blood volume status and cause of hyponatraemia were based solely on documentation in the case notes.

Finally, a detailed review of case notes and laboratory results of all fatal cases with severe hyponatraemia was carried out to determine the clinical course, the causes of death, the cause of hyponatraemia and the potential contribution of hyponatraemia to death.

2.1.8 Statistical analysis

Data were analysed using SPSS (version 21.0, Chicago, IL, USA). The skewed distribution of data imposed reporting the median and interquartile range (IQR) rather than the mean and standard deviation (SD). For serum Na values recorded at various time points, the median values with IQR were also chosen for data representation.

Univariate associations between subjects (cases / controls) and categorical variables such as comorbidities, drug use and mortality rate were determined by chi-squared test. Groupwise differences in continuous variables such as serum Na values were calculated with Mann–Whitney U-test. Univariate logistic regression models for the association of the study population (cases/controls) with comorbidities, medications, serum Na values and inpatient mortality rate enabled computation of ORs (odds ratios) with 95% CIs (95% confidence intervals). A P value of 0.05 was considered significant.

2.2 Results

2.2.1 Cases: demographic characteristics and causes of hyponatraemia

One hundred thirty-nine cases (69 males, 70 females) with a median age (IQR) of 74 (59–82) years developed serum Na ≤ 128 mmol/l over the 3-month study period. Amongst 139 cases, 14 subjects had more than 1 admissions with inpatient hyponatraemia.

Of note, clinical assessment of volume status was recorded in 86 (61.9%) of cases, while the aetiology of hyponatraemia was documented in only 58 subjects, an even smaller proportion (41.7%). The distribution of cases according to the documented aetiology of hyponatraemia is shown in Table 3. Among 4 recorded cases of malignant SIADH, 3 were attributed to small cell lung cancer and 1 to prostate cancer. SIADH due to various causes included 1 drug-induced case related to mirtazapine, 1 case of haemophagocytic lymphohistiocytosis and 1 case of influenza. Finally, miscellaneous causes included 1 case of excess water intake and 1 of bladder irrigation.

Table 3. Classification of cases according to documented aetiology

Aetiology	**N=58 (%)**
Hypovolaemic	**27 (46.6%)**
Diuretics	14 (24.1%)
Gastrointestinal Na losses	8 (13.9%)
Poor oral intake	5 (8.6%)
Euvolaemic	**18 (34.5%)**
SIADH† due to pneumonia	6 (10.3%)
SIADH of unknown cause	5 (8.6%)
Malignant SIADH	4 (6.9%)
SIADH due to various causes	3 (5.2%)
Miscellaneous causes	2 (3.5%)
Hypervolaemic	**11 (18.9%)**
Decompensated liver disease	6 (10.3%)
Heart failure	5 (8.6%)

†SIADH: Syndrome of inappropriate antidiuretic hormone secretion

2.2.2 Controls: demographic characteristics and subgroups

By study design, the case:control ratio was 1:2. As a result, 278 individuals were recruited to become controls, amongst whom 24 were excluded either because they developed sufficiently severe hyponatraemia to become ‘cases’ or because they were admitted for less than 24 hours. Thus, data were finally analysed for 254 controls (131 males, 123 females) with a median age (IQR) of 72 (60–80) years.

These controls were further classified into 3 subgroups: 116 controls (45.7%) remained constantly normonatraemic throughout their admission (serum Na 135–145 mmol/l), 72 controls (28.3%) developed mild hyponatraemia (lowest serum Na value 129-134 mmol/l) and 66 controls (26.0%) at some point developed hypernatraemia (serum Na > 145 mmol/l).

2.2.3 Comparison between cases and controls: speciality distribution, frequency of comorbidities and drug use

Cases and controls had similar distribution to specialities, as expected in line with the protocol of control recruitment (Table 4). There was a wide distribution of cases to different specialities with 77.0% under the care of medical specialities and 19.4% under the care of surgical specialities. The relatively large percentages of patients under the care of Hepatology (14.4%), Oncology (8.6%), Renal (5.0%) and Hepatobiliary Surgery (2.9%) reflected the specialist services our institution offers.

With respect to the prevalence of various comorbidities, no statistically significant difference was detected, as illustrated in Table 5. In terms of drug use, the only statistically significant difference found was related to the frequency of glucocorticoid use which was lower in hyponatraemic patients compared with controls, as per Table 6.

Table 4. Speciality distribution of cases and controls

Specialities	**Cases**		**Controls**	
	N=139	(%)	N=254	(%)
Medical Specialities	**107**	**(77.0%)**	**189**	**(74.4%)**
Care of the Elderly	23	(16.5%)	44	(17.3%)
Hepatology	20	(14.4%)	22	(8.7%)
General Medicine	19	(13.7%)	28	(11.0%)
Oncology	12	(8.6%)	15	(5.9%)
Cardiology	8	(5.8%)	14	(5.5%)
Neurology	7	(5.0%)	19	(7.5%)
Renal	7	(5.0%)	14	(5.5%)
Gastroenterology	4	(2.9%)	5	(2.0%)
Respiratory	3	(2.2%)	10	(3.9%)
Haematology	3	(2.2%)	12	(4.7%)
Infectious Diseases	1	(0.7%)	4	(1.6%)
Rheumatology	0	(0.0%)	2	(0.8%)
Surgical Specialities	**27**	**(19.4%)**	**60**	**(23.6%)**
Orthopaedics	8	(5.8%)	11	(4.3%)
General Surgery	6	(4.3%)	10	(3.9%)
Hepatobiliary	4	(2.9%)	18	(7.1%)
Urology	4	(2.9%)	10	(3.9%)
Vascular	3	(2.2%)	8	(3.1%)
Plastics	1	(0.7%)	1	(0.4%)
Obstetrics/Gynaecology	1	(0.7%)	2	(0.8%)

Various	**5**	**(3.6%)**	**5**	**(2.0%)**
ICU	3	(2.2%)	3	(1.2%)
A+E	2	(1.4%)	2	(0.8%)

Table 5. Prevalence of common comorbidities in cases and controls.

Comorbidities	**Cases**		**Controls**		**OR**	**95%CI**		**P value**
	N=139	(%)	N=254	(%)				
Heart Disease	65	(46.8%)	108	(42.5%)	1.19	(0.78,	1.80)	0.418
Arrhythmia	35	(25.2%)	57	(22.4%)	1.16	(0.72,	1.89)	0.540
Heart Failure	30	(21.6%)	40	(15.7%)	1.47	(0.87,	2.49)	0.150
IHD†	29	(20.9%)	64	(25.2%)	0.78	(0.48,	1.29)	0.334
Stroke / TIA*	16	(11.5%)	42	(16.5%)	0.66	(0.35,	1.22)	0.182
Hypertension	70	(50.4%)	132	(52.0%)	0.94	(0.62,	1.42)	0.760
Diabetes	35	(25.2%)	76	(29.9%)	0.79	(0.49,	1.26)	0.319
CKD¥	30	(21.6%)	62	(24.4%)	0.85	(0.52,	1.40)	0.527
ESRD‡	10	(7.2%)	14	(5.5%)	1.33	(0.57,	3.08)	0.507
Lung Disease	40	(28.8%)	71	(28.0%)	1.04	(0.66,	1.65)	0.862
COPD**	18	(12.9%)	37	(14.6%)	0.87	(0.48,	1.60)	0.659
Liver disease	35	(25.2%)	50	(19.7%)	1.37	(0.84,	2.25)	0.207
Cirrhosis	23	(16.5%)	34	(13.4%)	1.28	(0.72,	2.28)	0.396
Dec cirrhosis§	20	(14.4%)	24	(9.5%)	1.61	(0.81,	3.12)	0.180
Active Cancer	34	(24.5%)	63	(24.8%)	0.98	(0.61,	1.59)	0.940
Depression	13	(9.4%)	31	(12.2%)	0.74	(0.37,	1.47)	0.393
Dementia	12	(8.6%)	26	(10.2%)	0.83	(0.40,	1.70)	0.608
Hypothyroidism	18	(12.9%)	34	(13.4%)	0.96	(0.52,	1.78)	0.903

† IHD: Ischaemic heart disease; * TIA: Transient ischaemic attack; ¥CKD: Chronic kidney disease; ‡ ESRD: End-stage renal disease; ** COPD: Chronic obstructive pulmonary disease; § Dec cirrhosis: Decompensated cirrhosis

Table 6. Frequency of drug use in cases and controls

Medications	**Cases**		**Controls**		**OR**	**95%CI**		**P value**
	N=139	(%)	N=254	(%)				
Loop diuretics	38	(27.3%)	71	(28.0%)	0.97	(0.61,	1.54)	0.896
K-sparing diuretic	19	(13.7%)	26	(10.2%)	1.39	(0.74,	2.61)	0.308
Thiazide diuretics	13	(9.4%)	23	(9.1%)	1.04	(0.51,	2.12)	0.922
ACE-i†	37	(26.6%)	47	(18.5%)	1.60	(0.98,	2.61)	0.062
ARBs*	17	(12.2%)	22	(8.7%)	1.47	(0.75,	2.87)	0.260
Opioids	40	(28.8%)	98	(38.6%)	0.64	(0.41,	1.00)	0.052
SSRIs¥	10	(7.2%)	32	(12.6%)	0.54	(0.26,	1.13)	0.102
Carbamazepine	1	(0.7%)	5	(2.0%)	0.36	(0.04,	3.12)	0.354
Tricyclics	9	(6.5%)	10	(3.9%)	1.69	(0.67,	4.26)	0.267
Antiepileptics	6	(4.3%)	8	(3.1%)	1.39	(0.47,	4.08)	0.552
PPIs‡	69	(49.6%)	142	(55.9%)	0.78	(0.51,	1.18)	0.234
Thyroxine	17	(12.2%)	34	(13.4%)	0.90	(0.48,	1.68)	0.745
Steroids	**13**	**(9.4%)**	**44**	**(17.3%)**	**0.49**	**(0.26,**	**0.95)**	**0.035**

† ACE-i: Angiotensin converting enzyme – inhibitor; * ARBs: Angiotensin receptor blockers; ¥SSRIs: Selective serotonin receptor inhibitors; ‡ PPIs: Proton pump inhibitors

Bold values denote statistical significance, $P < 0.05$

2.2.4 Comparison of mortality between cases and controls

The in-hospital mortality rate was significantly higher in cases (17.3%) compared with controls (5.9%; P < 0.01), with hyponatraemic patients more than three times as likely as controls to die during hospitalisation (OR 3.33, 95% CI 1.68-6.58). No statistically significant difference was observed between cases and controls with respect to age, gender, creatinine levels, ICU admission rate and length of hospital stay (Table 7).

Table 7. Serum Na values and outcomes in cases and controls

Variable	**Cases** N=139	**Controls** N=254	**P value**
Age (years)*	74 (59-82)	72 (60-80)	0.380
Gender (male:female)	69:70	131:123	0.397
Creatinine (umol/l)*	90 (67-142)	96 (68.7-139.2)	0.351
Admission Na (mmol/l)*	130 (126-134)	139 (136-141.2)	
Lowest Na (mmol/l)*	125 (122-127)	136 (133-138)	
Median Na (mmol/l)*	131 (128-133.5)	139.5 (137.5-141)	
Discharge Na (mmol/l)*	132 (128-136)	140 (137-142)	
ICU admission	15 (10.8%)	30 (11.8%)	0.450
ICU LOS‡ (days)*	10 (2-19)	7 (4-13)	0.717
LOS (days)*	12 (7-24)	15 (6-31)	0.195
Mortality	**24 (17.3%)**	**15 (5.9%)**	**<0.01**

* Expressed as median (interquartile range), ‡LOS: Length of stay

Bold values denote statistical significance, P < 0.05

2.2.5 Comparison of mortality between cases and normonatraemic controls

Another comparison was undertaken between cases and the subgroup of controls who remained constantly normonatraemic throughout their admission, including 116 subjects (54 males, 62 females) with a median age (IQR) of 71.5 (59–79.7) years. No statistically significant difference was recorded with respect to the presence of 17 common comorbid conditions and the frequency of use of various medications, with the exception of opioids being used less often in cases than normonatraemic controls (OR 0.57, 95% CI 0.34–0.96, P = 0.036). Other key variables such as age, gender distribution, serum creatinine and rate of ICU admission were similar between the groups, but cases had longer median duration of hospitalisation than normonatraemic controls (12 vs 8 days, P < 0.01), as shown in Table 8.

A statistically highly significant difference existed between mortality rate in cases (17.3%) and normonatraemic controls (1.7%) with an OR of 11.89 (95% CI 2.75–51.51, P < 0.01).

Table 8. Serum Na values and outcomes in cases and normonatraemic controls

Variable	**Cases** N=139	**Normonatraemic controls** N=116	**P value**
Age (years)*	74 (59-82)	71.5 (59-79.7)	0.180
Gender (male:female)	69:70	54:62	0.706
Creatinine (umol/l)*	90 (67-142)	89.5 (69.2-118)	0.974
Admission Na (mmol/l)*	130 (126-134)	140 (138-141)	**<0.01**
Lowest Na (mmol/l)*	125 (122-127)	137 (136-139)	**<0.01**
Median Na (mmol/l)*	131 (128-133.5)	140 (138.5-141)	**<0.01**
Discharge Na (mmol/l)*	132 (128-136)	140 (138-141)	**<0.01**
ICU admission	15 (10.8%)	7 (6.4%)	0.262
ICU LOS‡ (days)*	10 (2-19)	4 (2-10)	0.166
LOS (days)*	12 (7-24)	8 (4-18)	**<0.01**
Mortality	**24 (17.3%)**	**2 (1.7%)**	**<0.01**

* Expressed as median (interquartile range)

‡LOS: Length of stay

Bold values denote statistical significance, P < 0.05

2.2.6 Severity of biochemical hyponatraemia and mortality

All subjects recruited in this study, excluding 66 controls whose serum Na exceeded 145 mmol/l at some stage during hospitalisation, were classified into subgroups according to their nadir serum Na levels. The association of in-hospital mortality rate with magnitude of biochemical hyponatraemia is illustrated in Table 9. Of note, high in-hospital mortality rate (15.1%) was also recorded amongst 66 hypernatraemic controls with 10 fatalities during their hospital stay.

Table 9. Association between nadir serum Na value and mortality rate

Nadir sNa (mmol/l)	N = 327	Mortality
≤ 120	27	3 **(11.1%)**
121-125	60	13 **(21.6%)**
126-128	52	8 **(15.4%)**
129-134	72	3 **(4.2%)**
135-145	116	2 **(1.7%)**

2.2.7 Clinical outcomes of admission vs hospital-acquired hyponatraemia

With regards to the timing of onset of hyponatraemia, 61 patients (43.9%) were admitted with serum Na ≤ 128 mmol/l in comparison to 78 patients (56.1%) who developed severe hyponatraemia during hospitalisation with a median time between admission and onset of severe hyponatraemia of 4 days (IQR 3-10 days). No statistically significant difference was found in the mortality rate between patients with hyponatraemia on admission and hospital-acquired hyponatraemia (Table 10).

Table 10. Comparison of clinical outcomes between admission and hospital-acquired severe hyponatraemia

Variable	**Admission** **N=61**	**Hospital-acquired** **N=78**	**P value**
Age (years)*	74 (60.5 – 81)	74 (59 – 83)	0.753
Gender (male:female)	34:27	35:43	0.234
Creatinine (umol/l)*	89 (66-114.5)	90.5 (67-180.2)	0.248
Admission Na (mmol/l)*	125 (122-127)	134 (131-136)	**<0.01**
Lowest Na (mmol/l)*	124 (120-125)	125.5 (123-128))	**<0.01**
Median Na (mmol/l)*	129 (126.2-132.2)	132 (130.3-135)	**<0.01**
Discharge Na (mmol/l)*	132 (128-136)	132 (128-136)	0.682
ICU admission	4 (6.6%)	11 (14.1%)	0.179
LOS‡ (days)*	8 (6-17.5)	17 (8-29)	**<0.01**
Mortality	**9 (14.7%)**	**15 (19.2%)**	**0.652**

* Expressed as median (interquartile range), ‡LOS: Length of stay

Bold values denote statistical significance, P < 0.05

2.2.8 Analysis of fatal hyponatraemic cases

Amongst 139 hyponatraemic cases, 24 patients (13 males, 11 females) with a median (IQR) age of 75.5 (60.2–82.7) years died during hospitalisation. Dividing hyponatraemic cases according to the main clinical outcomes (in-hospital death or discharge), fatalities did not differ significantly from participants who survived in any parameter, apart from having longer hospital stay. At the time of death, the median (IQR) serum Na concentration was 135.5 (128 –142.5) mmol/l, with 41.7% of patients being hyponatraemic, 45.8% normonatraemic and 12.5% hypernatraemic, as shown in Table 11.

Table 11. Distribution of patients as per serum Na levels at the time of death

sNa (mmol/l) at time of death	**N=24**	**(%)**
≤ 125	2	(8.4%)
126 - 128	5	(20.8%)
129 - 134	3	(12.5%)
135 -145	11	(45.8%)
> 145	3	(12.5%)

The commonest primary causes of death were pneumonia (7 cases), metastatic malignancy (5 cases), liver cirrhosis (3 cases), decompensated heart failure (2 cases), myocardial infarction (2 cases), visceral perforation (2 cases), followed by single cases of acute kidney injury, stroke and cerebral vasculitis. Thorough chart review did not suggest any cases of direct contribution of hyponatraemia to death through severe hyponatraemic encephalopathy. In addition, no cases of osmotic demyelination syndrome (ODS) were documented in the case notes, but also no patients exhibited symptomatology or followed the classic biphasic clinical course, suspicious of ODS.

The investigators reviewed in detail the medical case notes and laboratory results to identify the most likely cause of hyponatraemia. Amongst 24 fatalities, there were 12 cases of SIADH (including 7 due to pneumonia, 4 due to malignancy, and 1 due to cerebral vasculitis), 8 of hypovolaemic hyponatraemia (4 due to poor oral intake, 2 due to gastrointestinal losses, 2 diuretic-induced) and 4 of hypervolaemic hyponatraemia (2 with cirrhosis, 2 with heart failure).

Individualised data for all fatal hyponatraemic cases, including demographic characteristics, serum Na values at different time points, cause of death and aetiology of hyponatraemia, are described in Appendix A.

2.2.9 Association between treatment of hyponatraemia and mortality

Amongst 139 hyponatraemic cases, the mortality rate in 89 patients who received treatment for hyponatraemia (15.7%) was similar with the mortality rate in 50 patients having no specific treatment for hyponatraemia (20.0%; P = 0.685).

In terms of the potential impact correction of hyponatraemia has on mortality, the median (IQR) serum Na at the time of discharge was 131 (128-135) mmol/l in patients who survived vs 135.5 (128-142.5) mmol/l in fatal cases. Interestingly, among 18 patients with their last serum Na value during hospitalisation ≥ 139 mmol/l, 9 individuals (50%) died.

The review of case notes explained the apparently paradoxical finding that corrected hyponatraemia was associated with higher mortality than persistent hyponatraemia. Normalisation of serum sodium often occurs during the last few days prior to death and usually does not indicate adequate treatment of hyponatraemia, but a rapid clinical deterioration with subsequent development of significant water deficit because of factors such as poor oral intake, reduced consciousness level, increased insensible losses due to sepsis and high gastrointestinal fluid losses due to perforation or bleeding.

2.3 Conclusions

This case-control study, by minimising the effect of most potential confounding variables, confirmed an independent strong association between hyponatraemia and inpatient mortality. This study showed that patients with serum Na ≤ 128 mmol/l were more than three times more likely to die compared to controls with serum Na > 128 mmol/l (OR 3.33, 95% CI 1.68–6.58, P < 0.01), despite no statistically significant difference in age, gender, serum creatinine, presence of main comorbidities, use of common drugs, ICU admission rate and length of hospital stay. Compared with normonatraemic controls (serum Na 135-145 mmol/l), patients with serum Na concentration ≤ 128 mmol/l were more than 11 times more likely to die (OR 11.89, 95% CI 2.75-51.51, P < 0.01), but also stayed longer in the hospital, suggesting that they might constitute a potentially 'sicker' group of patients than normonatraemic controls. However, this possible difference in disease severity on its own would be unlikely to account for all the excess mortality. In total, this OR for in-hospital mortality is much higher compared to an OR of 2 reported by Waikar et al[125], an OR of 2.54 found by Wald et al[121] and an OR around 2 recorded in a large meta-analysis of all studies on hyponatraemia and mortality by Corona et al[311].

In contrast to our reported odds ratio being much higher than previous studies, the actual mortality rate in the current study for subjects with nadir serum Na ≤ 125 mmol/l of 18.4% was comparable to rates of around 11%[124] 15.2%[312], 20%[126], 22.5%[122], 27%[135] reported in other contemporary studies using the same cut-off. This variability between all these single-centre series may reflect differences in the case mix of different populations.

One of the interesting findings of our study was that the mortality rate increased as serum sodium decreased, but this trend reversed for serum Na concentration ≤ 120 mmol/l. However, the importance of this observation is limited due to the very small sample size (N=27) of this subgroup with very low sodium. This paradoxical fall in mortality has been reported in some past studies[123 124 125], whereas other studies[121 122 135], including an extensive meta-analysis[311], suggest a U-shaped relationship with hyponatraemia-related risk of mortality being inversely correlated with levels of serum Na. There is still great debate about the relationship between hyponatraemia and mortality when serum sodium reaches very low levels. Our study also concluded that hospital-acquired hyponatraemia has similar mortality rate with admission hyponatraemia, as previously shown[54 121].

The retrospective chart review of fatal hyponatraemic cases showed that most patients had acute severe progressive illnesses with no obvious instances of causality discerned between hyponatraemia and death. The main limitation of the analysis of fatal cases was that, due to its retrospective nature, it was often based on incomplete information contained in the medical records. Nevertheless, deaths due to brain oedema or osmotic demyelination were unlikely to be missed due to their easily recognisable clinical presentations. In the light of the findings of this case–control study, the results of the retrospective analysis of fatal cases seem, on the face of it, counter-intuitive. On the one hand, hyponatraemic patients were more likely to die than controls; on the other hand, all hyponatraemic fatal cases had severe, potentially lethal illnesses with no identifiable plausible causal links between hyponatraemia and death. There are three possible explanations for these apparent contradictions; first, hyponatraemia reflects the severity of the underlying disease rather than contributing directly to mortality; second, hyponatraemia could be a direct

cause of death; third, hyponatraemia contributes indirectly to excess mortality through organ dysfunction[136 137].

With respect to the potential effect of management of hyponatraemia on mortality, Huda et al, after a retrospective chart review of 104 patients, found that inappropriate management of hyponatraemia was associated with higher mortality[222]. Our study did not assess the appropriateness of management of hyponatraemia and whether it affected outcomes. Waikar et al, in a prospective cohort study of more than 90000 patients, showed that resolution of hyponatraemia during hospitalisation attenuated the increased mortality risk conferred by hyponatraemia[125]. Additionally, a large meta-analysis, addressing the effect of hyponatraemia improvement on mortality and including data from observational studies, mainly in subjects with heart failure[313 314 315], but also unselected hospitalised patients, was published in 2015[316]. This meta-analysis showed that improvement of serum sodium reduced the mortality rate by up to 60% compared to patients whose hyponatraemia did not improve, but a cause-effect relationship could not be extrapolated from these data[316]. Contrary to the conclusion of this meta-analysis, the findings from our hospital cohort demonstrated that normalisation of serum sodium may in some occasions be associated with excess mortality. As suggested by a comprehensive chart review, this may be explained by the observation that the rise of serum sodium often occurred due development of water deficit as a result of severe clinical deterioration rather than due to effective treatment of hyponatraemia.

One of the main strengths of this study was that it obtained data after thorough review of the medical case notes. Thus, it should provide more accurate and detailed information than most recent large studies, which were based solely on International Statistical Classification of Diseases and Related Health Problem Diagnostic

Codes[121 122 125]. Wald et al examined a cohort of more than 53000 acute unselected hospital admissions over an 8-year period and showed that hyponatraemia was independently associated with in-hospital mortality, adjusting for age, gender, race, and the Deyo-Charlson Comorbidity Index score[317], summarising the number and severity of various comorbid conditions[121]. These results have been strengthened by the findings of the present study which matched cases and controls from the outset for additional variables such as provider and level of health care and took into consideration other potential confounders such as drug use and serum creatinine. In comparison to previous case-control studies of hyponatraemia with similar design, the advantage of this study was that it matched cases and controls with regard to more variables. The previous studies matched cases with controls either only for gender[135] or for age, gender, and admission date[134]. For example, Gill et al showed in a landmark study published in 2006 that severe hyponatraemia in hospital patients was associated with prolonged admissions and significantly increased mortality compared with normonatraemic patients[135]. However, hyponatraemic patients had more comorbidities and worse renal function; as a result, they might die more frequently because of disease severity rather than hyponatraemia per se[135]. In our study, cases and controls were not only matched from the outset for age, gender and admission date, but also for hospital ward to minimise the potential effect of differences in the standard of care and in underlying disease category. Morevoer, the findings of the case–control study were supplemented by a comprehensive case notes review of the clinical course and the causes of death for each patient, thereby providing more clinical insight.

The main weakness of this case–control study was its inability to accurately match hyponatraemic cases with controls of the same level of severity of the principal

pathology, taking into consideration that common conditions, such as pneumonia, heart failure, cancer and cirrhosis, have variable prognosis depending on their severity. This proves an insurmountable challenge because hyponatraemic patients represent a very heterogeneous group with a variety of underlying conditions making it virtually impossible to match controls for main illness category and severity. The inability to incorporate the severity of these illnesses in this relatively small cohort might have led to some unmeasured confounding effect, which could contribute to some excess mortality. However, the absence of statistically significant differences in variables indicative of global disease burden, such as length of hospitalization, ICU admission rate, presence of severe comorbidities, use of medications suggested that cases and controls should not, at least, have concomitant major differences in the severity of overall clinical condition.

In conclusion, this study demonstrated a strong association between hyponatraemia and excess mortality despite no difference between cases and controls with regards to age, gender, comorbidities, and medication use. Thus, hyponatraemia seems to be an independent predictor of mortality. Hyponatraemia per se is likely to contribute to excess mortality, but a case-control study cannot prove a causal relationship. Further studies are required to prove causality in the relationship between hyponatraemia and mortality and to examine whether correction of hyponatraemia can reduce mortality.

2.4 Summary of main findings

- This study found a strong independent association between hyponatraemia and inpatient mortality.
- Patients with serum Na ≤ 128 mmol/l had a high in-hospital mortality rate of 17% and were more than three times more likely to die than subjects with serum Na > 128 mmol/l.
- Patients presenting with hyponatraemia at admission had inpatient mortality rate similar to that of those with hospital-acquired hyponatraemia.
- All hyponatraemic fatalities had severe, potentially lethal illnesses with no identifiable causal links between hyponatraemia and death.
- In most fatalities, serum sodium was normalised prior to death, as a result of clinical deterioration leading to development of water deficit.
- This case-control study, demonstrating hyponatraemia as an independent predictor for inpatient mortality, could not prove a causal relationship.
- It is still unknown whether hyponatraemia *per se* could contribute to excess mortality.
- Physiological studies are warranted to examine mechanisms through which hyponatraemia could contribute to death.
- These findings highlight the need to undertake prospective studies examining whether correcting hyponatraemia can reduce excess mortality.

Chapter 3

Single-centre study of current practice in investigation of hyponatraemia and prevalence of endocrine causes

3.1 Materials and methods

3.2 Results

3.3 Conclusions

3.4 Summary of main findings

3.1. Materials and methods

3.1.1. Study rationale

Numerous studies in the past have consistently shown that hyponatraemia is frequently underinvestigated[126 222 223 224 225 226]. Since tolvaptan, a vasopressin receptor antagonist which is an effective pharmacological agent for the treatment of SIADH, was licensed by the European regulatory authorities in 2009, the field of hyponatraemia has evolved considerably, including a wealth of data on the relationship between hyponatraemia and mortality as well as on the clinical significance of mild chronic hyponatraemia. The availability of new pharmacological therapies like vaptans highlights the need for optimal investigation of hyponatraemia since appropriate diagnosis is essential to guide right utilisation of different therapeutic manoeuvres to achieve correction of hyponatraemia. However, there are very little to no data concerning whether investigation of hyponatraemia in clinical practice has improved in recent years. Also, in spite of recent well-designed studies assessing the contribution of adrenocortical insufficiency to hyponatraemia in neurosurgical cohorts[156 180], there is a lack of data on the prevalence of endocrine disorders as a cause of inpatient hyponatraemia in a general hospital population.

3.1.2 Aims and objectives

The primary objective of this study was to evaluate the adequacy of diagnostic work-up of hyponatraemia in a real life hospital setting.

The secondary objectives were:

- To study the impact of factors, such as baseline serum sodium concentration, speciality of caring clinical team and provision of expert input, on the adequacy of investigation.
- To determine the proportion of hyponatraemic patients being assessed for adrenal insufficiency and hypothyroidism.
- To measure the frequency of adrenocortical insufficiency and hypothyroidism as primary causes of hyponatraemia.

3.1.3 Study design

This was a retrospective, single-centre study, including all inpatients with serum Na levels ≤ 128 mmol/l at any point during hospitalisation at the Royal Free Hospital over a 3-month period (1st March 2013 to 31st May 2013). The study was registered with the Clinical Governance and Clinical Audit Department of the Royal Free Hospital.

3.1.4 Patient selection

This study examined the same cohort with the study described in detail in Chapter 2, with the inclusion and exclusion criteria being the same with the ones used to recruit hyponatraemic cases in Chapter 2. In effect, all adult (> 18 years old) inpatients, under any speciality, with at least one serum Na value ≤ 128 mmol/l during hospitalisation over a 3-month period were included.

3.1.5 Data collection

Hospital case notes, drug prescription charts, discharge letters and laboratory results were reviewed for each patient in detail with respect to investigations of hyponatraemia, documented blood volume status, aetiology of hyponatraemia, and whether the clinical team liaised with Endocrinologists about the management of hyponatraemia. In order for a patient to qualify as having undergone clinical assessment of volume status, the detailed retrospective review of case notes needed to identify at least one comment in case notes such as hypovolaemic/volume depleted/dehydrated/dry or euvolaemic/well-filled/adequately hydrated/not dry or hypervolaemic/overloaded/oedematous. Data were also collected on demographic characteristics, the speciality team responsible for patient care, serum Na levels at various time points, and clinical outcomes.

In addition, we reviewed the results of thyroid function tests and of the assessment of adrenal reserve, either in the form of random serum cortisol or in the form of a short Synacthen test (SST), during which basal serum cortisol concentration was supplemented by measurement of serum cortisol 30 and 60 minutes after intravenous or intramuscular administration of 250 mcg cosyntropin (a synthetic peptide consisting of the first 24 amino acids of corticotropin; ACTH 1–24). A random basal serum cortisol > 450 nmol/l was considered sufficient to rule out adrenal insufficiency[318]. Normal response to SST was defined by a peak cortisol value > 550 nmol/l[319 320]. The normal reference range for thyroid function tests in our laboratory was 12–22 pmol/l for free T4 (fT4) and 0.3–4.2 mU/l for thyroid-stimulating hormone (TSH). Since non-thyroidal illness is very common, it reduces dramatically the specificity of thyroid function tests for diagnosing thyroid illness in hospitalised patients. Using a TSH cut-off of 20 mU/l to diagnose hypothyroidism in acutely ill

patients has a high specificity of > 95%[321]. For this reason, the combination of serum TSH value above a cut-off of 20 mU/l with fT4 levels below the reference range were the diagnostic criteria for, at least severe, primary hypothyroidism.

3.1.6 Statistical analysis

Data were analysed using SPSS (version 21.0; Chicago, IL, USA). Continuous variables were expressed as median (interquartile range (IQR)). Univariate associations between subject groups according to specialty and serum Na levels, and categorical variables, such as laboratory investigations, were determined by Chi-squared test. Univariate logistic regression models for the association of the study groups (medical vs surgical patients and ≤ 125 vs 126–128 mmol/l for serum Na) with the frequency of performance of various investigations enabled computation of relative risk (RR) with 95% confidence intervals (CIs). A P value of 0.05 was considered to indicate a statistically significant difference.

3.2 Results

3.2.1 Baseline characteristics

In total, data on 139 hyponatraemic patients (69 males, 70 females) with a median (IQR) age of 74 (59–82) years and nadir sodium concentration of 125 (122-127) mmol/l were analysed. Data about their distribution to different specialities, frequency of medication use, prevalence of common comorbidities, serum sodium values at different time points and clinical outcomes were analysed in detail in Chapter 2 since this group of patients constituted the ‘cases’ in the previous study.

3.2.2 Investigations

Amongst 139 hyponatraemic subjects, only 86 patients (61.9%) had clinical assessment of blood volume status. According to volume status, 46.6% of individuals were classified as hypovolaemic, 30.2% as euvolaemic and 23.2% as hypervolaemic. The proportion of hyponatraemic patients having paired measurement of serum and urine osmolality and sodium was 28.8%, as illustrated in Table 12. Complete work-up, defined as clinical evaluation of volume status in combination with measurement of serum and urine osmolality and sodium, TSH and basal cortisol, was performed only in 15.8% of individuals.

Table 12. Frequency of investigations performed on hyponatraemic patients

Investigations	**N=139**
Volume status	86 (61.9%)
Serum osmolality	53 (38.1%)
Urine osmolality	52 (37.4%)
Urine Na	49 (35.2%)
Paired osmolality + Na	40 (28.8%)
TSH	85 (61.1%)
Serum cortisol	44 (31.6%)
Serum urate	33 (23.7%)
Complete work-up	22 (15.8%)

3.2.3 Diagnosis

The aetiology of hyponatraemia was recorded only in 58 out of 139 cases (41.7%) and patients' ascertainment is accordingly summarised in Table 13.

Table 13. Classification of cases according to documented aetiology

Aetiology	**N=58 (%)**
Hypovolaemic	**27 (46.6%)**
Diuretics	14 (24.1%)
Gastrointestinal Na losses	8 (13.9%)
Poor oral intake	5 (8.6%)
Euvolaemic	**18 (31.0%)**
SIADH† due to pneumonia	6 (10.3%)
SIADH of unknown cause	5 (8.6%)
Malignant SIADH	4 (6.9%)
SIADH due to various causes	3 (5.2%)
Hypervolaemic	**11 (18.9%)**
Decompensated liver disease	6 (10.3%)
Heart failure	5 (8.6%)
Miscellaneous causes	**2 (3.5%)**

†SIADH: Syndrome of inappropriate antidiuretic hormone secretion

To diagnose SIADH, at least all of the following essential criteria must be met: euvolaemia, hyponatraemia and low serum osmolality with inappropriately raised urine osmolality and urine Na > 30 mmol/l, in the presence of normal thyroid and adrenal function[162] [163]. Amongst 18 patients diagnosed with SIADH, 10 of those had all these tests performed, while the remaining 8 individuals did not undergo full work-up. The most commonly overlooked laboratory tests were measurement of urine sodium (5 cases), followed by urine osmolality (3 cases) and serum cortisol (3 cases).

3.2.4 Effect of endocrine input on adequacy of investigation

Of 139 hyponatraemic inpatients, 20 patients (14.4%) received endocrine input; 80% of them underwent complete clinical and laboratory assessment compared with only 6 out of 119 patients (5%) managed without endocrine input. This difference was statistically significant (P <0.001; RR, 15.86; 95% CI, 7.17–31.06).

In addition, 9 out of 10 patients with SIADH who met all essential diagnostic criteria were reviewed by endocrinologists. Regarding the frequency of diagnosing the cause of hyponatraemia, 80% of individuals receiving endocrine input had their aetiology of hyponatraemia documented versus 35.3% in patients without endocrine input. The median (IQR) time interval between development of serum Na ≤ 128 mmol/l and referral to endocrine liaison service was 4 (1-12) days with patients requiring, on average, two consultations.

3.2.5 Effect of serum sodium levels on adequacy of investigation

There was a highly significant difference in the frequency of performing all tests between individuals with lowest serum Na ≤ 125 mmol/l and those with nadir serum Na 126-128 mmol/l. Patients with nadir serum Na ≤ 125 mmol/l were more than 4 times more likely (P value < 0.001, RR 4.18, 95% CI 1.74 – 11.76) to have measurement of paired serum and urine osmolality and Na and almost 6 times more likely (P value < 0.001, RR 5.97, 95% CI 2.29 – 19.15) to have measurement of serum cortisol than patients with serum Na 126-128 mmol/l, as shown in Table 14. With regard to full work-up of hyponatraemia, as defined above, none of the 52 patients with nadir serum Na 126-128 mmol/l had complete assessment compared with 28.7% of patients with lowest serum Na ≤ 125 mmol/l.

Table 14. The proportion of hyponatraemic patients undergoing essential investigations according to nadir serum Na concentration

Investigations	**Nadir sNa ≤ 125** N=87 (%)	**Nadir sNa 126-128** N=52 (%)	**RR**	**95% CI**	**P value**
Volume status	64 (73.6%)	22 (42.3%)	1.74	1.24-2.50	**<0.001**
Serum osmo	46 (52.9%)	7 (13.5%)	4.53	2.27-10.26	**<0.001**
Urine osmo	44 (50.6%)	8 (15.4%)	3.28	1.68-7.14	**<0.001**
Urine Na	41 (47.1%)	8 (15.4%)	3.06	1.55-6.67	**<0.001**
Paired osmo + Na	35 (40.2%)	5 (9.1%)	4.18	1.74-11.76	**<0.001**
TSH	61 (70.1%)	24 (46.2%)	1.51	1.09-2.16	**0.007**
Serum cortisol	40 (45.6%)	4 (7.7%)	5.97	2.29-19.15	**<0.001**
Endocrine input	15 (17.2%)	5 (9.1%)	1.79	0.65-5.48	0.318

3.2.6 Effect of speciality on adequacy of investigation

Hyponatraemia was not investigated in most patients with liver cirrhosis under the care of Hepatologists (N = 20) and those with advanced renal disease under the care of Nephrologists (N = 7). Besides Hepatology and Nephrology, the proportion of patients under the care of medical specialities having the appropriate laboratory investigations was numerically higher compared with patients looked after by surgical specialities. However, this difference did not reach statistical significance, apart from TSH which was tested significantly more frequently in medical than surgical patients, as shown in Table 15.

Table 15. Comparison in the frequency of performing essential investigations between medical and surgical specialities

Investigations	**Medicine** N=80	**Surgery** N=27	**RR**	**95% CI**	**P value**
Volume status	56 (70.0%)	17 (63.0%)	1.11	0.82 - 1.66	0.633
Serum osmo	38 (47.5%)	10 (37.0%)	1.28	0.75 - 2.48	0.379
Urine osmo	40 (50.0%)	8 (29.6%)	1.68	0.91 - 3.59	0.077
Urine Na	36 (45.0%)	8 (29.6%)	1.51	0.81 - 3.26	0.182
Paired osmo-Na	31 (38.7%)	8 (29.6%)	1.31	0.68 - 2.85	0.490
TSH	**63 (78.7%)**	**13 (48.1%)**	**1.63**	**1.11 - 2.61**	**0.006**
Serum cortisol	33 (41.2%)	6 (22.2%)	1.85	0.88 – 4.64	0.105
Endocrine input	15 (18.7%)	5 (18.5%)	1.01	0.29 – 3.63	1.000

3.2.7 Relationship of adequacy of investigaton and endocrine input with clinical outcomes

Patients undergoing complete evaluation had lower nadir serum Na values (median nadir serum Na, 121 vs 125 mmol/l) and longer hospital stay (median duration, 17 vs 6.5 days) in comparison to individuals who did not have all essential tests. Participants who underwent full diagnostic work-up had a numerically higher ICU admission rate of 18.2% vs 9.4% (P value 0.258) and mortality rate of 22.7% vs 16.2% (P value 0.538) than patients having incomplete evaluation. However, these differences were not statistically significant.

With respect to the relationship between endocrine input and patient outcomes, patients receiving expert input had lower serum Na values (median nadir serum Na, 119 vs 125 mmol/l), required longer hospitalisation (median length of hospital stay, 18.5 vs 11 days) and had a higher ICU admission rate (30% vs 7.5%; P value 0.009; RR, 3.967; 95% CI, 1.341–10.636) in comparison to patients not referred for specialist assessment of hyponatraemia. However, patients referred for endocrine review had in-hospital mortality rate (4 patients; 20%) similar to individuals managed without specialist input (20 patients; 16.8%; P value 0.751).

3.2.8 Assessment of glucocorticoid reserve

In our cohort, 13 patients were treated with glucocorticoids for various indications such as exacerbation of airways disease, autoimmune conditions and advanced malignancy. Among the remaining 126 patients, only 44 patients (34.9%) had measurement of basal serum cortisol levels with the median (IQR) basal serum cortisol levels being 584 (442-754) nmol/l. A large proportion (75%) of these subjects had random serum cortisol levels above the cut-off of 450 mmol/l, excluding the possibility of adrenal insufficiency, including 36.4% with levels of 450-700 nmol/l and 38.6% with levels > 700 nmol/l. The remaining 11 patients (25%) had basal cortisol concentration < 450 mmol/l, with measured levels ranging between 211 and 439 nmol/l. These patients justified a short Synacthen test to exclude the possibility of glucocorticoid deficiency, but this was carried out in 3 patients only. Two patients had an appropriate response, whereas one patient, admitted with septic shock in the ICU, had basal cortisol levels of 337 nmol/l and stimulated levels of 472 nmol/l, prompting a diagnosis of adrenal insufficiency and initiation of glucocorticoid replacement therapy.

In terms of the time of the day when basal cortisol was measured, it was performed in 31 cases in the early morning (before 10 am), in 7 cases in the afternoon and in 6 cases between 5 pm and 2 am. Among 13 cases when serum cortisol was not measured in the morning, 10 patients had basal levels > 450 nmol/l and 3 patients < 450 nmol/l.

3.2.9 Assessment of thyroid function

Our cohort included 18 patients who were already on thyroxine replacement for hypothyroidism. Serum fT4 and TSH levels were measured in 85 patients with 73% having both fT4 and TSH values within the reference range and the remaining 27% with one or both values outside the reference range. The median (IQR) value for fT4 was 16.8 (14.5-19.7) pmol/l (reference range, 12-22 pmol/l) and 2.08 (1.23-3.95) mU/l (reference range, 0.3-4.2 mU/l) for TSH.

Classifying patients according to TSH values, none had TSH suppressed below 0.3 mU/l, 69 individuals (81.2%) had TSH within the reference range and 16 subjects (18.8%) had elevated TSH above 4.2 mU/l, amongst whom 10 had normal fT4 and 6 low fT4 levels. Taking into account fT4 levels in the serum, 4 patients (4.7%) had fT4 above the reference range (range 22.9-35.2 pmol/l), all with normal TSH values. Most patients (84.7%) had serum fT4 levels within the normal range, including 2 cases on thyroxine replacement with TSH > 10 mU/l (20.77 and 23.17 mU/l respectively). Finally, 9 patients (10.6%) had fT4 below the reference range with normal TSH in 3 cases and elevated TSH in 6 cases, including 2 cases with TSH > 10 mU/l; these 2 patients had TSH 16.62 and 16.82 mU/l with fT4 9.8 and 10 pmol/l respectively. In terms of the lowest fT4 levels recorded in this cohort, fT4 was below 9.7 pmol/l in 4 individuals, but all these patients had TSH below 8 mU/l. Overall, no patients met the criteria of fT4 below the reference range and TSH levels >20 mU/l, which would be strongly indicative of severe primary hypothyroidism in hospitalised patients.

3.3 Conclusions

The present study confirmed that hyponatraemia was frequently underinvestigated, as shown in previous studies in the UK[126 222 223 224 225]. Less than one third of hyponatraemic patients had measurement of paired serum and urine osmolality and sodium, while only 15.8% of individuals had complete diagnostic work-up with the most commonly overlooked tests being measurement of urinary sodium and serum cortisol. Of note, some subgroups of hyponatraemic patients, such as subjects with cirrhosis or advanced kidney disease, have a well-established aetiology of hyponatraemia, not necessarily requiring complete work-up. Even taking into account these subgroups of our cohort, suboptimal investigation remained a common occurrence, evidenced by the fact that almost half of all SIADH patients did not undergo complete assessment.

This study also demonstrated that review by an endocrinologist and the levels of serum Na were the two main factors affecting the adequacy of investigation of hyponatraemia. Interestingly, amongst individuals not reviewed by an endocrinologist, only 5% had complete clinical and laboratory work-up of hyponatraemia. In cases when an endocrinologist was consulted, patients were almost 16 times more likely to undergo full investigation than patients not referred to endocrine services. With respect to serum Na levels, clinicians were 4-6 times more likely to perform the basic laboratory investigations in cases with serum Na value ≤ 125 mmol/l than in cases with serum Na levels of 126-128 mmol/l. Noteworthy, not even a single patient with serum Na concentration of 126-128 mmol/l underwent a complete work-up for hyponatraemia. This observation suggests that many clinicians used 125 mmol/l as a pragmatic, memorable threshold below which they initiated an

investigative algorithm. Finally, the standards of investigation did not significantly differ between medical and surgical patients.

This study did not record a reduced inpatient mortality rate or length of hospital stay in patients undergoing complete diagnostic work-up or receiving expert input. A possible interpretation of these findings is that adequate diagnostic evaluation and specialist care provision cannot improve patient outcomes. However, patients undergoing complete evaluation or receiving expert input had lower serum Na levels, higher ICU admission rate, and longer duration of hospitalisation than the rest of the cohort. This observation probably reflects a significant selection bias, suggesting that endocrinology consultations are usually limited to the sickest individuals and most complex cases in routine clinical practice. Therefore, our study findings might be misleading due to the distorting effect of this selection bias.

With regards to adrenal insufficiency, its frequency as the cause of hyponatraemia in our cohort was only 0.7%. However, its true prevalence might be higher and it might have been overlooked in some cases since almost two thirds of the patients did not have laboratory evaluation of adrenocortical reserve. Of note, measurement of serum basal cortisol, using a threshold of 450 nmol/l as representative of appropriate adrenal response to physiological stress during acute illness, sufficed to exclude adrenal insufficiency in 75% of patients in our cohort.

Measurement of serum TSH was the most commonly performed laboratory test for hyponatraemia, having been undertaken in 61.1% of cases. With respect to hypothyroidism as a cause of hyponatraemia, interpretation of thyroid function tests in combination with a review of case notes did not identify any cases of, at least, severe primary hypothyroidism. However, this study reported fT4 or TSH values

being outside the reference range in more than a quarter of hyponatraemic inpatients, either due to mild hypothyroidism or, more commonly, ‘non-thyroidal illness’[321].

One of the strengths of this study was that it examined the largest hospital cohort among UK studies of investigation of hyponatraemia. This was the first study which evaluated how various factors, especially specialist input, influenced the adequacy of diagnostic evaluation of hyponatraemia. It also represented the first study in the UK which evaluated standards of clinical practice in the field of hyponatraemia, following the considerable development of knowledge in the field since 2009.

The main limitation of this study was that it only contained data from a single tertiary centre, where endocrinologists have developed a special interest in the management of hyponatraemia and the case mix, including for example a large number of subjects with advanced liver and renal disease, may differ from other hospitals. Thus, it is unclear to which extent these findings reflect the UK clinical practice in general. Also the design and retrospective nature of this study might introduce a selection bias with more severe cases being consulted by Endocrinologists. Thus, this selection bias might distort our findings regarding the potential impact of specialist input on clinical outcomes.

In total, hyponatraemia was found to be frequently underinvestigated and underdiagnosed, especially when not referred to endocrinologists and when serum sodium is above 125 mmol/l. Endocrine pathologies, such as adrenal insufficiency and profound hypothyroidism, seemed to be rare primary causes of hyponatraemia, but adrenal insufficiency might be frequently overlooked since adrenal reserve is usually not tested.

3.4 Summary of main findings

- Hyponatraemia was frequently underinvestigated in real-life clinical practice, as evidenced by measurement of paired serum and urine osmolality and sodium in less than a third of hyponatraemic inpatients.
- Complete diagnostic work-up of hyponatraemia was undertaken in only 16% of cases.
- Only half of patients, who were diagnosed with SIADH, had all the essential tests performed.
- Review by an Endocrinologist was the main factor determining the adequacy of investigation, with complete assessment being undertaken in 80% of individuals consulted by an Endocrinologist compared to 5% of those not receiving expert input.
- Clinicians were 4-6 times more likely to perform the basic laboratory tests in patients with nadir serum Na ≤ 125 mmol/l in comparison to those with nadir Na 126-128 mmol/l.Adrenal insufficiency might have been overlooked in some cases since two thirds of patients did not have assessment of adrenocortical function.
- The reported frequency of adrenal insufficiency was very low at 0.7%.
- No cases of hypothyroidism-induced hyponatraemia were identified, confirming that hypothyroidism is a very rare cause of hyponatraemia.
- In total, suboptimal investigation of hyponatraemia and underutilisation of biochemical tests were a common occurrence in a real-life hospital setting.
- Prospective studies should examine whether widespread provision of expert input or other models of care provision could improve adequacy of investigation and patient outcomes.

Chapter 4

Multicentre study of current practice in investigation and management of inpatient hyponatraemia

4.1 Materials and methods

4.2 Results

4.3 Conclusions

4.4 Summary of main findings

4.1. Materials and methods

4.1.1. Study rationale

Although several single-centre studies in the UK have highlighted suboptimal clinical standards in the investigation of hyponatraemia[126 222 223 224 225], it is questionable whether these findings reflect local inadequacies or represent UK clinical practice in general. Nationwide data from UK audits and databases currently exist for some common conditions such as myocardial infarction[322] as well as rare disorders such as congenital adrenal hyperplasia[323] and they have shed light into the management and outcomes of these diseases. Also, by enabling clinicians to compare their performance against national standards, these national audits have been a driving force behind change and improvement of clinical practice. There has never been an attempt at a national, or even regional, level to review the investigation and management of hyponatraemia in the UK. Also, at the time this study was conducted, there was a paucity of data about the utilisation of various treatment modalities for hyponatraemia as well as their efficacy and safety in a real world setting.

4.1.2 Aims and objectives

The primary aim of this real-life study was to evaluate the effectiveness of the contemporary management of hyponatraemia across various UK clinical settings.

The secondary objectives were:

- To study the clinical characteristics and determine the distribution of aetiologies for hyponatraemia in a large cohort of hyponatraemic inpatients across three institutions.
- To evaluate the clinical outcomes of hospitalised patients with hyponatraemia.
- To assess the current standards and adequacy of the investigation of hyponatraemia.
- To assess the utilisation and effectiveness of different therapeutic modalities.

4.1.3 Study design

This multicentre, retrospective, observational study examined the characteristics, investigation, management and clinical outcomes of 100 consecutive inpatients with serum sodium ≤ 128 mmol/l at any point during hospitalisation. Patient recruitment started on 1st March 2013 and ended on 28th March 2013 when the target sample size of 100 patients across three sites was met.

It was conducted simultaneously at three acute NHS Trusts in London. Centre 1 was the Royal Free Hospital, a major 900-bed teaching hospital, which is also a regional renal and liver centre. Centre 2 included 850 beds across two teaching hospitals, Hammersmith and Charing Cross Hospital. Centre 3 was the Whittington Hospital, a 450-bed district general hospital. At the time of the study, none of the three institutions had local guidelines for the management of hyponatraemia. However, Royal Free Hospital had a Consultant Endocrinologist who had developed a special interest in hyponatraemia and was granted access to tolvaptan for use in selected SIADH cases. In the other sites, tolvaptan was not readily available for routine clinical use.

The study was reviewed and approved by the Clinical Governance & Clinical Audit Departments of all three institutions.

4.1.4 Patient selection

The same inclusion and exclusion criteria were used for patient recruitment in all three sites and were identical with the ones used to include patients in studies described in Chapter 2 and 3. In effect, all adult (> 18 years old) inpatients, under any speciality, with at least one serum Na value ≤ 128 mmol/l during hospitalisation were included. Subjects with hyperglycaemia were included only if their corrected serum Na was ≤ 128mmol/l. If venous glucose was 15.0-24.4 mmol/l, serum Na was corrected by 1.6 mmol/l for every 5.6 mmol/l increase in glucose concentration above 7 mmol/l[151]; if glucose was > 24.4 mmol/l, a correction factor of 2.4 mmol/l was used[150].

4.1.5 Data collection

Hospital case notes, laboratory results, drug prescription charts and discharge letters were retrospectively reviewed for each patient after hospital discharge. Data were collected on age, gender, speciality responsible for each patient, drug history, admission to the intensive care unit, length of hospital stay, outcome of admission, investigations and documented aetiology of hyponatraemia, serum Na levels at various time points, frequency of use of therapeutic modalities, serum Na change 24 and 72 hours following initiation of any treatment episode, and serum Na concentration at hospital discharge.

Adequate investigation of hyponatraemia should include clinical assessment of volume status, measurement of paired serum and urine osmolality and Na, thyroid function tests and serum cortisol measurement[162 163]. The overall effectiveness of hyponatraemia treatment was assessed by serum Na concentration at hospital discharge. For the purpose of evaluating the effectiveness of different therapeutic modalities, ‘clear failure’ of treatment was defined as a total serum Na increase of ≤ 3 mmol/l over a 72-hour period after initiation of therapy. Overly rapid correction of hyponatraemia, known to increase risk of osmotic demyelination syndrome, was defined as a serum Na increase of > 12 mmol/l/day.

4.1.6 Statistical analysis

Data were analysed using SPSS (version 21.0; Chicago, IL, USA). Data were analysed separately for each hospital and for all three hospitals together. Data were summarised using descriptive statistics, with continuous variables being expressed as mean ± SD (standard deviation), and categorical variables as percentages. Adequacy of investigation was assessed by the percentage of patients who underwent each of the recommended tests. The proportion of patients with normonatraemia and different degrees of biochemical hyponatraemia (mild / moderate / severe) was used to determine the effectiveness of management of hyponatraemia. The percentage of patients who had ‘clear failure’ and too rapid correction determined the effectiveness and safety respectively of each therapeutic modality.

4.2 Results

4.2.1 Demographic characteristics

Across three hospitals in London, 100 patients (47 males, 53 females) were included with a mean ± SD age of 71.3 ± 15.4 years and nadir serum Na of 123.4 ± 4.3 mmol/l, as shown in Table 16. Among participants, 58% presented on admission with serum Na ≤ 128 mmol/L compared to 42% with hospital-acquired hyponatraemia. All three cohorts had similar demographic characteristics.

Table 16. Demographic characteristics of population across three sites

Characteristics	**Total** **N=100**	**Centre 1** **N=38**	**Centre 2** **N=30**	**Centre 3** **N=32**
Age (years)*	**71.3 ± 15.4**	73.6 ± 15.1	68.5 ± 15.5	70.4 ± 15.4
Gender (male/female)	**47 / 53**	19 / 19	13 / 17	15 / 17
Admission Na (mmol/l)*	**128.1 ± 7.1**	130.1 ± 6.7	126.9 ± 7.7	126.8 ± 6.5
Lowest Na (mmol/l)*	**123.4 ± 4.3**	123.4 ± 3.1	123.4 ± 3.9	124.4 ± 4.6

*mean ± SD (standard deviation)

4.2.2 Speciality distribution and drug history

There was a wide distribution of participants within different specialities, including 81% of patients under the care of medical specialities and 19% under surgical specialities, as illustrated in Table 17. The more commonly used medications in our cohort were angiotensin-converting enzyme inhibitors (35%), loop diuretics (23%), thiazide diuretics (22%), selective serotonin reuptake inhibitors or SSRIs (15%), potassium-sparing diuretics (14%), angiotensin-II receptor antagonists (12%) and tricyclic antidepressants (6%).

Table 17. Speciality distribution of patients

Specialities	**Overall N=100**
Medical Specialities	**81**
Care of the Elderly	18
General Medicine	11
Respiratory	9
Gastroenterology	9
Oncology	6
Hepatology	6
Cardiology	5
Infectious diseases	5
Endocrinology	4
Neurology/Stroke	3
Nephrology	3
Rheumatology	2
Surgical Specialities	**19**
General Surgery	5
Urology	5
Orthopaedics	4
Cardiothoracics	3
Obstetrics/Gynaecology	2

4.2.3 Investigations

Clinical assessment of volume status was recorded in 62 patients who were accordingly classified as hypovolaemic (N=31), euvolaemic (N=19) and hypervolaemic (N=12). Paired serum and urine osmolality and sodium were measured in 23%, while complete work-up was undertaken only in 18% of patients, as shown in table 18. Of note, 10 out of 16 individuals (62.5%) who were reviewed by endocrinologists underwent complete diagnostic evaluation compared to 8 out of 84 subjects (9.5%) not having specialist input for hyponatraemia.

Table 18. Frequency of investigations in hyponatraemic patients

Investigations	**Total N=100 (%)**	**Centre 1 N=38 (%)**	**Centre 2 N=30 (%)**	**Centre 3 N=32 (%)**
Volume status	**62%**	71%	53%	59%
Serum osmolality	**39%**	39%	33%	44%
Urine osmolality	**33%**	39%	30%	28%
Urine Na	**29%**	34%	37%	16%
Paired osmo + Na	**23%**	26%	27%	16%
Serum TSH	**61%**	71%	63%	47%
Serum cortisol	**31%**	34%	27%	31%
Full work-up	**18%**	24%	20%	9%
Expert input	**16%**	13%	13%	22%

4.2.4 Diagnosis

The aetiology of hyponatraemia was unrecorded in the case notes of 58% of patients. Review of case notes was used to ascertain the aetiology of hyponatraemia in the remaining patients with hypovolaemic hyponatraemia observed much more frequently (54.7%) than SIADH (26.2%) and hypervolaemic hyponatraemia (19.1%), as summarised in Table 19. Commonest cause of SIADH was pneumonia in 4 cases, followed by drug-induced SIADH in 3 cases (SSRIs in 2 cases and mirtazapine in 1 case), malignancy in 2 cases (small cell lung cancer in 1 case and chronic lymphocytic leukaemia in 1 case) and finally miscellaneous causes in 2 cases (SIADH post transsphenoidal surgery and SIADH of unknown cause). Only 6 out of 11 patients diagnosed with SIADH had all the essential tests performed, including clinical assessment of volume status, measurement of paired serum/urine osmolality and Na, and assessment of thyroid and adrenal function.

Table 19. Classification of cases according to documented aetiology of hyponatraemia

Aetiology	**N=42 %**
Hypovolaemic	**23 (54.7%)**
Gastrointestinal Na losses	9 (21.4%)
Poor oral intake	7 (16.6%)
Diuretics	6 (14.3%)
Primary adrenal insufficiency	1 (2.4%)
Euvolaemic	**11 (26.2%)**
SIADH due to pneumonia	4 (9.5%)
Drug-induced SIADH	3 (7.1%)
Malignant SIADH	2 (4.8%)
SIADH due to various causes	2 (4.8%)
Hypervolaemic	**8 (19.1%)**
Decompensated liver disease	4 (9.5%)
Heart failure	4 (9.5%)

4.2.5 Clinical outcomes

The inpatient mortality rate in our cohort was 16%. The mean length of hospital stay was 17.5 ± 14.8 days with 9% of patients requiring admission to Intensive Care Unit.

Table 20. Patient outcomes of cohort across three sites

Outcomes	**Total** **N=100**	**Centre 1** **N=38**	**Centre 2** **N=30**	**Centre 3** **N=32**
Discharge Na (mmol/l)*	**133.5 ± 5.2**	133.6 ± 5.8	132.8 ± 5.3	133.9 ± 4.4
ICU admission	**9 (9%)**	3 (7.9%)	3 (10.0%)	3 (9.4%)
LOS (days)*	**17.5 ± 14.8**	17.7 ± 13.2	20.0 ± 18.8	14.1 ± 11.7
Mortality	**16 (16%)**	8 (21.0%)	6 (20.0%)	2 (6.2%)

*mean ± SD (standard deviation)

4.2.6 Effectiveness of treatment of hyponatraemia

Correction of serum Na ≥ 130 mmol/l was observed in 70/84 (83.3%) patients at some point during hospitalisation, but hyponatraemia with serum Na < 130 mmol/l recurred in 6/84 (7.1%) patients. The proportion of patients who achieved specific correction benchmarks, determined by the last serum sodium concentration nearest to the time of discharge or death, was illustrated in Table 21.

Table 21. Proportion of patients achieving correction benchmarks

Correction benchmarks	**Overall N=100**
sNa change by ≥ 5 mmol/l	74%
sNa ≥ 130 mmol/l	77%
sNa ≥ 135 mmol/l	42%

The mean (± SD) serum Na value at hospital discharge was 132.8 (± 4.7) mmol/l. Amongst 84 individuals discharged from hospital, a significant proportion (63.1%) had persistent hyponatraemia, including 23.8% of individuals with serum Na < 130 mmol/l, as shown in table 22. Concerning the remaining 16 fatal hyponatraemic cases, 31.3% were persistently hyponatraemic, while the majority (68.7%) had become normonatraemic prior to death.

Table 22. Serum sodium concentration at hospital discharge

SNa at discharge	**N=84**
Percentage of patients with sNa < 125 mmol/l	4.8%
Percentage of patients with sNa 125-129 mmol/l	19.0%
Percentage of patients with sNa 130-134 mmol/l	39.3%
Percentage of patients with sNa ≥ 135 mmol/l	36.9%

4.2.7 Utilisation of treatment modalities

Overall, 37% patients did not have any active treatment for hyponatraemia, including withdrawal of potentially hyponatraemia-inducing medicines. Of the 63 patients treated for hyponatraemia, 53 received one therapeutic modality, 7 received two modalities, and 3 received three treatment modalities. In total, only 10% of our cohort received 2 or more therapeutic modalities for hyponatraemia.

Out of all 76 episodes of treatment, the commonest therapeutic option was isotonic saline in 38/76 (50%) cases, followed by drug discontinuation in 16/76 (21.1%), fluid restriction in 16/76 (21.1%), hypertonic saline in 2/76 (2.6%), human albumin solution in 2/76 (2.6%), hydrocortisone replacement in 1/76 (1.3%) and demeclocycline in 1/76 (1.3%) cases. Potentially offending drugs were discontinued in 36% of patients, with the most common being ACE-inhibitors or angiotensin-II receptor antagonists (18%), loop diuretics (15%), thiazide diuretics (10%), potassium-sparing diuretics (10%) and SSRIs (3%). Other drug therapies for SIADH, such as tolvaptan, urea or combination of loop diuretics with oral sodium chloride, were not prescribed.

With regards to first-line therapy, isotonic saline was used in most cases (34/63, 54%), while other options included discontinuation of potentially offending drugs in 16/63 (25.4%), fluid restriction in 10/63 (15.9%), infusion of human albumin solution in 2/63 (3.2%), and initiation of hydrocortisone replacement in 1/63 (1.5%). Second-line therapy was isotonic saline in 4/10 cases, fluid restriction in 4/10, and hypertonic saline in 2/10. Only three patients received third-line treatment, including two cases of fluid restriction and one case of demeclocycline.

4.2.8 Effectiveness and safety of isotonic saline and fluid restriction

Fluid restriction was imposed on 16 patients with various volumes prescribed per 24 hours (1500 ml in 4 cases, 1000 ml in 9 cases, 750 ml in 1 case and 500 ml in 2 cases). In our assessment of patients' response to infusion of isotonic saline and fluid restriction, we included only therapeutic episodes with a minimum 3-day duration. 'Clear failure' of treatment, defined as a total serum Na increase of ≤ 3 mmol/l in the 72-hour period after initiation of therapy, was recorded in 4/26 (15.4%) patients treated with isotonic saline compared with 8/10 (80%) individuals managed with fluid restriction, as shown in table 23. Despite the fact that 8 subjects were clearly 'non-responders' to fluid restriction, the treating clinicians offered a second treatment only in 3 cases.

Table 23. Effectiveness of different treatment modalities in correcting hyponatraemia

SNa correction after treatment	**Isotonic saline**	**Fluid restriction**
First 72 hours	N=26	N=10
Mean (± SD) change in sNa (mmol/l)*	7.3 ± 5.0	2.8 ± 3.2
Percentage of patients		
SNa increase < 2 mmol/l	7.7%	30.0%
SNa increase 2-3 mmol/l	7.7%	50.0%
SNa increase 4-8 mmol/l	50.0%	10.0%
SNa increase 9-12 mmol/l	19.2%	10.0%
SNa increase >12 mmol/l	15.4%	0

*mean ± SD (standard deviation)

Overly rapid correction of hyponatraemia, defined as serum Na increase of > 12 mmol/l during any 24-hour period of therapy or > 18 mmol/l in any 48-hour period, was recorded in 3.9% of therapeutic episodes. All 3 patients, 2 treated with isotonic saline for hypovolaemic hyponatraemia and 1 with infusion of 1000 ml of hypertonic 1.8% saline over 18 hours for SIADH, had serum Na increase of 13 mmol/l within 24 hours without any adverse neurological sequelae.

4.3 Conclusions

This multicentre study across 3 London hospitals confirmed that hyponatraemia remains underinvestigated in routine clinical practice. A clear example of underutilisation of biochemical investigations is the fact that urine Na, the key test to diagnose the aetiology of hyponatraemia[163 154], was measured in less than one third of patients. In addition, clinical assessment of volume status was not undertaken in as many as 38% of patients, suggesting inadequate clinical evaluation. As a result, less than a fifth of patients had adequate diagnostic work-up for hyponatraemia. This study confirmed that endocrine input provision was the key factor that increased the likelihood for complete diagnostic evaluation. Otherwise, when a specialist was not consulted, patients had less than a 10% likelihood of undergoing full diagnostic work-up.

Regarding potential differences in the adequacy of investigation between different institutions, centre 3, a district general hospital, seemed to have numerically lower frequency for performing some tests, especially urine sodium and serum TSH. Due to the small sample size, it is difficult to conclude if this difference was indicative of inferior clinical standards in hyponatraemia evaluation at the district general hospital versus teaching hospital setting. Surprisingly, this difference was observed despite the fact that more subjects at the district general hospital were reviewed by endocrinologists than in the tertiary centre setting. However, in this context, endocrinologists acted often as their primary physicians being in charge of their overall care rather than as subspecialists being consulted regarding hyponatraemia management.

The underlying aetiology of hyponatraemia, despite being essential to guide appropriate treatment, was not ascertained in more than half of the cases. Also, in agreement with our observation in another study described in Chapter 2, the current study reported hypovolaemic hyponatraemia as the commonest type of hyponatraemia according to classification as per volume status. Our cohort of hyponatraemic inpatients stayed on average 17 days in the hospital, with around 1 out of 10 requiring admission to Intensive care Unit and 1 in 6 individuals dying during hospitalisation. These poor clinical outcomes reflect their severity of clinical condition and underlying illnesses.

This study provided further evidence about the poor efficacy of real-life hyponatraemia management in the UK, as evidenced by the fact that almost two thirds of patients were discharged with persistent hyponatraemia, including a quarter of patients with moderate to severe hyponatraemia. Another interesting finding in our cohort was that hyponatraemia correction was observed much more frequently in fatal hyponatraemic cases than in patients discharged from the hospital.

The poor efficacy of hyponatraemia management may be explained by several of our observations, such as the lack of hyponatraemia treatment recorded in more than a third of patients. Another important factor might be that the great majority of patients received in total only one therapy, most commonly either isotonic saline or fluid restriction. In specific, failure to respond to fluid restriction was usually not followed by second-line therapy. For example, amongst second-line pharmacological agents for SIADH, tolvaptan and urea were not prescribed in any cases, while one patient was treated with demeclocycline. Of note, fluid restriction had low efficacy, with 80% of patients failing to increase serum sodium by > 3 mmol/l over a 3-day period of

treatment. These data suggested that a large proportion of patients received ineffective therapy or no therapy at all.

The main strength of this study was that it contained for the first time real-world data from several UK hospital sites, including both teaching and district general hospitals. Thus, it provided unique insight into the contemporary investigation and management of hyponatraemia in the UK, since very little to no data exist on current hyponatraemia treatment practices in the UK.

However, it had a number of limitations. First and foremost, it could not, by its design, test whether undertreatment of hyponatraemia contributed to adverse patient outcomes and, more importantly, whether correcting hyponatraemia could improve clinical outcomes. Second, the fact that all three hospitals were located in London raised the question whether these findings apply to UK clinical practice in general. Third, the small sample size of subgroups did not allow us to draw conclusions about potential differences between current practice in different settings, depending on the model of care and clinical setting. Finally, its retrospective nature did not allow us to ascertain accurately the cause of hyponatraemia in all cases. As a result, its ability to evaluate the effectiveness of different therapeutic modalities was limited because failure of treatment might sometimes reflect misdiagnosis.

In conclusion, underinvestigation and undertreatment of hyponatraemia is a common occurrence in routine UK clinical practice across various healthcare settings. Good clinical practice necessitates accurate diagnosis of the aetiology of hyponatraemia that guides appropriate treatment. Therefore, this study highlights the urgent need to improve clinical practice.

4.4 Summary of main findings

- Real-world data from 3 UK hospitals confirmed that hyponatraemia was frequently underrecognised and mismanaged.
- The aetiology of hyponatraemia was ascertained in only 42% of cases.
- The standards of investigation and treatment did not significantly differ between teaching hospitals and district general hospitals.
- A third of hyponatraemic patients did not receive any specific therapy for hyponatraemia.
- The commonest treatment modalities were isotonic saline, discontinuation of potentially offending drugs and fluid restriction, while less than 5% of patients were treated with more specific therapies, such as hypertonic saline, demeclocycline, tolvaptan or urea.
- Fluid restriction was often ineffective in correcting hyponatraemia with an 80% non-response rate.
- Real-life management of hyponatraemia was characterised by poor effectiveness, as evidenced by two thirds of patients being discharged with persistent hyponatraemia, including one quarter with serum Na < 130 mmol/l.
- This study, demonstrating insufficient diagnostic work-up and ineffective treatment, highlighted the need to improve clinical practice.
- There is a need for studies evaluating the effectiveness of innovative models of care delivery, such as electronic alert systems or development of ‘hyponatraemia teams’.

Chapter 5

Real-life experience of tolvaptan use in the treatment of severe hyponatraemia due to SIADH

5.1 Materials and methods

5.2 Results

5.3 Conclusions

5.4 Summary of main findings

5.1. Materials and methods

5.1.1. Study rationale

At the time this study was designed and conducted, very little data existed about the effectiveness and safety of tolvaptan for treatment of SIADH in a real-life clinical setting. In everyday clinical practice, tolvaptan use is usually reserved for a more severe degree of hyponatraemia than in clinical trials. Most clinicians have been using tolvaptan sparingly, mainly for the treatment of severe biochemical hyponatraemia (serum Na < 125 mmol/l). However, the landmark SALT-1 and SALT-2 studies, based on which tolvaptan was granted marketing authorisation, recruited mostly individuals with mild to moderate biochemical hyponatraemia (serum Na ≥ 125 mmol/l). In fact, very few patients with serum Na < 120 mmol/l participated in SALT studies since hyponatraemia below this cut-off in association with neurological impairment was an exclusion criterion[284 285]. In addition to the paucity of efficacy and safety data for tolvaptan use in patients with low baseline serum Na, SALT studies reported that lower starting serum Na levels were associated with higher rates of correction[284]. In light of these findings, the European guideline development group recommended against the use of vaptans in patients with serum Na concentration < 125 mmol/l, raising safety concerns related to the increased risk for overly rapid correction of hyponatraemia[154]. Besides the recommendation against vaptans in profound hyponatraemia, the 'European Clinical Practice Guidelines on the treatment of hyponatraemia' did not recommend the use of vaptans for mild to moderate biochemical hyponatraemia due to SIADH[154]. This decision to not recommend a place for tolvaptan within its licensed indication stands in marked contrast with other

recent recommendations and guidelines[152 245 253 260] which, in general, recommend tolvaptan as the second line treatment option for patients who are not suitable for or are resistant to fluid restriction[274]. Therefore, tolvaptan, the only pharmacological therapy approved across three continents for the treatment of SIADH, has become the subject of controversy with the European guidelines stimulating a debate about its role in the current management of SIADH. Contrary to the European guidelines, expert panel recommendations by Verbalis et al placed tolvaptan as second-line treatment for SIADH after fluid restriction, including even patients with starting serum Na < 120 mmol/l, provided that patients are carefully monitored[152]. Thus, the current treatment guidelines, based mainly on expert opinions rather than on high quality evidence, have failed to achieve agreement on the role of vaptans on SIADH management[274]. All these factors highlighted the need for a real-life evaluation of effectiveness and safety of tolvaptan for treatment of profound hyponatraemia in order to test to which extent results of SALT studies are reproducible in real-world clinical practice and in hospital populations with more severe degree of biochemical hyponatraemia.

5.1.2 Aims and objectives

This retrospective case series aimed to assess the effectiveness and safety of tolvaptan use for the treatment of SIADH in day-to-day clinical practice.

The secondary objectives were:

- To test the hypothesis that the magnitude of correction in serum sodium is correlated to the baseline serum sodium concentration.
- To study the association between baseline biochemical parameters and the rate of hyponatraemia correction.
- To examine whether clinicians follow the recommendations of regulatory authorities about electrolyte monitoring and whether they take appropriate measures to prevent or reverse overly rapid hyponatraemia correction.
- To evaluate the effectiveness and safety of low-dose tolvaptan for the treatment of SIADH.

5.1.3 Study design

This study was a retrospective consecutive case series of all hospitalised patients treated with tolvaptan for SIADH in 2 London hospitals between November 2010 and February 2014. Centre A (Royal Free Hospital), a 900-bed teaching hospital, was at the time of study a major centre for neurosurgery and has a large oncology and haematology unit. Centre B (Barnet Hospital) is a 450-bed district general hospital.

According to local policy of both institutions, authorisation of tolvaptan prescriptions was solely restricted to Consultant Endocrinologists. All patients were treated with tolvaptan as monotherapy, with other therapeutic modalities being withdrawn at least 12 hours before tolvaptan initiation. Tolvaptan-treated patients were clearly advised to drink ad libitum, as documented in case notes. Both hospitals lacked local guidelines stating when tolvaptan should be prescribed and algorithms to specify the frequency and mode of patient monitoring, and when and how to halt further increase of serum sodium. A small number of patients were initiated on a lower starting tolvaptan dose of 7.5 mg, instead of 15 mg, based on previous reports suggesting that ‘off-label’ low initiation dose may be associated with a reduced risk for overly rapid correction[297].

The study was registered with the Clinical Governance & Clinical Audit Department of both institutions, and ethics approval was not required.

5.1.4 Patient selection

All adult hospitalised patients with SIADH who were administered at least one dose of tolvaptan were included. The participants underwent full diagnostic work-up and met all essential criteria for SIADH, including euvolaemia, hyponatraemia and low serum osmolality with inappropriately raised urine osmolality and sodium, normal adrenocortical reserve and exclusion of hypothyroidism[162] [163]. Tolvaptan-treated patients who had hypervolaemic or hypovolaemic hyponatraemia were excluded.

5.1.5 Data collection

Hospital case notes, drug prescription charts, discharge letters and laboratory results were reviewed retrospectively for each patient. Data were collected about: age, gender, ethnic origin, comorbidities, drug history, aetiology of SIADH, history of prior hyponatraemia, therapeutic modalities used for treatment of SIADH and sodium response, serum biochemistry (sodium, osmolality, urea, creatinine, potassium, urate, cortisol, free thyroxine, thyrotropin) and urine biochemistry (osmolality, sodium, potassium), initiation dose of tolvaptan, duration of tolvaptan therapy, length of hospitalisation and inpatient mortality.

For the purpose of evaluating the effectiveness of tolvaptan, response to treatment was defined as achieving serum Na increase from baseline of ≥ 5 mmol/l or meeting the target of serum Na > 130 mmol/l at the end of the treatment episode[164 302]. Safety was assessed based on the percentage of patients exceeding safe limits for hyponatraemia correction, defined as a serum sodium increase by ≤ 12 mmol/l in 24 hours and ≤ 18 mmol/l in 48 hours[227 231]. Optimal electrolyte monitoring was defined as measurement of serum sodium at 6-hour intervals for the first 24 hours following tolvaptan initiation. Recurrence of hyponatraemia after withdrawal of therapy was defined as serum Na decrease by ≥ 5 mmol/l within first 5 days after stopping tolvaptan. Finally, patients in this case series were classified, according to the magnitude of biochemical hyponatraemia, into having moderate hyponatraemia (serum Na 125-129 mmol/l) and severe hyponatraemia (serum Na < 125 mmol/l).

5.1.6 Statistical analysis

Data from each hospital were first analysed individually, and then, the combined data from both hospitals were analysed. Data were summarised using descriptive statistics, with continuous variables being expressed as mean ± SD (standard deviation), and categorical variables as percentages. Linear regression models were applied to investigate the relationship of serum Na change in first 24 hours after tolvaptan therapy with baseline biochemical parameters in the serum (Na, osmolality, urea, creatinine) and in the urine (Na, osmolality), including urine / plasma electrolyte ratio (calculated as urine Na + urine K / serum Na). Fisher's exact test was used to compare the incidence of overly rapid correction between patients with moderate hyponatraemia (baseline serum Na ≥ 125 mmol/l) and severe hyponatraemia (baseline serum Na < 125 mmol/l). An unpaired t-test was used to examine the treatment effect of different initiation doses of tolvaptan. A threshold P value < 0.05 was chosen as the level of statistical significance.

5.2 Results

5.2.1 Demographic characteristics

Data were collected on 61 consecutive patients (49 in Centre A and 12 in Centre B). Participants (33 females, 28 males) had a (mean ± SD) age of 74.4 ± 15.3 years. With respect to ethnic origin, the largest ethnic group was Caucasian accounting for 78.7%, while 18.0% of patients were of Asian origin and 3.3% of Afro-Caribbean origin.

There was a wide distribution of patients within different specialities: 45/61 (73.7%) patients were under the care of medical specialities, including Geriatrics (26.2%), General Medicine (18.0%), Oncology (9.8%), Endocrinology (6.6%), Neurology (4.9%), Respiratory (3.3%), Haematology (3.3%), and Infectious Diseases (1.6%); 16/61 (26.3%) patients were under the care of surgical specialities, including Neurosurgery (13.1%), Orthopaedics (6.6%), and other surgical specialities (6.6%).

5.2.2 Aetiology and duration of SIADH

Following detailed review of the medical case notes, the commonest type of SIADH in our series was malignant SIADH, as illustrated in Table 24.

Table 24. Classification of cases according to aetiology of SIADH

Aetiology	N=61	(%)
Malignancy	15	24.6%
Unknown	15	24.6%
CNS¶ pathology	10	16.4%
Pulmonary illness	9	14.7%
Drug-induced	6	9.8%
Postoperative	4	6.6%
Miscellaneous causes	2	3.3%

¶ CNS: central nervous system

Among 15 cases of malignant SIADH, 6 were related to small-cell lung cancer, 2 to breast cancer, 1 to mesothelioma, 1 to lymphoma, 1 to oesophageal cancer, 1 to pancreatic cancer, 1 to prostate cancer, 1 to bladder carcinoma, and 1 to metastatic neuroendocrine tumour of unknown primary. Among 10 individuals with CNS pathology-related SIADH, 2 had meningioma, 2 subarachnoid haemorrhage, 2 subdural haematoma, 2 occurred after spinal decompression (1 lumbar spine laminectomy and 1 cervical spine), 1 had ischaemic stroke and 1 underwent trans-sphenoidal resection of a pituitary tumour. Almost all (8/9) patients with pulmonary

illness-related SIADH had pneumonia apart from 1 patient with pulmonary tuberculosis. Four out of six cases of drug-induced SIADH were attributed to selective serotonin reuptake inhibitors (SSRIs), in specific to citalopram in 3 patients and sertraline in 1 patient, while 1 case was related to amitriptyline and 1 to carbamazepine.

Hyponatraemia was newly diagnosed in 41 of 61 patients (67.2%). The remaining 20 of 61 (32.8%) patients had hyponatraemia in the recent past as evidenced by at least one serum Na value < 135 mmol/l in the preceding 6 months.

5.2.3 Baseline biochemical parameters

Prior to initiation of tolvaptan, the (mean ± SD) serum sodium concentration was 119.9 ± 5.5 mmol/l. Amongst 61 patients, 12 had moderate hyponatraemia with serum Na levels ≥ 125 mmol/l (range 125-130 mmol/l). Out of the remaining 49 individuals, 25 had serum Na concentration of 120-124 mmol/l and 24 had serum Na < 120 mmol/l (range 103-119 mmol/l), including 8 individuals with serum Na < 115 mmol/l. Of note, 68.9% of patients had urine osmolality > 400 mOsm/kg and 50.8% had U/P ratio >1. All the baseline biochemical parameters are shown in Table 25.

Table 25. Baseline biochemical parameters at tolvaptan initiation

Biochemical parameter	**Mean ± SD**
Serum	
Na (mmol/l)	119.9 ± 5.5
K (mmol/l)	4.3 ± 5.5
Urea (mmol/l)	4.8 ± 2.1
Creatinine (umol/l)	64.6 ± 27.1
Osmolality (mOsm/kg)	252.4 ± 12.4
Urine	
Na (mmol/l)	84.2 ± 43.0
K (mmol/l)	38.3 ± 16.6
Osmolality (mOsm/kg)	468.6 ± 151.2
U/P ratio*	1 ± 0.4

* U/P ratio: Urine / Plasma electrolyte ratio

5.2.4 Initial therapy of hyponatraemia

The mean time interval between serum Na levels reaching ≤ 128 mmol/l and initiation of tolvaptan was 6.7 ± 6.5 days. Tolvaptan was used as first-line agent only in 9/61 cases (14.8%). Tolvaptan was mostly used as second-line treatment (37/61 patients; 60.6%), with 1st line treatment being fluid restriction (28 cases), isotonic saline (4 cases), fluid restriction (4 cases) and salt tablets (1 case). In the remaining 15 cases (24.6%), tolvaptan was third-line treatment after failure of other therapeutic modalities, such as fluid restriction followed by demeclocycline (7 cases), isotonic saline followed by fluid restriction (7 cases) and hypertonic saline followed by fluid restriction (1 case). The mean duration of first-line therapy preceding tolvaptan was 3.4 days with subsequent (mean ± SD) serum Na change of - 0.1 ± 3.5 mmol/l at the end of therapy.

5.2.5 Effectiveness and safety of tolvaptan

Tolvaptan, initiated at a dose of 15 mg in 55 cases and 7.5 mg in 6 cases, increased serum Na concentration from a baseline of 119.9 mmol/l by a mean of 9 mmol/l in the first 24 hours. Overly rapid correction of serum sodium, defined as serum Na increase of > 12 mmol/l within 24 hours or > 18 mmol/l within 48 hours, was observed in 14/61 (23.0%) of patients, as shown in Table 26. However, none of those patients subsequently exhibited neurological symptoms or signs indicative of ODS, as evidenced by detailed review of medical charts.

Table 26. Serum sodium changes in first 24 and 48 hours of tolvaptan therapy

Correction of serum Na over first 24 and 48 hours	
sNa change in first 24 hours (mmol/l)*	9 ± 3.9
Percentage with over rapid 24-hour correction†	18%
sNa change in first 48 hours (mmol/l)*	11.4 ± 5.6
Percentage with over rapid 24-hour or 48-hour correction‡	23%

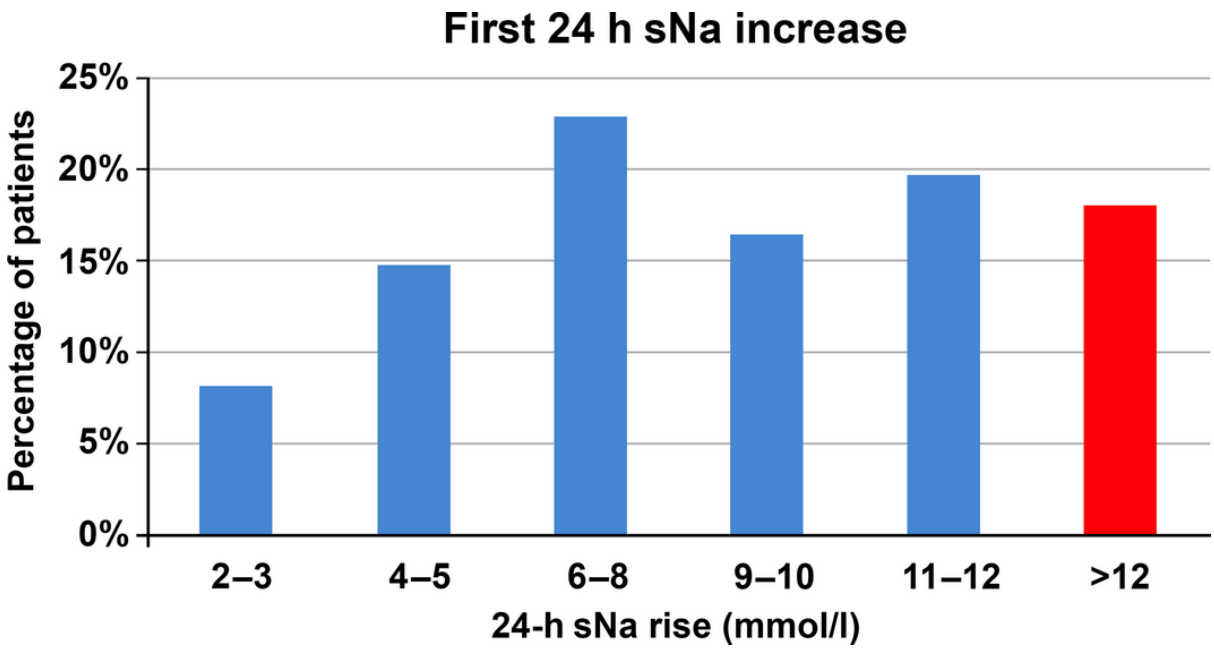
* Mean ± standard deviation

† Over rapid 24-hour correction defined as serum Na increase of > 12 mmol/l

‡ Over rapid 24-hour or 48-hour correction defined as serum Na increase of > 12 mmol/l in 24 hours or > 18 mmol/l in 48 hours

The first 24-hour Na rise exceeded 12 mmol/l in 18% of patients, while 19.7% of patients corrected serum Na by 11-12 mmol/l. In 49.2% of cases tolvaptan increased serum Na concentration by 5-10 mmol/l, while it resulted in correction by 2-4 mmol/l in the remaining 13.1% of cases. The proportions of patients with differing magnitudes of serum Na increase in the first 24 h of tolvaptan therapy are illustrated in Figure 17.

Figure 17. Relative frequency distribution of serum Na change in first 24 hours after tolvaptan therapy.



After tolvaptan therapy, 59 of 61 patients (96.7%) were responders, as evidenced by an incremental serum Na rise of ≥ 5 mmol/l which was achieved in all these cases within 48 hours following tolvaptan initiation, as shown in Table 27. Of note, 27 patients (44.3%) received only 1 or 2 doses of tolvaptan. At the end of tolvaptan therapy, mean (± SD) values were for serum Na 133.5 ± 4.5 mmol/l, for K 4.4 ± 0.5 mmol/l, for urea 6.1 ± 3.9 mmol/l and for creatinine 71.8 ± 31.1 umol/l.

Table 27. Serum sodium correction at the completion of tolvaptan therapy

At the end of tolvaptan therapy	
Duration of therapy (days)*	4.2 ± 4
sNa rise (mmol/l)*	13.5 ± 5.9
Percentage of patients with sNa rise of ≥ 5 mmol/l	96.7%
sNa (mmol/l)*	133.5 ± 4.5
Percentage of patients with sNa > 130 mmol/	80.3%

* Mean ± standard deviation

5.2.6 Frequency of serum sodium monitoring and measures to prevent overly rapid correction

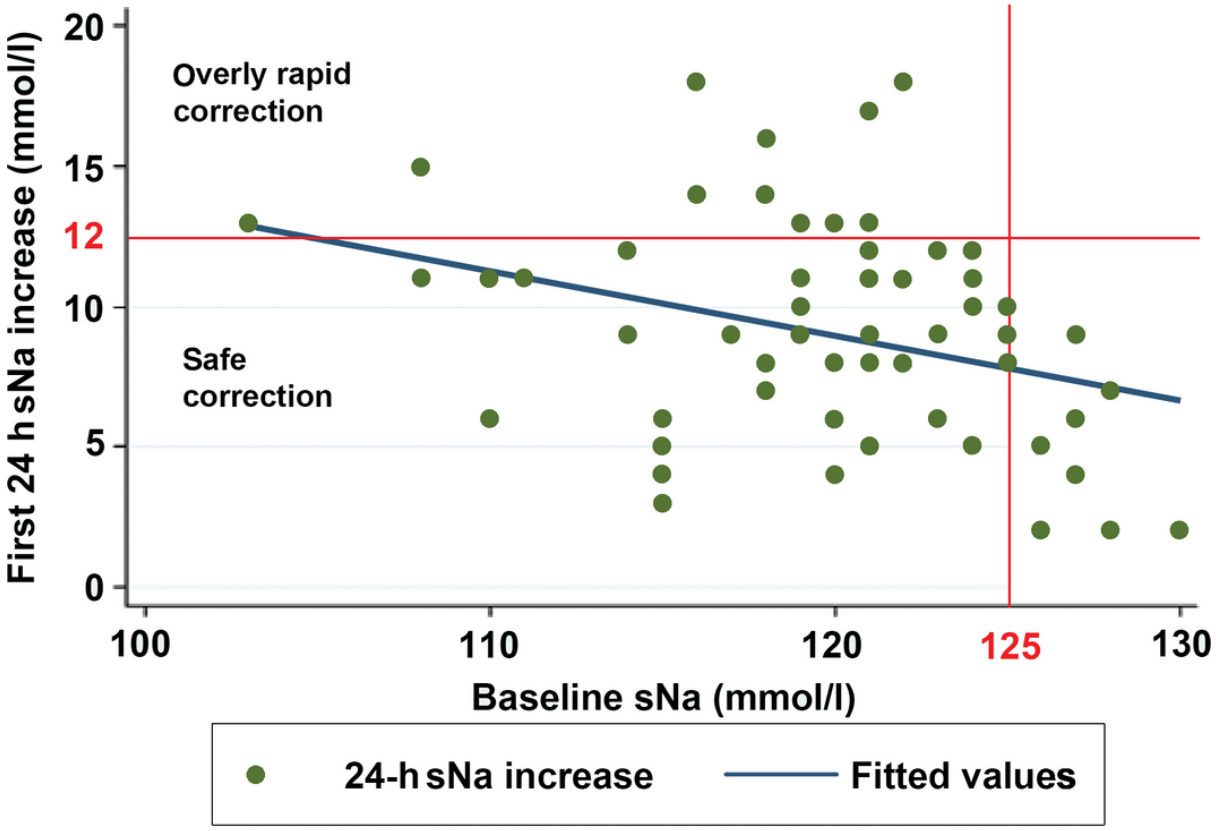
While serum Na concentration was measured in all patients 24 hours after initiation of tolvaptan, there was not a single patient who underwent serum Na measurement at 6-hour intervals during the first day of tolvaptan treatment. At least one measurement at any time point during the first 24 hours was performed only in 13 out of 61 individuals (21.3%), with 5 subjects having serum sodium checked twice and the remaining 8 subjects having sodium tested once. Serum Na was measured 6 hours after administration of tolvaptan in 7 of 61 patients with increase of 5.3 ± 2.1 mmol/l and 12 hours after in 11 of 61 patients with increase of 7.0 ± 3.9 mmol/l.

Out of 13 patients having electrolyte monitoring during the first day of tolvaptan therapy, 5 patients, who had 12-hour serum Na increase of 7, 8, 10, 10, 11 mmol/l, exceeded the safe daily limits for hyponatraemia correction. Measures to prevent too rapid sodium correction were taken in 1 patient who, despite hypotonic fluid infusion, exhibited a further Na rise from 10 mmol/l in the first 12 hours to 13 mmol/l at the end of 24-hour period. Measures to reverse overly rapid correction of hyponatraemia by infusing 5% dextrose in water were taken in 3 patients, in 2 cases 24 hours after and in 1 case 36 hours after tolvaptan initiation. No patients were administered desmopressin.

5.2.7 Relationship between baseline biochemical parameters and rate of hyponatraemia correction

There was a negative significant correlation (coefficient – 0.23, P value 0.012) between baseline serum Na and 24-hour Na change. For every 1 mmol/l reduction in baseline value, serum Na increased by an additional 0.23 mmol/l (95% CI, 0.05-0.41) at 24 hours after tolvaptan initiation, as shown in Figure 18.

Figure 18. Linear regression between baseline serum Na (x axis) and serum Na correction in first 24 hours after initiation of tolvaptan (y axis)



Red vertical line indicates baseline serum Na of 125 mmol/l

Red horizontal line indicates serum Na increase of 12 mmol/l in first 24 hours

Correlation coefficient: - 0.23 (P value 0.012)

In patients with baseline serum Na ≥ 125 mmol/l, the mean increase over first 24 hours was lower at 5.5 ± 2.9 mmol/l compared to 9.7 ± 3.6 mmol/l in patients with starting serum Na < 125 mmol/l. None among 12 patients with starting serum Na ≥ 125 mmol/l exceeded the safe rate for hyponatraemia correction at any time point compared to 14/49 (28.6 %) patients with serum Na < 125 mmol/l, as shown in Table 28. However, this difference did not reach statistical significance (P = 0.052). Of note, among patients exceeding the safe rate for Na correction, the highest starting serum Na was 122 mmol/l.

Table 28. Contingency table for rate of serum Na correction with tolvaptan

		Number of patients (N) (%) as per rate of serum Na correction	
Baseline serum Na (mmol/l)	Total N	N (%) (within safe limits)	N (%) (overly rapid)
<125	49	35 (71.4%)	14 (28.6%)
≥125	12	12 (100%)	0 (0)

Another negative significant correlation (coefficient – 0.04, P value 0.032) was observed between baseline serum creatinine and 24-hour serum Na change. For every 1 umol/l increase in baseline creatinine, the magnitude of Na rise at 24 hours after tolvaptan initiation decreased by 0.04 mmol/l (95% CI, 0.004-0.076). This correlation, albeit statistically significant, had limited clinical significance since a creatinine difference of 25 umol/l was required to result in a 1 mmol/l change in serum Na increase.

All other parameters tested with linear regression models, including patient's age, serum urea, serum osmolality, urine osmolality, urine Na, and urine / plasma electrolyte ratio, were not associated with the 24-hour Na rise.

5.2.8 Association of speciality, aetiology of SIADH, and previous therapies for hyponatraemia with rate of overly rapid correction

The rate of overly rapid correction in patients under the care of medical specialities was 20.0% (9/45) vs 31.2% (5/16) in surgical patients. The difference was not statistically significant (P = 0.490). In specific, 3 out of 8 (37.5%) neurosurgical patients exceeded a safe rate of correction.

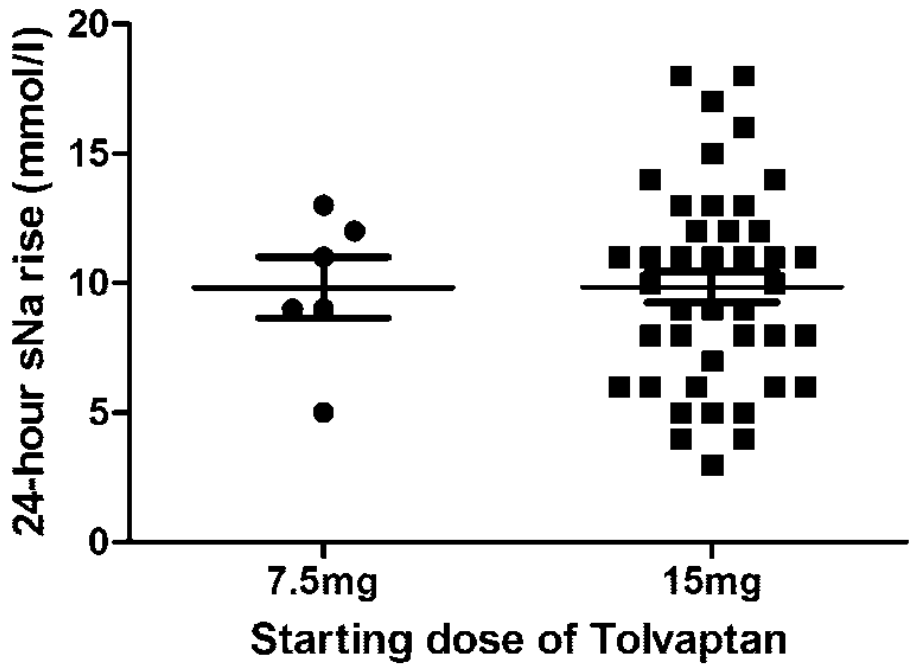
The cause of SIADH did not impact on the frequency of too rapid correction of hyponatraemia, with 4 cases being observed in malignant SIADH, 3 in neurosurgical SIADH, 3 in SIADH of unknown cause, 2 in drug-induced and 2 in post-operative SIADH.

With respect to previous therapeutic modalities for SIADH, none of 9 patients treated with demeclocycline prior to tolvaptan had overly rapid correction. In 2 out of 6 cases (33.0%) with drug-induced SIADH, where the offending drug was withdrawn, overly rapid correction occurred.

5.2.9 Effectiveness and safety of low tolvaptan doses

Among patients with baseline serum Na < 125 mmol/l, 6 individuals were prescribed 7.5mg, half the recommended starting dose, as the initiation dose. Among patients with serum Na < 125 mmol/l, patients initiated on 7.5 mg dose (mean starting Na 115.3 mmol/l) had 24-hour serum Na increase of 9.8 ± 2.9 mmol/l vs 9.9 ± 3.9 mmol/l in patients treated with 15 mg dose (mean starting Na 118.7 mmol/l). The initiation dose did not impact on the degree of serum Na increase in 24 hours (P = 0.989), as shown in Figure 19. One out of 6 patients treated with low-dose tolvaptan exceeded the safe limit for correction, by a sodium rise of 13 mmol/l from baseline 103 mmol/l in the first 24 hours.

Figure 19. Scatter plot of magnitude of serum Na rise for different initiation doses (7.5 mg vs 15 mg)



Horizontal lines indicate the mean 24-hour serum Na rise for each group

5.2.10 Serum sodium after discontinuation of tolvaptan and patient outcomes

In 49 individuals, serum Na was reassessed at 3 or 5 days after discontinuation of tolvaptan. Three days after discontinuation of tolvaptan, the mean change of serum Na was - 3.1 ± 5.0 mmol/l and five days after was - 3.9 ± 6.6 mmol/l. Serum Na decrease of ≥ 5 mmol/ within first five days after discontinuation of tolvaptan was observed in 21/49 (42.8%) patients, with half of these (11/21) patients being administered another course of tolvaptan as inpatients.

A significant proportion of patients (17/56 or 30.3%) were discharged with serum Na < 130 mmol/l. In total, 20/56 (35.7%) patients were discharged on therapy for SIADH, including 11 patients on fluid restriction, 6 on tolvaptan (all with malignant SIADH), and 3 on demeclocycline.

The inpatient mortality rate in this cohort was 8.2%. The mean length of hospital stay was 22.6 ± 17.2 days with serum Na of 132.5 ± 5.0 mmol/l at hospital discharge.

5.3 Conclusions

This ‘real-world’ study examined the efficacy and safety of tolvaptan in a cohort of patients with a mean baseline serum sodium of < 120 mmol/l, lower than in all other major studies[164 284 302]. This study found that tolvaptan resulted in an, unprecedently high, mean increase of 9 mmol/l in serum sodium concentration in the first day of therapy. This case series confirmed tolvaptan as an effective treatment modality in correcting severe hyponatraemia due to SIADH, with 96.7% of patients having increased sodium levels by an increment of ≥ 5 mmol/l within 48 hours of treatment.

However, greater efficacy was associated with a higher risk of too rapid correction of hyponatraemia. We observed a substantial rate (23.0%) of overly rapid correction of serum sodium which is the highest been reported to date in the literature of tolvaptan therapy. Adopting a more ‘conservative’ safe 24-hour correction limit of 10 mmol/l/day, as suggested by the authors of the European guidelines[154], more than one in three individuals in our case series did exceed this limit. Nonetheless, no cases of osmotic demyelination syndrome were recorded.

With regards to electrolyte monitoring, we found that our day-to-day clinical practice was suboptimal compared against monitoring guidance by FDA and EMA. Despite the ‘’black box warning’’ on the label of tolvaptan about the risk of too rapid correction and the clear advice for close monitoring of serum sodium, only a fifth of patients had their serum sodium concentration measured at least once during the first 24 hours following tolvaptan initiation.

This case series demonstrated an inverse relationship between baseline serum sodium concentration and magnitude of sodium correction after starting tolvaptan. The lower the starting sodium value, the greater the sodium correction following

tolvaptan administration. In specific, for baseline serum sodium ≥ 125 mmol/l the mean first 24-hour increase was 5.5 mmol/l, while for starting sodium < 125 mmol/l the mean first day increase was 9.7 mmol/l. In our case series, no patients with serum sodium > 122 mmol/l exceeded the safe limits for hyponatraemia correction, while as many as a third of individuals with serum sodium of ≤ 122 mmol/l had overly rapid correction of serum sodium. Interestingly, another baseline biochemical parameter, serum creatinine, was found to impact on the magnitude of hyponatraemia correction with tolvaptan. However, this correlation carried little weight since a creatinine difference of as much as 25 umol/l was required to result in a 1 mmol/l change in serum Na increase. Regarding the aetiology of SIADH, it did not seem to impact on the magnitude of response to tolvaptan, but the sample size of subgroups for each cause was very small.

Given the high incidence of overly rapid correction of hyponatraemia in individuals with very low starting serum sodium concentration, a small number of patients were treated with an ‘off-label’ low initiation dose of 7.5 mg. The daily sodium increase was almost identical with that seen in patients treated with the licensed initiation dose of 15 mg. These data suggested that lower doses of tolvaptan appear to be effective, but may still carry a risk of overcorrection. However, the sample size was too small to draw a firm conclusion about the efficacy and safety of lower tolvaptan doses.

Following discontinuation of tolvaptan, hyponatraemia recurred in almost half of cases, as previously reported in SALT studies[284]. Subsequently and in view of the high cost of tolvaptan restricting reimbursement in the outpatient setting, most of those patients were treated on long-term basis with an alternative therapeutic modality, such as fluid restriction or demeclocycline. The exception was selected

cases with refractory SIADH, almost exclusively patients with metastatic cancer and limited life expectancy.

The main strength of this case series was that it examined the efficacy and safety of tolvaptan in patients with severe hyponatraemia for whom little to no data exist. Our case series included a larger number than any other study of tolvaptan-treated patients at the severe end of the hyponatraemia spectrum, exceeding even the Hyponatraemia Registry in the sample size of the subgroup with serum sodium < 120 mmol/l. This is a population for which safety data concerning tolvaptan therapy is lacking and its use is a matter of intense debate with European guidelines recommending against its use[154], whereas US guidelines favouring its use with caution[152]. In addition, this study was the largest UK observational study evaluating the effectiveness and safety of tolvaptan use in 'real-life' clinical practice, with all participants having undergone rigorous diagnostic work-up and met all formal criteria for SIADH. Finally, this case series allowed for the first time comparison of monitoring in routine UK clinical practice against the standards set in the drug label.

Nonetheless, our study had a number of limitations, mainly because it was a retrospective observational study describing real-life clinical experience. Firstly, a case of ODS could not be categorically excluded. However, no neurological deterioration was recorded in medical notes, while manifestations of ODS, such as spastic quadriparesis, pseudobulbar palsy and impairment in the level of consciousness, would be unlikely to go unnoticed by healthcare professionals. They also typically occur within 7 days after correction[227 231], when most individuals in our cohort were still inpatients. Also such a 'real-life' retrospective study could not accurately assess clinical outcomes. Thus, it is unclear to what extent biochemical

correction translated into clinically significant improvement of symptoms, particularly as our cohort included many elderly patients with several chronic comorbidities who received active treatment for acute illnesses and might have symptomatology of multifactorial aetiology. A further inherent weakness of this ‘real-world’ study was its heterogeneity of SIADH aetiologies, ranging from self-limiting acute conditions, for example pneumonia, to chronic diseases with indefinite duration, such as advanced malignancies. In addition, parameters such as the initiation dose of tolvaptan, the frequency of monitoring and decision to withdraw therapy did not follow a specific protocol, but were based on the clinical judgement of the prescribing physician. Also frequent electrolyte monitoring after tolvaptan initiation, as per drug label instructions, was not systematically performed. Finally, the very small number of patients treated with low-dose initiation tolvaptan dose did not enable us to draw a conclusion about its efficacy and safety. The same limitation of small sample size also applies to subgroups of SIADH according to aetiology; as a result, this study cannot enlighten us about whether patients with SIADH of some aetiologies are more prone to overly rapid hyponatraemia correction.

In conclusion, this study confirmed that tolvaptan is highly efficacious in correcting severe hyponatraemia due to SIADH. However, it also reported an unprecedentedly high risk of tolvaptan-induced overly rapid sodium correction, especially when baseline serum sodium is < 125 mmol/l and rigorous electrolyte monitoring is not in place.

5.4 Summary of main findings

- A real-life study of tolvaptan therapy, administered to SIADH patients with a mean baseline serum Na of 120 mmol/l, found a mean first 24-hour Na increase of 9 mmol/l.
- Tolvaptan was highly efficacious in correcting hyponatraemia due to SIADH, as evidenced by a 97% response rate.
- Tolvaptan carried a high risk of overly rapid sodium correction, with the safe rates of correction being exceeded in 23% of patients.
- Clinicians did often not follow the monitoring guidelines of regulatory authorities, since electrolytes were measured only in a fifth of patients in the 24-hour period following tolvaptan initiation.
- There was an inverse relationship between baseline serum Na and magnitude of Na correction.
- All the patients exceeding the safe sodium correction limits had starting Na ≤ 122 mmol/l.
- A low (7.5 mg) starting tolvaptan dose might be effective.
- This real-world study of tolvaptan use in SIADH patients with severe hyponatraemia showed great effectiveness in combination with an unprecedentedly high incidence of overly rapid sodium correction.
- Tolvaptan should be used under close monitoring and with great caution.
- Prospective studies are warranted to examine the safety of tolvaptan use for severe hyponatraemia under stringent monitoring, the impact of tolvaptan on patient-related outcomes, the efficacy and safety of lower tolvaptan doses, and the parameters which can predict the magnitude of response to tolvaptan.

Chapter 6

A prospective intervention study of intensive endocrine input versus routine care in inpatients with hyponatraemia due to SIADH

6.1 Materials and methods

6.2 Results

6.3 Conclusions

6.4 Summary of main findings

6.1 Materials and methods

6.1.1 Study rationale

Despite the fact that determining the cause of hyponatraemia is crucial to guiding effective treatment, our real-world observational studies, described in detail in Chapters 3 and 4, found that most hyponatraemic patients were not adequately investigated with the exception of patients who received expert endocrine input[324] [325]. Large observational studies have also established undertreatment of SIADH, the commonest cause of hyponatraemia[174], as a frequent occurrence in clinical practice across the world with most patients being discharged with persistent hyponatraemia[164]. Nevertheless, no prospective studies have examined whether a consultation with a specialist and the application of an evidence-based algorithm could improve success rates in correcting hyponatraemia. In specific, the efficacy and safety of all treatment algorithms for SIADH, including the ones recommended by the European guideline development group[154] and by Verbalis et al[152], has not been rigorously tested in real-world clinical practice. Also, both the European and US guidelines have highlighted the lack of evidence that more effective treatment of inpatient hyponatraemia per se improves patient-important outcomes, such as mortality, length of hospital stay, readmission rate, and mild symptoms in association with hyponatraemia[154] [152].

6.1.2 Aims and objectives

The primary hypothesis of our study was that prompt and intensive endocrine input was superior to non-specialised routine clinical care in correcting hyponatraemia with the primary endpoint being time to achieve an increase in serum sodium concentration by ≥ 5 mmol/l.

The secondary objectives were:

(1) To compare the total rise in serum Na and the percentage of patients discharged with serum Na < 130 mmol/l between the intervention and control group.

(2) To compare the magnitude of hyponatraemia correction 2, 3, and 5 days following admission between the intervention and control arm.

(3) To examine the effect of endocrine input on inpatient mortality rate, length of hospital stay and readmission rate.

(4) To study the impact of hyponatraemia correction on neurocognitive symptoms.

6.1.3 Study design

This single-centre prospective controlled intervention study was conducted at the Royal Free Hospital over a 6-month period. This study assessed the efficacy of an intervention (intensive endocrine input) vs standard clinical care on the time for correction of hyponatraemia and patient outcomes in patients admitted with serum Na ≤ 127 mmol/l due to SIADH. During the first 3-month period (1st October 2014 to 31st December 2014) all patients underwent 'routine' care (control group), while in the following 3-month period (1st January 2015 to 31st March 2015) patients received intensive endocrine input (intervention group). The time required to achieve serum Na increase of ≥ 5 mmol/l was chosen as the primary endpoint since this magnitude of correction can be sufficient to improve symptoms of hyponatraemia[249].

We considered this study design using a historical control superior to a randomised controlled trial (RCT) using a concurrent control. The reason was that in the real-life clinical setting clinicians might often seek expert help from the investigators about patients allocated to the control arm, resulting in possible ''dilution'' of the control group with patients receiving the intervention. As a result, a concurrent control arm might include a higher proportion of patients receiving specialist input than in real-life routine care, potentially leading to underestimation of the true impact of endocrine input on patient outcomes.

The study received ethical approval from the London - Camden & Islington Research Ethics Committee, and all subjects provided written informed consent before participation.

6.1.4 Patient selection

All adult hospitalised patients with serum Na concentration ≤ 127 mmol/l both on hospital admission and on the following day were identified through an automated electronic laboratory system. This cut-off serum Na value was selected because previous data from our cohort, described in detail in Chapter 2, showed a significant upward inflection in inpatient mortality below that threshold[326]. Among these patients, only subjects who met all essential diagnostic criteria for SIADH, including euvolaemia, hyponatraemia and low serum osmolality with inappropriately raised urine osmolality and sodium, normal adrenocortical reserve, and exclusion of hypothyroidism[162 163], participated in the study. Both intervention and control groups had exactly the same inclusion and exclusion criteria.

Subjects were excluded if they met any of the following exclusion criteria: (1) aged < 18 years old, (2) presence of hypervolaemic hyponatraemia, (3) hypovolaemic hyponatraemia, (4) decompensated chronic liver disease, (5) decompensated heart failure, (6) renal impairment with serum creatinine > 200 umol/l or receiving renal replacement therapy, (7) uncontrolled hyperglycaemia with serum glucose > 15 mmol/l, (8) pregnancy / breastfeeding, (9) receiving end-of-life care.

In the light of preliminary data from our cohort indicating a mean time of 5.5 days to reach the primary endpoint of serum Na rise ≥ 5 mmol/l and considering a standard deviation of 1 day for each arm, power sample size was estimated as 18 patients in each arm in order to show 20% difference in the primary endpoint (1.1 day) due to the intervention with 90% power and 5% significance level.

6.1.5 Control group

Patients in the control arm received routine clinical care with no direct contact being made between the Investigators and these subjects. In real-life clinical practice, the mainstay of SIADH treatment was fluid restriction in combination with discontinuation of offending drugs and treatment of underlying cause. When hyponatraemia was refractory to fluid restriction, some patients were referred to Endocrinologists, usually after considerable delay, for consideration of pharmacological therapy. In addition to ‘standard’ clinical care, all patients had full biochemical work-up automatically performed, such as serum and urine osmolality and electrolytes, thyroid function tests and serum cortisol measurement, in order to help ascertain the aetiology of hyponatraemia and confirm the diagnosis of SIADH with the attending physicians being notified of the results.

6.1.6 Intervention group

All patients meeting the inclusion criteria and being admitted in the 3-month period between 1st January 2015 and 31st March 2015 were allocated to the intervention arm provided that they gave informed consent to study participation. Besides adults with capacity to give informed consent, incapacitated adults were also considered for participation in the study since they represented the subgroup of patients exhibiting the most severe neurological symptoms related to hyponatraemia and also a significant proportion of hyponatraemic inpatients were elderly with serious underlying comorbid conditions such as dementia. In cases when the patient's doctors determined that this individual did not have the capacity to give informed consent, the investigators acted according to the Mental Capacity Act 2005 and took every reasonable step to identify a "personal consultee" with the first person to be contacted being the person recorded as next of kin in the medical records. A "personal consultee" was a person who was engaged in caring for the participant (not professionally or for payment) or was interested in his/her welfare. If a ''personal consultee'' could not be identified, the investigators consulted a "nominated consultee", a person independent of the project appointed in accordance with the Department of Health's Guidance on nominating a consultee for research involving adults who lack capacity to consent. For this study, the ''nominated consultee'' was the Consultant or Specialist Registrar of the clinical team caring for the patient. The consultee gave advice rather than consent, but the advice of the consultee was respected. If the consultee so advised, the participant should not take part and, if already taking part, the patient would be withdrawn unless withdrawal of treatment would involve significant risk to the participant's health. Any advance statement by the participant was respected.

The purpose of the intervention was to implement current best clinical practice in the management of SIADH[152 154 245], including only investigations and therapeutic measures which are suggested by contemporary guidelines and consensus statements and are currently used in routine clinical care. Any novel diagnostic tests and therapeutic modalities were not utilised. The investigators, two senior Endocrinologists with special interest in hyponatraemia and a Research Nurse, provided daily input throughout hospitalisation to the attending medical and nursing team under whose care patients remained. Regular assessment by the Investigators included history taking, physical examination, evaluation of volume status, measurement of serum electrolytes and, in selected cases, additional tests such as urine electrolytes/urine osmolality/serum urate.

In selected cases when the clinical assessment of extracellular fluid volume was equivocal or key biochemical values such as urine Na were not available to the investigators yet, we adopted a low threshold to prescribe a diagnostic challenge of volume expansion with isotonic saline to differentiate euvolaemia from hypovolaemia[152 167]. When intravenous infusion of 2000 ml of isotonic saline over 24 hours resulted in correction of serum Na by < 5 mmol/l, this was regarded as confirmatory of SIADH[201]. We decided against the routine use of increase in fractional excretion of sodium (FENa) of > 0.5% as a supplementary criterion to reach the diagnosis of SIADH because, despite the fact that it can in some cases facilitate reliable classification of the type of hyponatraemia, it requires additional urine tests and calculations which are often impractical in day-to-day clinical practice.

Treatment options for SIADH included hypertonic saline, fluid restriction, demeclocycline and tolvaptan. In the light of the absence of high quality evidence supporting the efficacy of different treatment modalities in SIADH and the fact that

different guidelines have failed to reach a consensus, especially regarding the optimal pharmacological agent in cases of failure of fluid restriction, clinical judgement was exercised without adherence to a strict, rigid protocol and treatment was individualised. First line treatment was fluid restriction at a volume of 750 – 1,000 ml/day with the exception of cases of severe hyponatraemic encephalopathy who required urgent correction with intravenous infusion of 1.8% sodium chloride under close supervision in a High Dependency or Intensive Care Unit. In patients not responding to fluid restriction (defined as serum Na increase of < 4 mmol/l within 48-72 hours), the choice of 2nd line treatment was left to the discretion of the Investigators, being either tolvaptan or demeclocycline, while urea was not utilised because of lack of availability and absence of local experience in its use. Demeclocycline at a starting dose of 900 mg per day in divided doses was prescribed in patients with high probability of requiring treatment for longer than 1-2 weeks, such as malignant SIADH. Tolvaptan at a starting dose of 15 mg once per day was used when there was a clinical need for prompt hyponatraemia correction, for example to render a patient fit for chemotherapy or surgery, and in cases with likely short duration of SIADH, for example pneumonia[152]. In order to mitigate the risk of overly rapid serum Na correction after tolvaptan introduction, serum Na was measured at 6, 12, 18, and 24 hours after the first dose and 24-hourly afterwards and fluid balance was accurately recorded in a chart. In addition, a specific algorithm was followed which suggested intensifying the frequency of electrolyte monitoring and considering administration of hypotonic fluids in cases when serum Na correction exceeded 6 mmol/l during the first 6 hours or 8 mmol/l during the first 7-18 hours after tolvaptan initiation. Subsequently, appropriate adjustments of the tolvaptan dose were made according to the rate of hyponatraemia correction.

6.1.7 Data collection

After review of hospital case notes, drug prescription charts and laboratory results, data were collected on all subjects in both intervention and control arms about the following: demographic characteristics including age, gender and ethnic origin; speciality caring for patient; chronicity of hyponatraemia with hyponatraemia classified as chronic when most recent serum Na value measured within last 6 months was ≤ 132 mmol/l; presence of 12 common comorbid conditions; drug history; reason for admission; aetiology of SIADH; serum biochemistry (sodium, osmolality, urea, creatinine, potassium, urate, cortisol, free thyroxine, thyrotropin) and urine biochemistry (osmolality, sodium, potassium). With respect to treatment, data were collected on provision and timing of expert input as well as on the type, duration and effectiveness of all therapeutic episodes each individual had for treatment of SIADH. Data were also recorded about several endpoints, including serum Na correction at different time points (2, 3, and 5 days post admission); percentage of patients achieving correction benchmarks and time interval required to reach these targets (serum Na increase by ≥ 5 mmol/l from baseline serum Na, serum Na ≥ 132 mmol/l, and serum Na ≥ 135 mmol/l); nadir serum Na; serum Na on discharge; inpatient mortality rate; length of hospitalisation; readmission rate within 60 days post discharge.

In view of the lack of validated tools to evaluate neurocognitive symptoms related to hyponatraemia, Mini-Mental State Examination (MMSE) was chosen as a tool to undertake longitudinal assessment of neurocognitive function in patients of the intervention group. MMSE, a 30-point questionnaire that examines functions including registration, attention and calculation, recall, language, ability to follow

simple commands and orientation, has been used extensively to follow the course of cognitive changes in an individual over time[327 328]. MMSE was performed in all participants of the intervention group at 3 different time points; on admission, when serum Na increased by ≥ 5 mmol/l from baseline and when serum Na was ≥ 132 mmol/l.

6.1.8 Statistical analysis

Data were analysed using SPSS (version 21.0, Chicago, IL). Continuous variables were expressed as mean ± standard deviation (SD) or percentages. Analysis of variance (ANOVA) and Pearson's Chi-square test were used to test differences between the intervention and the control group. Logistic regression analysis models were implemented in order to test if patients in the intervention group were more likely than the control group to achieve correction benchmarks such as serum Na ≥ 132 mmol/l or serum Na ≥ 135 mmol/l after adjusting for baseline serum Na. Adjusted odds ratios (aOR) and 95% confidence intervals (95% CIs) were reported. P values of < 0.05 were considered significant.

6.2 Results

6.2.1 Demographic characteristics

The control group included 23 patients (11 males, 12 females) with a (mean ± SD) age of 77.6 ± 10.7 years compared to the intervention group of 18 subjects (12 males, 6 females) with a (mean ± SD) age of 72.7 ± 10.2 years. There was no statistically significant difference in age and gender distribution across the groups. Most participants in the control arm (82.6%) were Caucasian, while 13.0% had Asian and 4.4% Afro-Caribbean origin. The largest ethnic group in the intervention arm was Caucasian accounting for 83.3% with the remaining 16.7% being of Asian origin.

6.2.2 Speciality distribution and duration of SIADH

There was a wide distribution of patients within different specialities with most patients in both groups being under the care of medical specialities (86.9% medical vs 13.1% surgical in the control group and 61.1% medical vs 38.9% surgical in intervention group).

For the purpose of this study, chronic hyponatraemia was defined as the most recent serum Na value measured within previous 6 months being less than 132 mmol/l. The cases of acute hyponatraemia exceeded those of chronic hyponatraemia in both arms of the study (65.2% vs 34.8% in the control arm and 55.5% vs 44.5% in the intervention arm). The demographic characteristics along data about chronicity of hyponatraemia and caring speciality are summarised in Table 29.

Table 29. Demographic characteristics of control and intervention arms

Demographic variables	**Control arm** N=23	**Intervention arm** N=18	**P value**
Age (years)*	77.6 ± 10.7	72.7 ± 10.2	0.146
Gender (male:female)	11:12 (47.8%:52.2%)	12:6 (66.6%:33.3%)	0.228
Ethnic origin (Caucasian:Other)	19:4 (82.6%:17.4%)	15:3 (83.3%:16.7%)	0.672
Speciality (medical:surgical)	20:3 (86.9%:13.1%)	11:7 (61.1%:38.9%)	0.075
Acute:chronic	15:8 (65.2%:34.8%)	10:8 (55.5%:44.5%)	0.529

* Mean ± standard deviation

6.2.3 Frequency of comorbidities

The frequency of comorbidities was similar in both arms of the study with the commonest comorbid conditions in the control arm being hypertension (47.8%), active cancer (34.8%) and arrhythmia (30.4%). In the intervention arm, the most commonly recorded comorbidities were hypertension (44.4%), chronic obstructive pulmonary disease (38.9%) and active cancer (22.2%), as shown in Table 30.

Table 30. Prevalence of common comorbidities in control and intervention arm

Comorbidities	**Control arm** N=23 (%)	**Intervention arm** N=18 (%)	**P value**
Heart Disease	11 (47.8%)	6 (33.3%)	0.350
Arrhythmia	7 (30.4%)	3 (16.6%)	0.308
Heart Failure	5 (21.7%)	3 (16.6%)	0.684
IHD†	1 (4.3%)	3 (16.6%)	0.187
Stroke / TIA¥	6 (26.1%)	2 (11.1%)	0.230
Hypertension	11 (47.8%)	8 (44.4%)	0.829
Diabetes	4 (17.4%)	3 (16.6%)	0.951
Lung Disease	8 (34.8%)	9 (50.0%)	0.326
COPD¶	3 (13.1%)	7 (38.9%)	0.056
Active Cancer	8 (34.8%)	4 (22.2%)	0.380
Depression	4 (17.4%)	0	0.118
Dementia	3 (13.1%)	1 (5.5%)	0.628

† IHD: Ischaemic Heart Disease, ¥ TIA: Transient Ischaemic Attack, ¶ COPD: Chronic Obstructive Pulmonary Disease

6.2.4 Aetiology of SIADH

The commonest cause of SIADH in both groups was pulmonary disease, followed by unknown aetiology and malignancy. The distribution of patients according to the aetiology of SIADH did not differ significantly between two arms, as illustrated in Table 31. In specific, the control arm included 8 patients with pneumonic illness, 7 of whom had pneumonia and 1 influenza A, and 5 cases of malignant SIADH (3 patients with small cell lung cancer, 1 with prostate cancer and 1 with lymphoma). In the intervention arm, amongst 6 participants with respiratory illness, 3 had pneumonia, including 1 with pneumocystis pneumonia (PCP), 2 infective exacerbation of COPD and 1 influenza, while 2 patients had malignant SIADH, one due to non-small cell lung cancer and one due to bladder carcinoma.

Table 31. Classification of cases according to the aetiology of SIADH

Aetiology	**Control group** N=23 (%)	**Intervention group** N=18 (%)	**P value**
Pulmonary illness	8 (34.8%)	6 (33.3%)	0.923
Idiopathic	6 (26.1%)	6 (33.3%)	0.613
Malignancy	5 (21.8%)	2 (11.1%)	0.369
Drug-induced	1 (4.3%)	2 (11.1%)	0.573
CNS disorder**	2 (8.7%)	1 (5.6%)	0.702
Various	1 (4.3%)	1 (5.6%)	0.859

** CNS disorder: Central nervous system disorder

6.2.5 Baseline biochemical parameters

The mean serum Na concentration on admission was significantly lower in the intervention arm (120.7 mmol/l) in comparison with the control arm (124.1 mmol/l). Apart from serum osmolality which was also lower in the intervention arm in line with more severe hyponatraemia, all other biochemical parameters did not differ between two groups, as shown in Table 32.

Serum urate was measured in 10 patients of the ‘routine care’ arm and was ≤ 0.12 mmol/l in 8 cases, while it was 0.13-0.19 mmol/l in the other 2 cases. All 18 participants in the intervention arm had serum urate levels tested which were ≤ 0.12 mmol/l in 7 cases (38.9%), 0.13-0.18 mmol/l in 10 cases (55.6%) and 0.25 mmol/l in 1 case (5.5%).

Table 32. Baseline biochemical parameters in both study arms.

Biochemical parameters	**Control group** N=23	**Intervention group** N=18	**P value**
Serum	Mean ± SD	Mean ± SD	
Na (mmol/l)	**124.1 ± 3.1**	**120.7 ± 5.5**	**0.017**
K (mmol/l)	4.4 ± 0.7	4.5 ± 0.7	0.643
Urea (mmol/l)	4.9 ± 2.1	4.3 ± 2.0	0.365
Creatinine (umol/l)	58.7 ± 18.5	59.4 ± 20.5	0.916
Osmolality (mOsm/kg)	**259.1 ± 8.0**	**252 ± 10.2**	**0.017**
Urine			
Na (mmol/l)	88.1 ± 48.8	65.3 ± 29.2	0.088
K (mmol/l)	36.6 ± 20.3	36.3 ± 20.2	0.968
Osmolality (mOsm/kg)	445.1 ±138.0	401.6 ± 146.0	0.333
Urine / Plasma electrolyte ratio			
(UNa + UK) / PNa	1.05 ± 0.4	0.84 ± 0.3	0.135

6.2.6 Endocrine input

There was a statistically significant difference between control and intervention groups in the frequency and time of expert input provision, as expected by the study design. All patients (100%) in the intervention group received endocrine input compared with 12/23 patients (52.2%) in the control group ($P < 0.001$). The mean (± SD) time interval between admission and expert input in the intensive arm was 1.8 ± 1.3 days, much shorter than in the ‘routine care’ arm (5.7 ± 5.3 days; $P = 0.007$).

6.2.7 Utilisation of treatment modalities for SIADH

In the group receiving ‘routine’ clinical care, 6 out of 23 individuals (26.1%) had no specific treatment for SIADH, neither in the form of active therapy nor by discontinuing a potentially offending drug. In contrast, all patients in the intervention group underwent active hyponatraemia therapy (P = 0.027). The mean (± SD) number of therapeutic episodes used per patient in the control arm was 1.2 ± 0.9, significantly lower than in the intervention arm (1.9 ± 1.3; P = 0.041). Only 4.3% of patients receiving ‘routine’ care had more than two therapeutic episodes vs 22.2% in the intensive arm.

Specifically, 17 out of 23 patients (73.9%) in the control group received treatment for SIADH. First line treatment was in 13 patients (56.5%) fluid restriction, isotonic saline infusion in 3 cases (13.0%) and hypertonic saline in 1 case (4.4%). Nine out of 23 patients (39.1%) received second line treatment, including tolvaptan in 4 cases, fluid restriction in 3 cases, isotonic saline in 1 case and demeclocycline in 1 case. Only one individual was administered third line therapy in the form of tolvaptan. In the intervention group, all subjects received active treatment for SIADH, with first line therapy being fluid restriction in the majority of cases (83.3%) and isotonic saline infusion in the remaining 16.7%. Out of 18 participants in the intervention group, 8 (44.4%) had second line treatment such as fluid restriction (4 cases), tolvaptan (2 cases), demeclocycline (1 case) and hypertonic saline (1 case). Further therapy for SIADH was administered in 4 patients as third line (fluid restriction in 2, tolvaptan in 1, hypertonic saline in 1) and in 3 patients as fourth line (fluid restriction in 2 and tolvaptan in 1).

The frequency of utilisation of different therapeutic modalities did not differ significantly between the arms of the study, with the exception of fluid restriction which was prescribed in 100% of patients in the intervention group vs 69.6% in the control group, as shown in Table 33.

Table 33. Frequency of utilisation of different therapeutic modalities

Use of treatment modalities	**Control group** N=23	**Intervention group** N=18	**P value**
Fluid restriction	**16 (69.6%)**	**18 (100%)**	**0.010**
Drug discontinuation	5 (21.7%)	7 (38.9%)	0.231
Normal saline	4 (17.4%)	5 (27.8%)	0.425
Tolvaptan	5 (21.7%)	3 (16.7%)	0.684
Demeclocycline	2 (8.7%)	3 (16.7%)	0.439
Hypertonic saline	1 (4.3%)	2 (11.1%)	0.409

6.2.8 Efficacy of different therapeutic modalities

In total, 9 subjects across both study arms received a test infusion of isotonic saline, predominantly at a volume of 2000 ml over 24 hours. At baseline, all but one patients had urine osmolality in the range of 438-604 mOsm/kg. The mean (± SD) response to isotonic saline was increase in serum Na levels of 2.2 (± 1.9) mmol/l. Aggravation of hyponatraemia was recorded only in 1 subject with baseline urine osmolality 539 mOsm/kg and Urine/Plasma electrolyte ratio of 1.50 who experienced serum Na decrease of 2 mmol/l. The remaining 8 out of 9 individuals experienced a serum Na rise ranging between 1 and 4 mmol/l. Of note, among 4 patients with urine osmolality > 530 mOsm/kg, 3 of those responded to isotonic saline by a serum Na rise of 2-3 mmol/l. In addition, among 3 subjects with Urine/Plasma electrolyte ratio > 1.0, 2 of those increased serum Na levels by 2-3 mmol/l.

With regards to the effectiveness of fluid restriction in the 'routine' care group, fluid restriction at a mean (± SD) volume of 953 (± 245) ml/day was prescribed in 16 subjects for a duration of 4.7 ± 3.3 days with a total response of 2.6 ± 5.5 mmol/l. Amongst 16 patients, 5 (31.3%) responded to fluid restriction with a total serum Na rise of ≥ 5 mmol/l, 7 (43.7%) showed serum Na rise of 1-4 mmol/l and the remaining 4 (25.0%) did not correct at all or worsened hyponatraemia with a serum Na change between 0 and -9 mmol/l. Six out of 11 unsuccessful therapies with fluid restriction were followed by other modalities such as tolvaptan in 4 cases, isotonic saline in 1 case and demeclocycline in 1 case, while in the other 5 cases no further therapies were utilised. In the intervention arm, 21 therapeutic episodes of restricting fluid intake to 819 ± 167 ml/day were recorded over a duration of 6.6 ± 5.1 days with a total mean (± SD) response of 6.2 ± 8.6 mmol/l. Out of 21 therapies with fluid restriction, 15 (71.4%) episodes resulted in serum Na rise of ≥ 5 mmol/l, while the

other 6 therapeutic episodes were ineffective, either correcting serum Na by < 5 mmol/l in 2 cases (9.5%) or by aggravating hyponatraemia in 4 cases (19.1%). Four of those 6 unsuccessful therapeutic episodes of fluid restriction were followed by other treatments such as tolvaptan in 3 cases and hypertonic saline in 1 case.

Regarding the use of baseline biochemical parameters as predictors of failure of fluid restriction, no correlation was found between urine osmolality and urine / plasma electrolyte ratio with response to fluid restriction. Across both study arms, 26 subjects had fluid restriction as first line monotherapy with 11 ‘great responders’ having achieved serum Na increase of ≥ 7 mmol/l, 7 ‘partial responders’ having serum Na rise of 3-6 mmol/l and 8 ‘non-responders’ showing either increase of ≤ 2 mmol/l or even worsening of hyponatraemia. Among 11 ‘great responders’, 8/11 had urine osmolality < 500 mOsm/kg and 7/11 had U/P electrolyte ratio < 1.0. However, amongst the ‘great responders’, there were 3 subjects with urine osmolality > 500 mOsm/kg and 4 subjects with U/P ratio > 1.0, including 2 individuals with both values above the thresholds which usually predict high likelihood for fluid restriction to fail. Reviewing the biochemistry of ‘non-responders’, 6 out of 8 had urine osmolality ≥ 430 mOsm/kg and 7 out of 8 had U/P ratio ≥ 0.94.

With respect to tolvaptan use, 8 individuals across both study arms, 5 in the control and 3 in the intervention arm, were treated with tolvaptan, with one patient having two therapeutic episodes with tolvaptan following recurrence of severe hyponatraemia shortly after its discontinuation. Tolvaptan was highly effective in all 9 therapeutic episodes with (mean ± SD) serum Na rise of 11.7 ± 4.1 mmol/l ranging from 5 to 18 mmol/l over a treatment period of 3.2 ± 2.2 days. With the exception of one case, all 9 episodes lasted 4 days or less, including 4 episodes lasting ≤ 2 days. There was a single case of too rapid hyponatraemia correction in association with

tolvaptan therapy since a patient in the control group increased serum Na levels by 14 mmol/l in the first 24 hours following tolvaptan initiation without any adverse neurological sequelae.

6.2.9 Achievement of correction benchmarks

With regards to the primary endpoint of serum Na rise ≥ 5 mmol/l, the (mean ± SD) time interval needed to correct serum Na by ≥ 5 mmol/l was 3.5 ± 1.2 days in the intervention group, almost half the time (7.1 ± 4.5 days) required in the control group, with this difference being statistically significant (P = 0.005). However, the percentage of patients in the intervention group meeting this endpoint did not differ significantly between the intervention group (88.9%) and in the control group (73.9%) (P = 0.230). Of note, subgroup analysis indicated that all subjects in the control arm who did not reach the primary endpoint belonged to the subgroup not receiving endocrine input. Also, the success rates at reaching serum Na thresholds of ≥ 132 mmol/l and ≥ 135 mmol/l did not differ significantly between study arms, as shown in Table 34.

Table 34. Achievement of serum sodium correction benchmarks

Correction benchmarks	**Control group** N=23	**Intervention group** N=18	**P value**
Na increase by ≥ 5 mmol/l			
Number of cases (%)	17 (73.9%)	16 (88.9%)	0.230
Time required (days)*	**7.1 ± 4.5**	**3.5 ± 1.2**	**0.005**
Na ≥ 132 mmol/l			
Number of cases (%)	14 (60.9%)	13 (72.2%)	0.447
Time required (days)*	9.0 ± 4.9	8.1 ± 3.2	0.191
Na ≥ 135 mmol/l			
Number of cases (%)	8 (34.8%)	6 (33.3%)	0.923
Time required (days)*	9.6 ± 5.1	9.5 ± 3.7	0.898

* Mean ± standard deviation

6.2.10 Rate of hyponatraemia correction

Three days following admission, a further decrease from the baseline in serum Na value was observed in as many as 43.5% of patients in the control arm vs only 5.6% of subjects in the intervention arm (P = 0.007). As a result, the control arm had a mean nadir serum Na of 120.3 mmol/l, much lower than its baseline serum Na of 124.1 mmol/l, in comparison to a mean nadir value in the intervention arm being 119.1 mmol/l, slightly lower than its starting concentration of 120.7 mmol/l. At the time point of 5 days after admission, the intervention arm increased serum Na levels to a much larger degree (8.4 ± 3.3 mmol/l) than the control arm (1.9 ± 6.2 mmol/l), with this difference being statistically highly significant (P value < 0.001).

Overly rapid correction of serum sodium, defined as serum Na increase > 12 mmol/l during any 24 hour-period or > 18 mmol/l during any 48 hour-period, was not recorded in the intervention group. In the control group, 1 patient exceeded the safe limits for hyponatraemia correction with serum Na increase of 14 mmol/l in the first 24 hours following tolvaptan initiation. No cases of osmotic demyelination syndrome were documented.

Comparison of the magnitudes of hyponatraemia correction showed that the intervention arm was consistently superior to the control arm at all time points, as illustrated in Table 35.

Table 35. Correction of serum sodium 2, 3 and 5 days following admission

Correction of serum Na	**Control group** N=23	**Intervention group** N=18	**P value**
2 days			
Correction (mmol/l)*	0.3 ± 4.7	1.9 ± 3.5	0.234
Cases with sNa decrease (%)	12 (52.2%)	4 (22.2%)	0.051
3 days			
Correction (mmol/l)*	**0.5 ± 4.7**	**4.5 ± 3.3**	**0.004**
Cases with sNa decrease (%)	**10 (43.5%)**	**1 (5.6%)**	**0.007**
5 days			
Correction (mmol/l)*	**1.9 ± 6.2**	**8.4 ± 3.3**	**< 0.001**
Cases with sNa decrease (%)	**7 (31.8%)**	**0**	**0.015**

* Mean ± standard deviation

6.2.11 Serum sodium at discharge

The mean (± SD) total serum Na increase achieved during hospitalisation, defined as the difference between serum Na on admission and serum Na at discharge or death, was 12 ± 6.8 mmol/l in the intervention arm and 6.3 ± 0.3 mmol/l in the control arm. This difference in total serum Na rise was statistically highly significant ($P < 0.001$). Subgroup analysis of the control arm showed higher total serum Na rise in patients with endocrine input (9 ± 3.8 mmol/l) compared to patients not receiving endocrine input (4.5 ± 4.8 mmol/l).

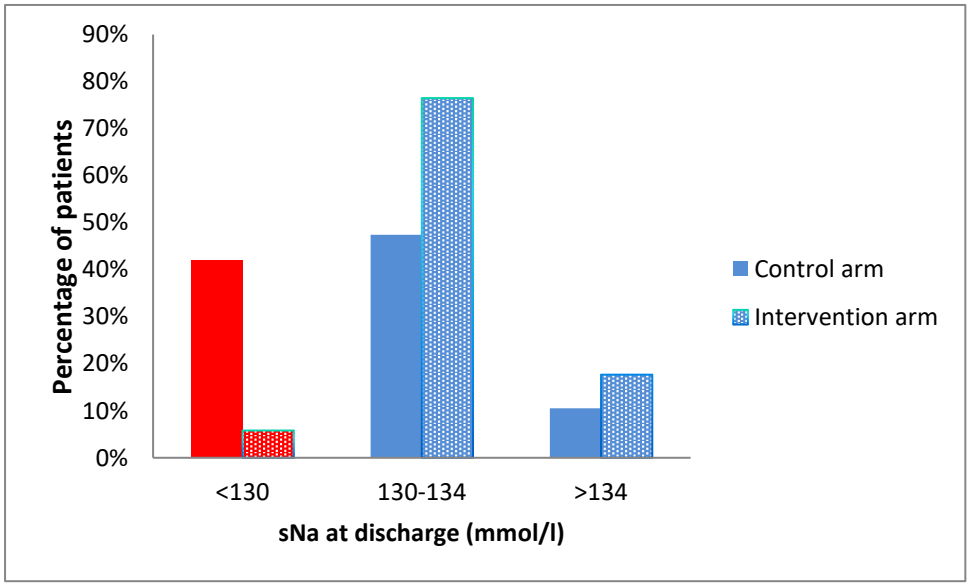
Excluding participants who died during hospitalisation, the mean serum Na at discharge in the intervention group was higher (132.1 mmol/l vs 130.3 mmol/l) than in the control group, despite the fact that their starting serum Na was singificantly lower. The proportions of patients in each arm of the study discharged with normonatraemia (135-145 mmol/l), mild hyponatraemia (130-134 mmol/l), moderate hyponatraemia (125-129 mmol/l) and severe hyponatraemia (< 125 mmol/l) are described in Table 36.

Table 36. Distribution of patients according to serum sodium at hospital discharge across study arms.

Number of patients (%)	**Control arm** N=19	**Intervention arm** N=17
Number of cases with sNa < 125 mmol/l (%)	2 (10.5%)	0
Number of cases with sNa 125-129mmol/l (%)	6 (31.6%)	1 (5.8%)
Number of cases with sNa 130-134 mmol/l (%)	9 (47.4%)	13 (76.5%)
Number of cases with sNa ≥ 135 mmol/l (%)	2 (10.5%)	3 (17.7%)

As illustrated in Figure 20, the proportion of patients discharged with moderate to severe hyponatraemia (serum Na < 130 mmol/l) in the intervention group (5.8%) was significantly lower than in the control group (42.1%; P = 0.012). Also subgroup analysis of the control arm demonstrated that 30% of cases receiving endocrine input were discharged with moderate to severe hyponatraemia vs 55.5% of cases not receiving endocrine input.

Figure 20. Bar chart illustrating relative frequency distribution of serum sodium (sNa) at hospital discharge in both groups. Solid bars represent control arm, while dotted bars represent intervention arm. Red bars show percentage of patients discharged with moderate to severe hyponatraemia (serum Na < 130 mmol/l).



6.2.12 Patient outcomes

As shown in Table 37, the mean length of hospital stay in the intervention group (10.9 days) was significantly shorter than in the control group (14.5 days) by 3.6 days (P = 0.004). The inpatient mortality rate in the intervention group was numerically lower than in the control group, 5.5% in comparison to 17.4%, but this difference did not reach statistical significance. In total, amongst the 5 fatal cases in both groups, only 2 patients, both subjects with SIADH due to pneumonia in the 'routine' care group, had persistent severe hyponatraemia at the time of death. The first patient did not receive any specific therapy for SIADH and died with a serum Na of 123 mmol/l, while the second patient was not given second line treatment for SIADH despite failing to respond to fluid restriction and died with a serum Na of 122 mmol/l.

A significantly larger proportion of individuals in the intervention group (58.8%) were discharged on therapy for SIADH, either on fluid restriction or on demeclocycline, vs 15.8% of patients in the control group (P = 0.004). Finally, the readmission rates within the following 60 days were similar across study arms in the range of 23.5-26.3%.

Table 37. Patient outcomes at discharge

Outcomes	**Control arm** N=23	**Intervention arm** N=18	**P value**
Inpatient mortality rate	4/23 (17.4%)	1/18 (5.5%)	0.250
Length of stay (days)*	**14.5 ± 7.9**	**10.9 ± 5.3**	**0.004**
Proportion of patients discharged on therapy	**3/19 (15.8%)**	**10/17 (58.8%)**	**0.004**
Readmission rate	5/19 (26.3%)	4/17 (23.5%)	0.970

* Mean ± standard deviation

6.2.13 Effect of hyponatraemia correction on cognitive function

Amongst 18 subjects in the intervention group, 4 patients exhibited severe neurological symptoms, such as acute changes in mental status and confusion, including 2 individuals with Glasgow Coma Score (GCS) of 12. All those patients showed marked improvement in symptomatology after serum Na increase. The remaining patients either had non-specific mild symptoms (9 cases) or seemed asymptomatic (5 cases). Improvement in MMSE score by ≥ 3 points when serum Na reached 132 mmol/l or increased by ≥ 5 mmol/l was recorded in 38.9% of subjects in the intervention arm, including 22.2% of patients with incremental rise of ≥ 10 points.

6.3 Conclusions

This study demonstrated that prompt endocrine input reduced the time needed to achieve clinically meaningful serum sodium increase and led to significantly shorter length of hospital stay. With respect to timely correction of hyponatraemia, this study found that intensive endocrine input shortened the time required for a rise in serum sodium ≥ 5 mmol/l by a mean of 3.6 days. Our study also demonstrated superiority of systematic endocrine input vs 'routine' clinical care in several secondary endpoints related to correction of hyponatraemia, such as in the magnitudes of serum sodium increase 3 and 5 days following admission. It is noteworthy that as many as almost half of subjects in the control arm experienced aggravation of hyponatraemia within 72 hours after admission, lowering serum sodium concentration below 120 mmol/l and exposing them to risk of hyponatraemic encephalopathy. In contrast, only around 5% of patients in the intensive arm had lower sodium values 3 days after admission than at the baseline. Surprisingly, the success rates at reaching serum sodium values of 132 and 135 mmol/l were similar across study groups. Nevertheless, the mean total rise in serum sodium during hospitalisation was significantly higher in the intervention arm (12 mmol/l) compared to the control arm (6.3 mmol/l), resulting in a much lower proportion of individuals receiving intensive input (5.8%) being discharged with moderate to severe hyponatraemia versus a high percentage (42.1%) of patients in the 'routine' care arm. The most likely explanation is that hyponatraemia correction was followed by recurrence or worsening in a respectable proportion of patients in the control group, while this phenomenon did not occur in the intervention group, owing to their close and intensive monitoring and ongoing SIADH treatment. Furthermore, subgroup analysis of the control group found that, amongst controls, participants who did not receive any endocrine input

achieved an even lower magnitude of total sodium rise and were more likely to be discharged with persistent hyponatraemia than subjects who had endocrine input.

Several factors may explain the superiority of intensive endocrine input to ‘routine’ clinical care in correcting hyponatraemia despite the fact that endocrine input was also provided to almost half of patients in the ‘routine’ care arm. A key factor may be that in the control arm the average time from presentation to referral for endocrine review was longer than 5 days. In addition, a considerable delay in therapy was frequently observed in the control group, while patients in the intervention group had prompt diagnosis and timely initiation of appropriate treatment for SIADH. In the control arm, around a quarter of patients did not receive any specific treatment for SIADH, whereas there were no untreated cases in the intervention arm. Comparison of the utilisation of therapeutic modalities in both study groups showed that patients in the intervention group received on average more therapies with the frequency of using fluid restriction being significantly higher by around 30% in the intervention compared to control arm. Also, with the exception of tolvaptan, patients in the intensive arm received more often any other therapies such as drug discontinuation, isotonic saline, hypertonic saline and demeclocycline. Interestingly, fluid restriction was not only more frequently imposed in the intensive arm, but it also had a higher success rate at rising serum sodium by ≥ 5 mmol/l in the intervention group (71%) versus the control group (31%). The higher effectiveness of fluid restriction in the intervention arm might be explained by its more rigorous implementation and increased levels of patients’ adherence to it. An alternative explanation could be that urine osmolality and urine/plasma electrolyte ratio were numerically lower, but not significantly different, in the intervention than in the control arm, potentially increasing the likelihood for response to fluid restriction. When fluid restriction was

ineffective, it was often not followed by an additional therapy in the control arm in contrast to second line treatment with tolvaptan or demeclocycline being administered in the intervention group, when indicated. Specialist care provision, apart from being effective, was safe without limits for sodium correction being exceeded in any cases.

In addition to superiority in correcting hyponatraemia, expert input reduced by 3.6 days the mean length of hospitalisation. This finding becomes even more noteworthy in light of the unprecedentedly low percentage of patients (5.8%) discharged with moderate or severe hyponatraemia, much lower than those observed in our recent multicentre UK observational study (23.8%)[325], described in detail in Chapter 4, and in the Hyponatraemia Registry (43%)[302]. Moreover, the intervention group had numerically lower inpatient mortality rate (5.5%) than the control group (17.4%), but this difference was not statistically significant. Chart review of two fatal cases with persistent severe hyponatraemia in the control group suggested that severe hyponatraemia did not directly lead to their death, but it might still have made an indirect contribution[136]. Finally, in a considerable proportion of patients, prompt correction of hyponatraemia resulted in a rapid improvement of cognitive function and symptomatology.

The main strength of our study was being the first prospective study assessing the effect of expert endocrine input on correction of hyponatraemia and patient-related outcomes. Also this intervention could be readily applicable in everyday clinical practice since the investigators used only tests and therapeutic measures routinely available. Taking into account that ‘routine’ care at our institution included referral of a large proportion of cases to Endocrinologists and that the subgroup of the control

arm without specialist input achieved even lower serum sodium increase than the subgroup with endocrine input, our study might underestimate the positive impact of the intervention. In addition, patients enrolled in each study group were similar in demographic characteristics, frequency of comorbidities and, very importantly, distribution of aetiologies of SIADH, minimising the effect of important confounding variables, such as age, gender, ethnicity, comorbid status. Finally, by study design, we chose to restrict the use of vaptans, by far the most effective and costly sodium-lowering pharmacological agents, in the intervention arm. The rationale behind this choice was to exclude the effect of vaptans in our evaluation of the impact of systematic input and application of best clinical practice on time for hyponatraemia correction and patient outcomes.

However, this study had a number of limitations. First and foremost, the study was not blinded since both the investigators and patients were aware that they were enrolled in the intervention arm of the study. This knowledge of group assignment and its potential benefits might have affected patients' behaviour, for example it might have increased their adherence to therapies such as fluid restriction, and their self-perceived wellbeing and expectations, for example they might feel subjectively well sooner. Also unblinded clinicians might possibly result in bias at any phase of the study, for example either by treating and discharging subjects aggressively to ensure that they achieved shortening of length of stay or by selectively using and reporting statistical tests to prove the superiority of intervention. To minimise the possibility of authors' bias resulting in shorter length of stay in the intervention group, the caring clinical teams responsible for patient care took all clinical decisions such as when a patient should be discharged, with the exception for decisions related to hyponatraemia management. In fact, in a few cases who were looked after surgical

specialities, the investigators' input contributed to prolongation rather than shortening of hospitalisation by strongly recommending against hospital discharge, based on a high probability of hyponatraemia recurrence and continuing need for close electrolyte monitoring. Second, the use of historical rather than concurrent control introduced a potential confounding bias as a result of comparing between two different times. In order to ameliorate any differences between groups separated in time, the intervention arm was studied immediately after the control arm to ensure that parameters, such as standards of medical and nursing care, discharge policy, characteristics of hospital population, and clinicians' prescribing habits, were similar. Another possible confounder was the seasonal effect on the distribution of SIADH aetiologies. However, the frequency of pulmonary infection-related SIADH cases was similar across groups since the first arm of the study took place in late autumn and at the beginning of winter, while the second arm in late winter and at the beginning of spring. Third, another limitation of our study was the absence of randomisation step to safeguard that there were no differences present between the two groups at the start of study. However, the fact that study groups did not differ significantly with regards to a variety of baseline characteristics, including demographics, comorbidities and aetiology of SIADH, supports the conclusion that any difference in the outcomes between the two groups was caused by the intervention per se rather than by differences present at start of the study. Fourth, a further limitation of this study was the small sample size which had adequate power to detect differences in time for correction of hyponatraemia, but it was not powered to identify differences, unless large, in mortality rate and length of stay. The small sample size might also increase the probability of type II statistical error. Significant differences in the underlying aetiology of SIADH might have introduced confounding

if, for example, the intervention group had a higher proportion of short duration SIADH cases, such as pulmonary infection-related and drug-induced SIADH, compared to the control arm. However the proportion of short duration SIADH cases with a high probability for prompt correction was almost identical between intervention and control arm. Additionally, all cases in the intervention arm with drug-induced SIADH, a condition which usually responds very well to drug withdrawal, did not discontinue the, regarded as essential, offending drug, but were treated with fluid restriction. Finally, the generalisability of the positive impact of endocrine input is questionable since it might be highly dependent on the clinical acumen, knowledge and skills of the physicians providing expert input, especially since investigators had extensive experience and expertise in management of SIADH. So the question to be answered is whether systematic input by Endocrinologists with less expertise in the management of hyponatraemia could provide comparable benefits for hyponatraemic patients or if, at least, this positive effect could be reproduced as physicians acquired more experience and knowledge in this field.

In conclusion, these preliminary data demonstrated for the first time that intensive endocrine input was superior to ‘routine’ care in correcting hyponatraemia and improved patient-important outcomes such as length of hospital stay and symptoms. If these results could be generalised, provision of systematic endocrine care for patients with SIADH should be widely adopted to improve clinical outcomes and potentially reduce utilisation of hospital resources.

6.4 Summary of main findings

- This study showed that intensive endocrine input was superior to routine care in correcting hyponatraemia, since the intervention group achieved a Na rise of ≥ 5 mmol/l in 3.5 days versus 7.1 days in the control group.
- Patients receiving expert input achieved a higher total Na rise (12 mmol/l) than those in the control arm (6 mmol/).
- The percentage of patients discharged with serum Na < 130 mmol/l was significantly lower in the intervention arm (6%) compared to 42% in the routine care group.
- The superiority of intensive endocrine input to routine care could be contributed to multiple factors, including prompt initiation of therapy, higher effectiveness of fluid restriction and utilisation of a higher number of different therapies.
- Endocrine input shortened the mean length of hospital stay by 3.6 days.
- The inpatient mortality rate was numerically lower in the intervention group, but the difference was not statistically significant.
- In the majority of patients, prompt correction of hyponatraemia resulted in a rapid improvement of neurocognitive symptoms.
- In total, intensive endocrine input reduced the time for a meaningful correction of hyponatraemia and shortened length of hospitalisation.
- These findings highlighted the need for studies to examine whether hyponatraemia correction can improve patient-related outcomes.
- Provided our findings could be generalised, widespread provision of endocrine care for hyponatraemic patients should be strongly considered.

7. Discussion

7.1 Key areas for further research in the field of hyponatraemia; from basic science to practical management

Emerging data about the potential role of vasopressin in modulating social cognition and behaviour highlights the need for further research in this area. Development of selective positron emission tomography (PET) ligands for vasopressin receptors would be essential in order to conduct in vivo studies of receptor expression and shed new light on correlations between genetic polymorphisms, brain receptor variability, and human social cognition in humans. In addition, further studies are warranted in order to examine the effect of peripherally, usually intranasally, administered AVP on different aspects of social behaviour and interaction. Since AVP is proven to affect behaviour through V1 receptor activation, the question arises about whether intrinsically elevated AVP levels found in most patients with hyponatraemia, rather than hypoosmolality per se, could be involved in the neurocognitive symptomatology of these patients. It remains to be seen what effect vasopressin receptor antagonists may have on these symptoms and how selective V2 receptor antagonists compare to combined V1a/V2 receptor antagonists with regards to their impact on social cognition and interaction.

The role of hyponatraemia as a risk factor for osteoporosis and fractures raises several questions. Firstly, it remains to be answered whether BMD measurement is indicated in all, or at least a subgroup of, patients with chronic hyponatraemia. It is also essential to examine the potential reversibility of bone loss induced by hyponatraemia, as suggested so far by a single case report of a patient with SIADH and severe osteoporosis who showed significant spontaneous improvement of BMD

in lumbar vertebrae partial following restoration of normonatraemia and normal AVP levels in the serum[329]. Even if correcting hyponatraemia can improve BMD, proof that management of hyponatraemia will also result in a reduction of fractures is needed. For these reasons, randomised controlled trials evaluating risk reduction of osteoporosis and fractures after treatment of hyponatraemia are warranted. Furthermore, recent evidence about the role of AVP signalling in bone mass regulation through V1a and V2 receptors in osteoblasts and osteoclasts highlight the need for studies comparing the effect of different therapeutic modalities on BMD and skeletal metabolism. In specific, we should compare treatment options which restore hyponatraemia with no direct effect on AVP receptors, such as urea or fluid restriction, with selective V2 receptor antagonists and combined V1a/V2 receptor antagonists which correct hyponatraemia in combination with a direct action on AVP receptors. Finally, it is debatable whether serum sodium concentration should become part of the Fracture Risk Assessment Tool (FRAX) which was developed by the WHO Collaborating Centre for metabolic bone diseases to evaluate fracture risk of patients. Hyponatraemia is a strong candidate for several reasons, such as its high prevalence, the ease and reliability of serum sodium measurement, its relationship with unsteady gait and falls, and its independent association with the risk of fractures[330]. Provided more data will be generated on the association between different degrees of severity and duration of hyponatraemia and risk of fractures, inclusion of serum sodium in the FRAX model could improve its performance as a tool which quantifies fracture risk.

The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, an event-driven, randomised, double-blind, placebo-controlled study, randomly assigned 4133 patients hospitalised with heart failure to

tolvaptan or placebo, in addition to standard therapy, demonstrating the failure of tolvaptan to improve long-term mortality or heart failure-related morbidity in patients with heart failure[266]. Analysis of EVEREST data showed that tolvaptan, a selective AVPR2 antagonist, significantly increased AVP levels as early as on day 1 with this rise in AVP levels persisting over the course of 52-week therapy[331]. The same observation has been reported in other studies of tolvaptan-treated patients with heart failure, probably due to increase in plasma osmolality or reduction in cardiac preload[296]. This long-term reactive increase in plasma AVP levels leads to increased activation of AVPR1a in the myocardium and vascular wall[332] and has also been associated with an increase in aldosterone levels[333]. The fact that tolvaptan increased AVP levels without an adverse effect on long-term outcomes is not fully explained. One possibility is that the incremental increase in V1a activation was insufficient to produce additional harm. Alternatively, the adverse effects from V1a stimulation were negated or obscured by the beneficial effects from V2 antagonism[331]. In total, these data should inform further investigation into potential beneficial methods of manipulating the AVP pathway for the treatment of heart failure and explore the role of selective V2 versus combined V1a/V2 antagonism[334]. On a different note, studies are also warranted to examine whether marked sex differences in V2R expression in animal models[69] apply also to humans. If this is the case, we need to study whether increased V2R expression in females increases their susceptibility to more severe hyponatraemia due to slower escape from antidiuresis. Furthermore, the potential impact of gender on the aquaretic effect and response rate to vaptans should be assessed.

The field of AQP-based therapeutics presents a compelling opportunity since the bench science in AQP biology suggests multiple potential indications of AQP

modulators. With studies in mice and naturally occurring human AQP mutations offering proof of concept for several indications, human clinical trials are warranted to ultimately establish the suitability of AQP-based therapeutics in human disease. On the one hand, various pharmacological agents which can increase apical plasma membrane expression of AQP2 have been tested as potential treatment options for nephrogenic diabetes insipidus: PDE-5 inhibitor sildenafil seems ineffective despite increase in cyclic GMP pathway activation; calcitonin which increases intracellular cyclic AMP levels needs to be studied further; statins which modulate AQP2 trafficking by affecting the actin cytoskeleton, a key factor in endo- and exocytotic events, have some promising data so far[335]; erlotinib, a selective EGF receptor inhibitor which increases AQP2 phosphorylation and exocytosis, while decreases its endocytosis, was recently shown to enhance APQ2 apical membrane expression in collecting duct principal cells and significantly reduce urine volume by 45% in mice[336]. On the other hand, a novel approach to treat water retention states, including SIADH and hypervolaemic hyponatraemia, would use chemical compounds which inhibit cAMP-induced AQP2 membrane accumulation[337]. Studies are also needed to evaluate various AQP inhibitors, including AQP1 inhibitors which may have utility in diuretic-refractory oedematous states, AQP4 inhibitors which may reduce brain swelling in cytotoxic edema, and inhibitors of AQPs in tumour cells and microvessels which may have the potential to reduce tumour spread and angiogenesis, offering adjunctive tumour chemotherapy[36].

7.2 Hyponatraemia is an independent predictor for inpatient mortality

Hyponatraemia is an independent predictor for inpatient mortality

The case-control study, described in Chapter 2, confirmed and extended the strong association between hyponatraemia and in-hospital mortality, already shown in numerous studies[121 122 123 124 125 126 128 129 130 134 135] as well as a large meta-analysis[311]. The key question still remains whether hyponatraemia contributes to excess mortality or simply reflects severity of underlying illnesses. On the one hand, this study mitigated confounding in the relationship between hyponatraemia and mortality since it matched subjects for more factors than previous studies[134 135 312] and it found that characteristics indicative of disease burden and severity, such as presence of comorbidities, use of frequent medications, length of stay, did not differ between patients with or without exposure to severe hyponatraemia. Thus, this case-control study indicated that hyponatraemia per se may contribute to mortality. On the other hand, improvement of hyponatraemia in our cohort was not associated with mortality reduction in contrast to the findings of a recent meta-analysis by Corona et al[316]. Also, our detailed chart review reported that most fatal cases exhibited significant rise in serum sodium levels prior to death and had life threatening primary pathologies without clinical signs of severe hyponatraemic encephalopathy. In total, this case-control study cannot prove a causal relationship between low serum sodium and death. Three possible scenarios, originally proposed by Hoorn et al[136], could explain why hyponatraemia is a poor prognostic factor.

First scenario: Do patients die directly from severe complications of hyponatraemia?

Hyponatraemia-related severe brain oedema and osmotic demyelination syndrome following too rapid rise in serum sodium are well described clinical entities and can be potentially fatal. However, their very low incidence suggests that they should not play, at least major, role in the epidemiological association between hyponatraemia and mortality.

Second scenario: Do hyponatraemic patients die more often because they are 'sicker'?

Hyponatraemia predicts excess short-term and long-term mortality in patients with heart failure[127 338 339 340], myocardial infarction[341 342 343 344 345], liver cirrhosis[346], pulmonary hypertension[347] and pulmonary embolism[348]. The denominator of all these conditions is their ability to induce a neurohumoral response[137]. In these clinical settings, hyponatraemia has been shown to be a marker of increased activation of neurohumoral axis as a response to arterial underfilling either due to decrease in cardiac output (heart failure) or systemic arterial vasodilatation (cirrhosis)[349]. Unloading of high-pressure baroreceptors results in the activation of the sympathetic nervous system which is the primary integrator of the neurohumoral vasoconstrictor response to arterial underfilling. As a result, there is non-osmotic mediated synthesis and release of arginine vasopressin as well as activation of the renin-angiotensin-aldosterone system[349]. Compared to normonatraemic individuals, those with hyponatraemia have higher levels of AVP; higher plasma levels of renin, angiotensin II and aldosterone; elevated levels of cortisol, epinephrine and norepinephrine; a greater degree of impairment of renal and hepatic blood flow and glomerular filtration rate[338]. All these characteristics in combination with the clinical profile of hyponatraemic patients, especially in the context of heart failure, provide evidence that hyponatraemia reflects more advanced disease and an association with attenuation of baroreceptor-mediated, non-osmotic excess release of AVP[338 339]. Therefore, at least in conditions such as heart failure and cirrhosis, hyponatraemia seems to be a marker of the degree of neurohumoral activation and therefore of the severity of the underlying disease. Hyponatraemia is also related to a different group of conditions characterised by inflammation or acute phase response, including

infections (pneumonia, tuberculosis, meningitis, encephalitis, HIV infection, malaria), postoperative state and strenuous exercise[350]. In inflammatory conditions, such as bacteraemia, urinary tract infection and Kawasaki disease, serum sodium levels have been found to be inversely correlated with the percentage of neutrophils, C-reactive protein, and levels of pro-inflammatory cytokines such as IL-1β and IL-6[351] [352] [353]. Animal and human data have revealed that IL-1β and IL-6, by stimulating both central and peripheral release of vasopressin, are involved in the development of hyponatraemia associated with inflammatory conditions[353] [354]. Therefore, hyponatraemia, a good surrogate marker of the degree of inflammatory response, tends to reflect the severity of infection. For example, patients with pneumonia and hyponatraemia at the time of admission have a higher severity index and higher mortality rate[355]. However, if hyponatraemia was merely a marker of underlying disease severity, our study should show no difference in mortality between hyponatraemic patients and controls, as cases seemed to be as ‘sick’ as controls, or at least show a smaller difference than previous studies when hyponatraemic patients were ‘sicker’ than controls. Thus, the hypothesis that hyponatraemia may act also as a mediator of adverse patient outcomes has become very topical.

Third scenario: Does hyponatraemia contribute indirectly to excess mortality by causing organ dysfunction?

In light of the paucity of data about the potential effects of hyponatraemia on organs and systems, aside brain, hyponatraemia may have other, poorly understood, significant physiological effects[136]. Animal studies have detected increased concentrations of oxidative damage DNA product in sera of hyponatraemic rats, providing evidence in favour of the concept of hyponatraemia-induced oxidative stress[114].

A major question is whether hyponatraemia could compromise the cardiac function, especially taking into account the excess mortality hyponatraemic subjects have during myocardial infarction or in the setting of heart failure. Recent animal data found reduction of calcium channel current in response to low serum Na, in a rapid, reversible, and dose-dependent manner, with hyponatraemia inhibiting calcium channel currents in cardiac myocytes[356]. Decreased calcium conductance in response to decreasing sodium levels may in part explain the depressed cardiac contractility and poor outcomes encountered by hyponatraemic patients with cardiac disease. A recent study by Barsony et al in a rodent model of aging showed that chronic hyponatraemia can cause marked heart enlargement[357]. Histological analysis indicated that increase in heart weight did not represent cardiac hypertrophy, but a combination of increased water content and fibrosis, evidenced by a reduction of cardiac myocyte number as well as a marked increase of collagenous fibrotic material both perivascularly and interstistially[357]. With regards to direct AVP effects, data from rat hearts indicate that it promotes myocardial hypertrophy and remodelling by directly increasing the rate of protein synthesis, mediated via the V1 receptor by activation of the Na/H exchange system[358] and via IP3-mediated

intracellular calcium release[359]. In a rat model of myocardial infarction, hyponatraemia has also been found to impair tolerance to ischaemia reperfusion injury by increasing oxidative injury as well as to increase myocardial infarct size through increased expression of apoptotic proteins and decreased expression of antiapoptotic proteins[360]. Finally, there have been case reports of hyponatraemia triggering cardiac conduction defects[361] and causing apical ballooning, a transient cardiomyopathy mimicking myocardial infarction[362]. These findings from animal studies, in conjunction with numerous observational studies reporting that hyponatraemia predicts poor outcomes in patients with cardiac disease, make the hypothesis of hyponatraemia-induced cardiac compromise plausible.

Compromise of immune function has also been suggested as candidate mediator of hyponatraemia-related excess mortality. These is some epidemiological evidence that the presence of hyponatraemia on admission is associated with increased risk of developing hospital-acquired staphylococcus aureus bacteraemia[363]. AVP, both in vitro and in vivo, was shown to induce a marked fall in proinflammatory mediators and neutrophil recruitment, and a dramatic rise in the renal bacterial burden in mice inoculated with uropathogenic Escherichia Coli (UPEC)[364]. Conversely, administration of the V2 receptor antagonist to UPEC-infected mice stimulated both the local innate response and the antibacterial host defence. These findings evidenced a novel hormonal regulation of innate immune cellular activation and demonstrated that vasopressin, present in abundance in most hyponatraemic subjects, simultaneously reduces host inflammatory responses and favours renal bacterial invasion[364]. In total, there is some suggestive evidence so far supporting the hypothesis that hyponatraemia may result in an immunocompromised state, but no concrete clinical evidence of such a problem.

Is hyponatraemia an innocent bystander?

In a proportion of cases, hyponatraemia can be ‘’an innocent bystander’’ in mortality, since there is substantial evidence that hyponatraemia can often be a marker of disease severity, reflecting underlying haemodynamic alterations in heart failure and cirrhosis and the degree of inflammatory response in infectious diseases. However, hyponatraemia can also can cause directly death in rare circumstances, either due to brain oedema or osmotic demyelination. But the key question is whether hyponatraemia is ‘’the silent killer’’ in a substantial proportion of hyponatraemic patients by causing organ dysfunction and, therefore, indirectly contributing to mortality. This third possibility remains to be proven. In total, all three possibilities analysed above are not mutually exclusive and may be true in different cases[136].

Do mortality rates in SIADH differ from hypervolaemic and hypovolaemic hyponatraemia?

A large prospective study published in June 2017 confirmed that hyponatraemia is associated with higher all-cause mortality (9.1%) than normonatraemia (3.3%, P < 0.0001), with excessive mortality not being explained on the basis of comorbidities[365]. Cuesta et al undertook the first prospective study designed to evaluate the mortality specifically associated with SIADH, as opposed to all-cause hyponatraemia, recruiting 1323 patients with hyponatraemia (serum Na ≤ 130 mmol/l) admitted to hospital and 1136 contemporaneous normonatraemic controls[365]. Cuesta et al reported the novel observation that patients with SIADH had lower mortality rate than patients with hypovolaemic or hypervolaemic hyponatraemia. In specific, the risk ratios (RRs) for in-hospital mortality compared to normonatraemia were for SIADH 1.76 (95% CI 1.08-2.8, P=0.02), hypovolaemic hyponatraemia 2.77 (95% CI 1.8-4.3, P < 0.0001) and hypervolaemic hyponatraemia 4.9 (95% CI 3.2-7.4, P < 0.0001). The mortality rate was higher in hypervolaemic hyponatraemia (RR 2.85; 95% CI 1.86-4.37, P < 0.0001) and in hypovolaemic hyponatraemia (RR 1.6; 95% CI 1.04-2.52; P=0.03) in comparison to SIADH[365]. Finally, this study confirmed our finding that very few SIADH patients had severe hyponatraemia at the time of death. In conclusion, this study revealed that mortality figures for all-cause hyponatraemia should not be extrapolated and assumed to apply to patients with SIADH. Thus, these data highlight the need for aetiology-specific mortality figures which are essential in designing and conducting intervention studies, assessing the effect of therapeutic interventions on hard outcomes such as mortality.

Future studies

It is yet to be proven whether correction of hyponatraemia could improve outcomes and reduce mortality. The reason is that a recent meta-analysis, concluding that improvement in serum sodium was associated with reduced mortality, had several limitations. It included only observational studies; none of these studies were designed to address this question; no placebo-controlled studies were available for inclusion in analysis; data adjustment only for age and gender meant that several unmeasured confounders might have caused confounding bias; cohorts of patients were often very heterogenous[316]. All these factors highlight the need for prospective randomised studies designed to address the crucial outstanding question whether appropriate correction of hyponatraemia is able to revert or at least decrease excess mortality. In order to meet the challenge of heterogeneity, these studies should address this question separately on specific types of hyponatraemia (SIADH, hypovolaemic and hypervolaemic hyponatraemia) as well as subgroups such as heart failure, cirrhosis, pneumonia, and malignant SIADH. Finally, there is also an urgent need to conduct physiologic studies to examine plausible mechanisms through which hyponatraemia could contribute to death, such as possible deleterious effects of hyponatraemia on the immune system and the heart.

Conclusions

In conclusion, this study demonstrated that hyponatraemia is an independent predictor of mortality and that hyponatraemia per se is likely to contribute to excess mortality. Still, the key question for clinicians encountering hyponatraemia is whether the high mortality rates in patients with hyponatremia represent a fixed epidemiologic law or can be reduced with specific manoeuvres.

7.3 Single-centre study demonstrating underinvestigation of hyponatraemia and very low prevalence of endocrine causes

Underinvestigation of hyponatraemia; comparison with previous UK studies

This single-centre study, analysed in detail in Chapter 3, confirmed that hyponatraemia was frequently underinvestigated. However, the present study found that essential laboratory tests were performed more frequently than in previous UK studies. For example, amongst patients with serum Na ≤ 125 mmol/l in our hospital cohort, 47.1% had urine Na measured compared to 10%[222], 25%[224], 19%[225] and 40%[126] in other UK studies including patients with serum Na ≤ 125 mmol/l. Similar comparison for the frequency of urine osmolality found that it was measured in 51% in the subgroup of patients with serum Na ≤ 125 mmol/l in our cohort in comparison to 27%[222], 25%[224], 23%[225] and 47%[225]. The higher proportion of patients being optimally investigated in our study, compared to previous studies, might be due to a general rise of physicians' interest in hyponatraemia during recent years or could reflect local expertise and regular teaching sessions delivered by Endocrinologists in this field.

Underinvestigation of hyponatraemia; comparison with the Hyponatraemia Registry

It is worth reviewing the results of our study, taking into consideration the recently published findings of the Hyponatraemia Registry, the largest observational hyponatraemia study to date which included overall 225 diverse hospital settings in both the United States and the European Union[164 302]. Data analysis of 1524 hyponatraemic patients (serum Na ≤ 130 mmol/l) with SIADH diagnosed locally by treating physicians showed that serum osmolality was measured in 66%, urine osmolality in 68%, urine Na in 63%, paired serum/urine osmolality and Na in 47%, serum cortisol in 33% and TSH in 63% of patients[164]. Finally, among participants in the Hyponatraemia Registry with SIADH diagnosis by treating physicians, only 21%[164] had measurements of all the essential criteria[162 163] compared to 56% in our cohort. The results of this large-scale international multicentre observational study were almost the same for the EU and US cohorts, suggesting that incomplete diagnostic assessment and failure to make a precise diagnosis of SIADH are widespread. The hospital sites participating in the Registry often had specialists with an interest and expertise in the field who had raised awareness of the optimal management of hyponatraemia amongst other clinicians; the same applies to clinicians at hospitals where other observational studies took place. For this reason, the results of our study as well as previous UK studies and the Hyponatraemia Registry may even underestimate the extent of inadequacy of current investigation for hyponatraemia.

Causes of underinvestigation of hyponatraemia

The suboptimal investigation of hyponatraemia and underutilisation of biochemical tests should be multifactorial. At the time the current study was undertaken in 2013, a possible contributing factor might be the lack of international and national guidelines. Other possible barriers to good clinical practice could be the absence of diagnostic algorithms in most hospitals or their complexity where they existed and doctors' perception that hyponatraemia is a complicated condition to diagnose and treat, which often led them to overlook it or ignore it as an epiphenomenon of ilness[366]. In addition, recently diminished provision of undergraduate and postgraduate teaching of clinical chemistry has probably reduced junior doctors' confidence in requesting and interpreting the basic laboratory tests of hyponatraemia[367]. Besides doctors in training, the lack of awareness may also extend to senior doctors, as shown in an Italian survey with less than half of all Consultants using validated biochemical parameters to diagnose SIADH[368].

Initiatives to optimise investigation of hyponatraemia

This study demonstrated for the first time that provision of specialist input dramatically increased the, otherwise very low, frequency of complete diagnostic work-up, indicating that more widespread utilisation of expert input could improve standards of clinical practice. Specialist input can be primarily provided by Endocrinologists or Nephrologists, but also, depending on local expertise, in some occasions by Clinical Biochemists or General Physicians with a special interest in the field. Taking into consideration that inpatient hyponatraemia is a common and often complex disorder, which often poses diagnostic challenges even in the hands of the most experienced physicians, an innovative model of care provision by a dedicated hospital 'hyponatraemia team' could be developed in major healthcare institutions.

In addition, educational programmes at undergraduate and postgraduate level should pay more attention on the investigation and management of this complex disorder in order to improve currently suboptimal clinical practice. Clinicians should also be made aware that even mild to moderate hyponatraemia is associated with significant morbidity and mortality in order to expand their investigation and treatment to patients with serum Na above 125 mmol/l. Diagnostic algorithms and guidelines should be developed which, if applied in combination with experienced clinical acumen, could improve the assessment and management of these patients.

Impact of adequacy of diagnostic evaluation on patient outcomes

But the key, still unaswered, question is whether optimisation of diagnostic assessment could improve patient outcomes, such as mortality, morbidity, and length of stay. A complete diagnostic work-up, facilitating accurate diagnosis, is essential so that subsequent management will be appropriate and effective in correcting hyponatraemia. Given the adverse outcomes of hyponatraemia and the complexity of its aetiology in inpatients, adequate diagnostic evaluation may improve hard clinical outcomes. This sounds like a logical hypothesis, but it is supported by very little data. For example, Whyte et al found in a retrospective study that inadequate investigation, such as failure to measure serum and urine osmolality, was associated with excess mortality[223]. Contrary to these results, the current study described in Chapter 3 did not demonstrate an association between complete diagnostic work-up or provision of specialist input and clinical outcomes[324]. However, patients undergoing complete evaluation or receiving expert input in our cohort were ‘sicker’, as evidenced by lower serum Na levels, higher ICU admission rate, and longer duration of hospitalisation than the rest of participants. Therefore, our study, by design, cannot test this hypothesis since it might be distorted by a significant selection bias.

Adrenal insufficiency as a cause of hyponatraemia

The contribution of adrenal insufficiency to euvolaemic hyponatraemia remains unclear. Although exclusion of cortisol deficiency is one of the essential criteria for the diagnosis of SIADH, adrenocortical function is frequently not assessed in clinical practice. Amongst subjects with serum Na ≤ 125 mmol/l in our cohort, serum cortisol was measured in 46%[324] compared to 8%[222], 19%[224], and 15%[126] in three UK studies for the period 2005 – 2010. The, still low, frequency of serum cortisol measurement has improved in more recent studies, for example 33% in the Hyponatraemia Registry[164] and 33% in a more recent UK observational study published in 2015[226]. The poor ascertainment of plasma cortisol concentration in hyponatraemia, in combination with an observation that a large proportion of patients with hyponatraemia due to hypopituitarism had recurrent admissions with hyponatraemia prior to the diagnosis of secondary adrenal insufficiency[182], raises the question whether hypocortisolism is frequently overlooked as a cause of hyponatraemia.

The best study to date which assessed the true prevalence of adrenal insufficiency as a cause of euvolaemic hyponatraemia was a prospective, observational, single-centre study of 573 inpatients with euvolaemic hyponatraemia (serum Na ≤ 130 mmol/l)[369]. In this study, Cuesta et al reported a prevalence for cortisol deficiency of 3.8%, including 2.2% for secondary adrenal insufficiency due to exogenous glucocorticoid administration and 1.6% for new onset hypopituitarism[369]. Besides 0.5% of cases attributed to subarachnoid haemorrhage, reflecting the fact that the site of the study included also a neurosurgical unit, the authors suggested that this prevalence should be relevant to any hospital[369]. Another recent prospective multicentre observational study of patients with severe hyponatraemia reported a

similar rate of 2.9% for cortisol deficiency in the subgroup of euvolaemic hyponatraemia[72]. Comparing these rates with the frequency of 0.7% for hypocortisolism reported in our study, it seems plausible that some cases might be undiagnosed in our cohort, especially since almost two thirds of individulals did not have laboratory assessment of adrenal reserve.

With respect to investigation of adrenal function, Cuesta et al proposed a diagnostic algorithm, used by the same research group in previous studies of neurosurgical patients[156 181]. A 09:00 am serum cortisol value > 300 nmol/l was regarded as unlikely to reflect adrenal insufficiency of sufficient severity to cause hyponatraemia. Several factors, including correlation between appropriate cortisol levels and the severity and nature of acute illness, changes in levels of corticosteroid-binding globulin, tissue-specific resistance to corticosteroids, complicate the assessment of glucocorticoid reserve in patients with critical illness[318]. Therefore, any cut-off is arbitrary, with different authors having proposed various thresholds for appropriate cortisol value in acutely ill patients, ranging from 276 to 450 nmol/l[318]. In cases when serum cortisol was < 300 nmol/l, a short synacthen test (SST) was performed, unless it was thought that a recent insult to pituitary function, for example subarachnoid haemorrhage or meningitis, might have occurred within the last 6 weeks. An SST was also performed in selected cases with early morning serum cortisol of 300 - 414 nmol/l, if other parameters suggestive of adrenal insufficiency, such as hypoglycaemia or refractory hypotension, were present[318]. Normal response was defined as a cortisol peak above 500 nmol/l in SST. The authors of this study felt that the cut-off of 300 nmol/l represented a practical way to target dynamic testing in the population most likely to show abnormal results. Using this cut-off, only 8.4% of patients qualified for SST. Other studies have provided evidence in favour of

adopting a higher cut-off, for example a study of 28 cases of hyponatraemia due to secondary adrenal insufficiency demonstrated that a basal serum cortisol > 439 nmol/l would be needed so that no cases would be overlooked[182]. Using a threshold of 419 nmol/l for serum cortisol, basal levels would suffice in 77% of hyponatraemic cases to exclude cortisol deficiency[179], while a threshold of 450 nmol/l sufficed to exclude adrenal insufficiency in 75% of patients in our cohort. In conclusion, adopting a cut-off higher than 300 nmol/l may aid the diagnosis of very few additional cases of adrenal insufficiency at the expense of performing SST in an additional 15% of hyponatraemic patients.

Hypothyroidism as a cause of hyponatraemia

With respect to hypothyroidism as a cause of hyponatraemia, no cases of, at least, severe primary hypothyroidism were encountered. In agreement with our findings, a recent prospective observational study of 573 inpatients with euvolaemic hyponatraemia (serum Na ≤ 130 mmol/l) by Cuesta et al did not also report a single case of overt primary hypothyroidism[369], while analysis of a smaller unselected cohort of 204 hospitalised patients with hyponatraemia suggested that hypothyroidism was the cause in only 1% of hyponatraemic patients[370]. These observations support the opinion of most authors that hypothyroidism should be an exceptionally rare cause of euvolaemic hyponatraemia, limited only to patients with profound hypothyroidism[152 154 193].

However, the current study reported a high incidence of abnormal serum fT4 or TSH values among hospitalised hyponatraemic inpatients. The proportion of hyponatraemic inpatients in our cohort with TSH outside the reference range of 19% was very similar with the frequency of 17% reported in a large study of general hospital population[321], but it was much higher than 4.5% observed in the subgroup with euvolaemic hyponatraemia of the Hyponatraemia Registry[164]. A high prevalence of fT4 and TSH values outside the reference range in hospitalised patients is attributed in most cases to ‘’non-thyroidal illness’’ or ‘’sick euthyroid syndrome’’, a relatively common finding following any acute or chronic illness, which is defined by abnormal thyroid function tests despite the absence of an intrinsic abnormality of hypothalamus-pituitary-thyroid function[371]. For this reason, clinicians should avoid common pitfalls in the interpretation of thyroid function tests in hospitalised patients, such as overlooking the confounding effects of non-thyroidal illness and drugs[371] and

the methodological limitations of these measurements, such as wide discrepancy of fT4 estimates between different assays[372]. It is worth mentioning that even among hospitalised subjects with markedly elevated serum TSH > 20 mU/l, 45% of cases were related to ‘’non-thyroidal illness’’[321]. Therefore, thyroid function tests in the context of ill hospitalised patient should be interpreted very cautiously, with a much higher threshold of 20 mU/l being adopted to define pathologically elevated serum TSH in order to improve test specificity[321]. In conclusion, although thyroid function tests of hyponatraemic inpatients are frequently outside the reference range, our view is that hypothyroidism-related hyponatraemia is limited only to extremely rare cases of profound myxoedema.

Future studies

Several studies, consistently reporting suboptimal investigation and diagnosis of hyponatraemia, highlight the need to design and undertake prospective randomised controlled trials in order to examine whether adequate diagnostic work-up of hyponatraemia could improve patient outcomes. In specific, different models of care provision in inpatients with hyponatraemia should be evaluated. A potential model would be widespread provision of expert input in cases of hyponatraemia. An alternative, or even supplementary, initiative would be the introduction of automated ‘biochemical prompting’ systems, prompting clinicians to request laboratory tests and use available therapeutic options appropriately. Since the optimal concentration for basal serum cortisol which suffices to exclude adrenal insufficiency without dynamic testing is still a matter of debate, prospective studies in very large cohorts are warranted in order to assess the sensitivity and specificity for different thresholds of non-stimulated serum cortisol as well as the number of stimulation tests needed in order to diagnose one new case of cortisol deficiency for each cut-off.

Future algorithms for investigation of hyponatraemia

'The Co-MED Study', published in 2017, demonstrated that fractional excretion of urea and urate are superior to all other laboratory parameters in differentiating SIADH from other aetiologies of hyponatraemia[216]. Also, Fenske et al has previously found that the copeptin to urine Na ratio is valuable in discriminating volume-depleted from normovolaemic hyponatraemic patients[214]. These studies raise the question whether the time has come to incorporate tools such as fractional excretion or copeptin in contemporary diagnostic algorithms. So far, none of the current guidelines[154 152 245], all published between 2013 and 2015, have suggested calculating fractional excretion or measuring copeptin levels despite several studies providing evidence base for their use having been published until 2009[200 206 209 204 214]. A potential explanation may be that authors of guidelines might have been concerned about the complexity of these calculations which could discourage clinicians from using them, and possibly even from investigating hyponatraemia at all. However and especially in light of recent findings of 'The Co-MED Study', the largest prospective multicentre observational study to date confirming the high diagnostic accuracy of fractional excretion, the 'new generation' of guidelines which will be published until 2020 should integrate the use of fractional excretion. Moreover, as measurement of serum copeptin will become widely accessible and cheaper, it should play a role in investigating hyponatraemia in selected cases which pose major diagnostic challenges. Introduction of new guidelines should go hand in hand with raising the awareness of these tools amongst doctors and training physicians about their appropriate use. Moreover, Clinical Biochemists could update laboratory platforms with automated calculation of fractional excretion or serum copeptin:urine Na ratio in order to facilitate their utilisation in routine clinical care.

Finally, high quality studies are needed in order to further evaluate the potential utility of novel tests such as serum MR-proANP and bioimpendance spectroscopy (BIS) which have been suggested to be useful adjunct tools in differentiating SIADH from other types of hyponatraemia.

Conclusions

In conclusion, hyponatraemia remains inadequately investigated and underdiagnosed, with poor ascertainment of the cause of hyponatraemia resulting in frequent mismanagement of patients. Also infrequent evaluation of adrenal reserve may result in underdiagnosis of secondary adrenal sufficiency, a potentially fatal condition. Thus, new initiatives such widespread provision of endocrine input should be tested to determine whether they could improve adequacy of work-up and finally clinical outcomes.

7.4 Multicentre study confirming underdiagnosis and undertreatment of hyponatraemia in UK clinical practice

Current clinical practice in diagnosing SIADH

Real-world data from this multicentre study, described in detail in Chapter 4, suggested that only 18% of patients underwent complete diagnostic evaluation, defined as paired serum/urine osmolality and sodium measurement supplemented by assessment of thyroid and adrenal function. In specific, our study found that almost half of SIADH diagnoses in our cohort were made without fulfilling all the essential criteria[325]. This is a well-recognised problem, as shown in a past UK study where none of the 50 patients, in whom a diagnosis of SIADH was suspected on clinical grounds, met the generally accepted diagnostic criteria[126]. Additionally, an analysis of 1524 patients in the Hyponatraemia Registry, who were diagnosed with SIADH by treating physicians, demonstrated that all appropriate laboratory tests to diagnose SIADH were obtained only in 21% of cases, with results being identical for the European Union and US cohorts[164]. Finally, a retrospective cross-sectional study, evaluating the diagnosis of SIADH in 110 patients hospitalised in an Australian tertiary hospital, found complete diagnostic work-up in 20% of cases, with only 7.2% of patients meeting all the 8 essential criteria for a diagnosis of SIADH [373]. In this cohort, adrenal insufficiency and hypothyroidism were not excluded in as many as half of patients[373]. All these data indicate that the failure to make a precise diagnosis of SIADH is widespread with potentially important sequelae with regards to appropriate therapy.

Ascertainment of the aetiology of hyponatraemia

Noteworthy, the cause of hyponatraemia was not recorded in the majority of patients in our cohort. This observation resembles the strikingly large percentage of undiagnosed cases of hyponatraemia, as high as 49%[222], 53%[224] and 66%[225], reported in previous UK studies. Poor ascertainment of the aetiology of hyponatraemia is one of the major shortcomings in current clinical practice since it does not allow the clinicians to tailor their therapeutic approach to the underlying clinical condition.

Concerning classification of hyponatraemia as per blood volume status, more than half of individuals in our cohort were characterised as having hypovolaemic hyponatraemia and only a quarter as SIADH[325], in agreement with similar findings in our previous study described in Chapter 2[324]. This novel observation differs from results of most previous studies. Fenske et al used sophisticated diagnostic algorithms, containing all available diagnostic tools and tests, including copeptin measurement, to study 121 and 106 consecutive hyponatraemic subjects respectively[203 214]. Both studies concluded that the commonest type of hyponatraemia was due to SIADH (35-40%), followed by hypovolaemic hyponatraemia (27-32%), hypervolaemic hyponatraemia (20-21%), diuretic-induced hyponatraemia (7-8%), and primary polydipsia (4%)[203 214]. A recently published prospective observational study of 298 hyponatraemic patients with serum Na < 125 mmol/l reported that 36% of all cases had SIADH, meeting all essential criteria, 24% diuretic-induced hyponatraemia, 20% hypovolaemic hyponatraemia, 11% hypervolaemic hyponatraemia, 8% primary polydipsia, and 1% cortisol deficiency[72]. Recently, Cuesta et al prospectively evaluated 1323 patients with hyponatraemia (serum Na ≤ 130 mmol/l) admitted to hospital in a large prospective study which was

published in June 2017[365]. On the basis of clinical and biochemical data, 43.5% of hyponatraemic patients had SIADH, 32.6% hypovolaemic hyponatraemia, 20.8% hypervolaemic hyponatraemia, while 3.1% of participants could not be acurately classified into any subgroups[365]. All these recent prospective studies, designed to evaluate patients in detail, ascertained aetiology in all participants. Thus, they should reflect the true distribution of hyponatraemia into different types and aetiologies, indicating that SIADH might be underdiagnosed in our cohort.

Poor efficacy of treatment of hyponatraemia

Another important finding of our study was the lack of efficacy of our current treatment practice, since almost two thirds of individuals were discharged still hyponatraemic. Real-world data on 2948 hyponatraemic patients recruited in the multinational Hyponatraemia Registry showed that 78% of participants had persistent hyponatraemia at the time of discharge, including 49% of patients with moderate to severe hyponatraemia (serum Na ≤ 130 mmol/l)[302]. Therefore, these results confirmed that ineffective treatment of hyponatraemia is a widespread problem across the globe. The exclusion of patients with hypovolaemic hyponatraemia, which tends to resolve easily, from the Hyponatraemia Registry should explain the higher frequency of hyponatraemia at discharge reported in the Registry compared to our cohort.

Association of hyponatraemia correction with mortality rate

A novel finding emerged from analysis of our data was that hyponatraemia correction was reported more often in fatalities rather than in patients discharged from the hospital. This correlation does not equal causation and, in fact, it could imply reverse causality. Detailed chart review of fatal hyponatraemic cases in Chapter 2 provides evidence that patients, who eventually die at hospital, are characterised by high insensible fluid losses and very poor oral fluid intake as their clinical condition worsens. Therefore, restoration of normonatraemia prior to death is a common occurrence in most patients with SIADH or hypervolaemic hyponatraemia who die during their hospitalisation. This observation does not necessarily exclude the contribution of hyponatraemia to excess mortality since hyponatraemia-related organ dysfunction may lag behind the presence of hyponatraemia.

Pitfalls in the management of hyponatraemia

Several pitfalls in hyponatraemia management were identified in our cohort with more than a third of patients having not received any specific treatment for hyponatraemia. Our data about frequent lack of treatment were supported, once again, by analysis of Hyponatraemia Registry, demonstrating that 17% of individuals did not have active treatment for hyponatraemia beyond discontinuing potentially offending medications and treating underlying conditions, such as cancer, pneumonia or pain, contributing to hyponatraemia[302]. Another shortcoming of management in our cohort was the extremely limited rate of utilising other therapies than isotonic saline and fluid restriction, with only 10% of our patients having more than one therapy. This rate was very low compared to 46% of participants in the Hyponatraemia Registry receiving 2 or more therapeutic modalities[302]. Our study also demonstrated underutilisation of potent pharmacological therapies for hyponatraemia, with only 3.9% of subjects being treated with hypertonic saline or demeclocycline. Furthermore, tolvaptan and urea, despite being the second line agents for treating SIADH by the US[152] and the European[154] guidelines respectively, were not prescribed in any patients. In the SIADH subgroup of the Hyponatraemia Registry, the rate of using tolvaptan was 12.7%, hypertonic saline 5.3% and demeclocycline 3.2%, while the frequency of use for other agents was very low, such as 0.3% for the combination of loop diuretics with NaCl tablets and 0.2% for urea[164].

Effectiveness and safety of fluid restriction

With respect to fluid restriction, our study recorded low efficacy with 80% non-response rate. These results confirmed the findings of the Hyponatraemia Registry, showing that fluid restriction in patients with a median baseline serum Na 125 mmol/l led to a median 1.0 mmol/l/day rate of serum Na change[164]. Amongst 625 SIADH patients included in the Registry, as many as 56% were non-responders since they failed to increase serum Na by ≥ 5 mmol/l[164]. Following failure of fluid restriction, treating clinicians provided a second therapy in only 44% of cases. In total, our data were similar with the Hyponatraemia Registry, suggesting that fluid restriction, despite being ineffective in more than half of cases, is often not followed by next line therapy.

The authors of the Hyponatraemia Registry performed logistic regression analysis to identify characteristics of responders to fluid restriction, demonstrating that significant predictors of efficacy for fluid restriction were lower starting serum Na concentration, lower serum urea levels and lower urine osmolality[164]. Other biochemical parameters such as urine/plasma electrolyte ratio or urine volume were not evaluated, while the rigour of fluid restriction did not seem to impact on efficacy with fluid restriction of < 1000 ml/day resulting in the same response rate with restriction of > 1000 ml/day[164]. Finally, the rate of overly rapid correction in subjects treated with fluid restriction was extremely low (2.6%) and identical with the rate observed in cases not receiving any hyponatraemia treatment, providing further evidence in favour of its excellent safety profile[164].

Interestingly, Cuesta et al undertook a cross-sectional, two-centre study of 183 patients with a diagnosis of SIADH, in order to ascertain how many patients

displayed pre-treatment criteria which have been reported to predict failure of fluid restriction[374]. Amongst those, 47% had urine volume < 1500 ml per 24 hours, 41% urine osmolality > 500 mOsm/kg and 26% Furst ratio > 1. In total, 59% had one predictor, including 37% with two predictors, for nonresponse to fluid restriction[374]. These data intensify the debate about whether fluid restriction should remain the mainstay of treatment for SIADH and whether these predictors of response should influence clinical decision-making.

Based on these data and our clinical experience, we recommend implementing fluid restriction only after confirmation of SIADH diagnosis. Also, when clinicians have access to the values of urine electrolytes, we suggest prescribing fluid volumes according to Furst formula[254]. If urine electrolytes are not available, we restrict water intake to 750-1000 ml/day and no more than 1000 ml/day. In order to improve the efficacy of fluid restriction, we propose the use of fluid balance sheets, bedside notices and removal of excess bedside fluids. Also patients should be actively reminded and encouraged to comply with it and nursing staff should be made aware of the importance of the practice. Finally, fluid restricted individuals should undergo daily electrolyte monitoring and clinical review and, if they do not adequately respond within 48 hours, they should be prescribed pharmacotherapy.

Future directions to improve standards of investigation and management of hyponatraemia

Our data as well as other contemporary observational studies have confirmed inadequate investigation and underdiagnosis of hyponatraemia as a major problem encountered in routine clinical practice across the world. Thus, there is a pressing need to promote awareness of the value of appropriate biochemical tests amongst healthcare professionals and to integrate clinical biochemistry into medical curricula. However, a recent study in a US hospital, comparing diagnostic work-up of hyponatraemia in the 4 months prior to and in the 4 months after a continuing medical education initiative with a focus on kidney disease-related hyponatraemia, showed that this education activity did not improve the adequacy of investigation[375]. In addition to any educational interventions, as part of a quality improvement programme, it is essential to consider the introduction of reflex testing, an automated addition of further tests to a sample request based on a laboratory algorithm[376]. For example, if serum Na is ≤ 125 mmol/l, other tests, including serum osmolality, TSH and cortisol, could be automatically added. A potential valuable tool could also be electronic alert systems for severe hyponatraemia, similar with e-alerts for Acute Kidney Injury already introduced with success to several NHS hospitals[377 378]. By highlighting hyponatraemia and referring to local guidelines, electronic alerts could facilitate optimal investigation and treatment in a timely manner. Another innovative model of care delivery with the potential to improve standard of care could be the development of multidisciplinary hospital ‘hyponatraemia teams’ combining the expertise of Endocrinologists, Nephrologists, Chemical Pathologists and other Physicians.

Future studies

Since it is unknown whether poor efficacy of hyponatraemia treatment contributes to adverse clinical outcomes, there is an urgent need for studies evaluating the effect of hyponatraemia correction on patient outcomes such as symptoms, mortality and length of hospital stay. Moreover, the clinical and cost-effectiveness of innovative models of care provision, such as e-alerts and introduction of ‘hyponatraemia teams’, should be evaluated across different healthcare settings. Finally, randomised controlled trials are warranted to compare different therapeutic options for SIADH with regards to relative efficacy, safety and risk of overly rapid correction. In specific, fluid restriction, traditionally the mainstay of treatment for SIADH, should be evaluated further in order to inform clinicians about its efficacy, safety, predictors of response and the circumstances when it should remain first line treatment as well as when other therapies should be preferred. Furthermore, the validity of Furst formula, as a tool to predict the likelihood of patient’s successful response to fluid restriction and guide the volume at which it should be imposed, should be tested.

Conclusions

In conclusion, this study highlighted major shortcomings in the investigation, diagnosis and treatment of hyponatraemia. Thus, there is a pressing need to examine novel ways of care delivery which could improve standards of care. Finally, it remains to be tested whether optimal investigation and effective treatment of hyponatraemia could contribute to better patient outcomes, such as reduced mortality and shorter length of hospital stay.

7.5 A large case-series of tolvaptan-treated patients with SIADH demonstrating high effectiveness as well as great risk of overly rapid sodium correction

Effectiveness of tolvaptan

This retrospective case series of tolvaptan-treated patients with severe SIADH found that tolvaptan led to a mean 9 mmol/l increase in serum sodium concentration in the first 24 hours after initiation[379]. This magnitude of correction is the highest reported so far in the literature compared to a mean improvement of 5.3 mmol/l at day 4 in the SIADH subgroup of SALT-1 and SALT-2 studies[285], 8.4 mmol/l at day 4 in a recent tolvaptan study in Chinese patients with SIADH[287], and 4.9 mmol/l at day 4 in a meta-analysis by Jaber et al[289]. The incremental sodium change of 9 mmol/l in the first 24-hour window reported in our study was much higher than that in in the Hyponatraemia Registry. The Hyponatraemia Registry, the largest observational study to date which included 225 SIADH patients treated with tolvaptan, recorded a median first day change of 4 mmol/l in serum sodium concentration after tolvaptan administration[302]. Our case series also demonstrated that tolvaptan is highly efficacious in correcting serum sodium levels. In our cohort, the success rate at increasing serum sodium ≥ 5 mmol/l at the end of tolvaptan therapy was 96.7% in comparison to 78% of subjects in the Hyponatraemia Registry achieving this correction benchmark[302].

Risk of tolvaptan-related overly rapid hyponatraemia correction

The greater effectiveness in increasing serum sodium was also accompanied by greater risk for too rapid correction. In our cohort, we observed the highest rate of overly rapid correction ever recorded with as many as 23% of patients having a serum sodium increase > 12 mmol/l in 24 hours or > 18 mmol/l in 48 hours[379]. In comparison and using the same criteria to define too rapid correction of hyponatraemia, all other studies have found much lower rates. SALT-1 and SALT-2 studies showed that the desirable rates of sodium correction were exceeded in only 1.8% of tolvaptan-treated patients with euvolaemic or hypervolaemic hyponatraemia[284], but this rate rose to 5.9% in the tolvaptan-treated SIADH subgroup (N=51)[285]. Notable, INSIGHT, a recently published randomised trial of tolvaptan versus placebo in chronic euvolaemic or hypervolaemic hyponatraemia, did not report any cases of overly rapid correction among 29 patients in the tolvaptan arm[292]. Outside the clinical trial setting, the Hyponatraemia Registry reported a frequency of 12.1% for overly rapid correction of hyponatraemia in 225 tolvaptan-treated SIADH patients[164]. It is worth mentioning that, despite the high incidence of overly rapid correction in our case series, none of those patients exhibited neurological symptoms suggestive of osmotic demyelination syndrome (ODS). This applies to all tolvaptan clinical trials, including 6794 subjects worldwide exposed to tolvaptan, with no cases of ODS having been reported so far[380]. Even in real-life clinical practice, only a single case of ODS has been documented with tolvaptan monotherapy to date, when inappropriate continuation of tolvaptan caused serum sodium increase from 126 mmol/l to an extremely high sodium concentration of 187 mmol/l over 3 days[381]. Based on this, the frequency for tolvaptan-induced ODS is calculated as less than 1 in 10000 patients[380], but this may underestimate its true

incidence since drug adverse events is sometimes underreported in routine clinical practice for various reasons.

Predictors of rapidity of hyponatraemia correction with tolvaptan

The unprecedentedly high incidence of overly rapid hyponatraemia correction as well as the very high effectiveness of tolvaptan in our case series may be explained by the low mean serum sodium concentration (119.9 mmol/l) of our cohort, including approximately 40% of patients with serum Na < 120 mmol/l. In comparison, the landmark SALT studies had a mean serum sodium of 129 mmol/l and, in fact, had excluded subjects with serum Na < 120 mmol/l in the presence of neurological impairment[284]. Similarly, the mean starting serum sodium was 129 mmol/l in the INSIGHT trial[292], while tolvaptan-treated individuals in the Hyponatraemia Registry had a median baseline serum Na of 127 mmol/l[164]. Therefore, the greater mean magnitude of rise in serum sodium and higher rate of rapid correction of hyponatremia in our SIADH cohort may correspond to the lower mean baseline serum sodium concentration in our patients.

This explanation is supported by the inverse correlation between baseline serum sodium and magnitude of rate of hyponatraemia correction in our cohort, with all patients who exceeded the safe correction limits having starting serum Na ≤ 122 mmol/l[379]. A similar observation was recorded in SALT studies, showing that the greatest increase in serum sodium levels occurred in patients with more severe biochemical hyponatraemia at the baseline[284]. In agreement with the observation that the baseline sodium value is a predictor for the rate of correction, real-world data from Hyponatraemia Registry demonstrated that patients with starting serum Na < 120 mmol/l were more than 5 times more likely (relative risk 5.34) to experience overly rapid correction compared to patients with serum Na > 125 mmol/l[302]. Thus, a wealth of evidence suggests that patients with severe hyponatraemia, especially with serum Na < 120 mmol/l, have a greater likelihood to exhibit overly rapid correction of

hyponatraemia which exposes them to a risk of ODS. The lower the baseline serum sodium is, the higher the correction rate following tolvaptan therapy. The underlying explanation may be that patients with lower serum sodium have larger amounts of excess total body water; as a result, higher volume of free water becomes available for renal excretion when tolvaptan decreases the number of aquaporin-2 channels in the renal collecting tubules, resulting in a more pronounced aquaresis and greater increase in serum sodium.

In addition to low baseline serum sodium, it would be of great value to identify other parameters which may predict the magnitude of the rise in serum sodium concentration following administration of tolvaptan in SIADH patients. This would allow the clinicians to recognise patients at increased risk for rapid correction of hyponatraemia when they are treated with tolvaptan. A retrospective study of 18 patients with serum Na < 130 mmol/l due to SIADH treated with intravenous conivaptan demonstrated that, in addition to baseline value of serum sodium, blood urea nitrogen (BUN) and estimated glomerular filtration rate may help predicting the magnitude of response to therapy[382]. The novel finding of this study was the inverse correlation between the level of BUN at the time of initiation of treatment and the subsequent magnitude of the natraemic response to conivaptan[382]. Estimated glomerular filtration rate (GFR) also correlated with response to therapy, with individuals with baseline hyperfiltration having the largest rise in serum sodium after therapy[382]. Another study by Umbrello et al reported a number of variables predictive of the degree of response to tolvaptan, based on the results of a retrospective observational study in a general ICU, including 38 tolvaptan-treated patients with euvolaemic or hypervolaemic hyponatraemia[383]. Baseline serum sodium, BUN and

urine sodium were all inversely correlated with the absolute increase in serum sodium concentration after tolvaptan administration.

Therefore, BUN may serve as a useful pre-treatment marker of response to vaptans, with patients with a very low BUN showing a larger sodium rise. The mechanism is not clear, but subjects with the lowest BUN levels may have the largest increase in whole body water content, greatest extracellular fluid expansion, highest GFR, lowest proximal tubular reabsorption and greatest distal delivery of substrate, thereby making them more responsive to water diuresis[382]. With regards to the negative associaton of baseline urine sodium with rise of serum sodium, this may be explained by higher AVP activation leading to an elevated urine sodium, in line with the competitive nature of the AVP antagonism exerted by tolvaptan[383]. As a result, lower urine sodium which represents lower degree of AVP activation may predict higher response to tolvaptan. Future studies are warranted to identify the biochemical variables which can predict brisk response to tolvaptan.

Effectiveness and safety of low dose tolvaptan

Post-marketing assessments of tolvaptan use in Europe have reported that some physicians, on a patient-by-patient case basis, split tolvaptan tablets to use a 7.5 mg starting dose in the belief that a lower starting dose may reduce the risk of overly rapid correction of serum sodium. It is worth mentioning that ascending single-dose studies have demonstrated in the past that all tolvaptan doses between 60 and 480 mg produce maximal increases in urine output[384]. Saturation of response in urine excretion rate and urine volume was observed, with all doses inducing the same mean 0 to 12 hour urine volume (about 7 liters) and maximal urine excretion rate (around 12 ml/min). Therefore, doses greater than 60 mg produce a longer effect, but have the same maximal excretion rate[384]. In November 2017, the results of a multicentre, parallel-group, double-blind trial, which randomised 28 SIADH patients with serum Na 120-133 mmol/l to receive a single dose of tolvaptan at 3.75, 7.5 and 15 mg, were published[385]. The primary pharmacodynamic endpoints were the maximal increase from baseline and time of maximal increase from baseline in serum sodium concentration following tolvaptan administration. Rapid corrections of serum sodium (defined as increase of ≥ 8 mmol/l in the first 8 hours or ≥ 12 mmol/l within the first 24 hours) were observed in 4 of 28 (14.3%) subjects, including one case in the 3.75 mg, one case in the 7.5 mg, and two cases in the 15 mg treatment group. Noteworthy, the mean maximal increase in Na concentration was 3.6, 5.3 and 7.9 mmol/l for tolvaptan doses of 3.75, 7.5 and 15 mg respectively, while the mean baseline serum Na ranged between 131 and 132 mmol/l for all arms of the study[385]. In addition, responses in free water clearance and urine volume were similar for 3.75 and 7.5 mg doses, with mean change from baseline in fluid balance 24 hours following single dose of 3.75 or 7.5 mg being around – 500 ml in comparison to

about – 1500 ml for the 15 mg dose. The conclusion of the authors of his study, sponsored by drug manufacturers, was that 7.5 mg initiation tolvaptan dose will not eliminate the risk for rapid correction in serum sodium[385]. However, the small sample size in each arm in combination with numerically lower mean Na rise and smaller degree of tolvaptan-induced diuresis in the 7.5 mg compared to 15 mg arm suggest that this issue remains unresolved and warrants further studies, recruiting larger number of patients, including those with more severe degree of biochemical hyponatraemia.

Therefore, it is still unknown whether low starting doses of tolvaptan, such as 7.5 mg, half the lowest formally approved dose of 15 mg, could reduce the risk for an unduly rapid correction of hyponatraemia and at the same time retain their efficacy. The first report about the use of low-dose tolvaptan, a case series of 13 patients with paraneoplastic SIADH, was published by Kenz et al in 2011 and showed that 7.5 mg was usually effective, without causing any cases of too rapid correction[297]. Our case series included only 6 patients treated with an ‘off-label’ initiation dose of 7.5 mg and found similar correction rates with the licensed initiation dose[379]. Since then, three studies, all published in 2016, have further enlightened clinicians about this issue. The first study, a retrospective case series of 37 tolvaptan-treated patients for SIADH, included 15 patients being initially treated with 15 mg tolvaptan and 22 patients being administered 7.5 mg tolvaptan[386]. Despite baseline sodium values prior tolvaptan administration being significantly higher in the 7.5 mg group (mean 124.0 mmol/l) than in the 15 mg group (mean 120.4 mmol/l), serum sodium change was similar for both doses in the first 24 hours following administration of tolvaptan (6.0 mmol/l for 7.5 mg dose vs 6.5 mmol/l for 15 mg dose) and in the first 48 hours (8.0 mmol/l for 7.5 mg vs 8.5 mmol/l for 15 mg). Of note, 2 patients in the 15 mg

group and none in the 7.5 mg group exceeded the maximum recommended correction limit. The conclusion was that a lower starting dose of 7.5 mg may be an equally effective and potentially safer option than a 15 mg dose[386]. In view of the small sample size and the retrospective nature of this study, large prospective studies are needed to test whether this lower than approved dose will be sufficient to completely avoid an undue increase in sodium within the first 24-48 hours of treatment. The second study, a non-randomised open-label trial of 23 patients presenting to the emergency department with euvolaemic or hypervolaemic hyponatraemia, assigned 12 patients (median serum Na 125 mmol/l) to a 15 mg initiation dose of tolvaptan and 11 patients (median serum Na 124 mmol/l) to 7.5 mg starting dose[387]. The 15 mg group showed a median correction rate of 9 mmol/l at 12 hours and 12 mmol/l at 24 hours, with 42% of patients exceeding safe correction rates, compared to a median change of 4 mmol/l at 12 hours and 6 mmol/l at 24 hours in the 7.5 mg group without any cases of overly rapid correction[387]. In specific, subjects with baseline serum Na < 120 mmol/l showed a median 24-hour serum Na increase of 20 mmol/l in the 15 mg group vs 8 mmol/l in the 7.5 mg group[387]. This study demonstrated superiority of the 7.5 mg dose in terms of safety, especially for the treatment of more severe hyponatraemia, while the standard initiation dose of 15 mg implicates too high risk of overly rapid correction[387]. A third study by Umbrello et al assessed the efficacy and safety of tolvaptan, administered through nasogastric tube in 38 critically ill hyponatraemic patients in ICU[383]. This cohort included 24 patients who received a 7.5 mg tolvaptan dose, while the remaining 14 individuals received a 15 mg dose. The mean increase in serum sodium over baseline at 24 hours was 6.7 mmol/l. Most patients (81.6%) met the criterion for successful response, defined as serum sodium increase ≥ 4 mmol/l over first 24 hours, while

10.5% exceeded the safe 24-hour limits for hyponatraemia correction. The dose of tolvaptan was not a predictor of the response to tolvaptan administration, with 15 mg and 7.5 mg dose showing similar efficacy and safety[383].

Finally, in 2017, a case report was published of a 32-year-old man who responded very briskly to a lone single dose of 15 mg tolvaptan given for SIADH complicating traumatic brain injury[388]. Serum sodium increased too rapidly within 18 hours from 121 mmol/l to 139 mmol/l, while he had significant diuresis with urine output of around 6500 ml over 24 hours. The authors of this case report suggested the use of lower tolvaptan doses in younger patients with preserved renal function since the landmark studies, based on which the currently recommended standard initianting doses of tolvaptan have been approved, recruited older individuals with some degree of renal impairment. Furthermore, they proposed that tolvaptan should be dosed singly, with repeat daily doses only prescribed and administered after physician evaluation of response of hyponatraemia to an initial dose[388].

Reviewing these, still limited, real-world data on the use of lower than approved initiation tolvaptan dose, a 7.5 mg tolvaptan dose appears effective in treating hyponatraemia. However, it is still not clear if it reduces the risk of overly rapid correction. As a result and until higher quality data will become available, we recommend considering 7.5 mg tolvaptan as a starting dose for SIADH patients with baseline serum Na < 125 mmol/l and strongly considering 7.5 mg as suitable for patients with even lower baseline serum Na < 120 mmol/l.

Current recommendations about tolvaptan use

Taking into account the, undoubtedly, great efficacy of tolvaptan in correcting hyponatraemia as well as its association with overly rapid correction, especially in patients with severe hyponatraemia, the role of tolvaptan in the management of SIADH has been a matter of great debate. In recent years, several international and national recommendations and guidelines from various professional organisations have been published, offering guidance on decision-making in the management of SIADH[152 154 245 253]. These guidelines differ substantially in their recommendations about the use of tolvaptan, causing confusion to treating physicians. There are a number of obvious reasons why guidelines and recommendations may diverge in different countries and by different organisations, including variation in availability of drugs between countries, thus leading to different experiences or lack of experience with the use of particular agents; utilisation of different methodologies and scope in review of existing data; divergent interpretations of evidence[274]. In general, vaptans have been used to a much larger extent in the US and Japan than in some European countries. Also, urea, an alternative pharmacological agent for SIADH which has been shown to be effective and well tolerated[261], has been predominantly used in Belgium since 1980s. Some clinicians still dismiss it as a Belgian idiosyncrasy since its use is very limited to most countries, including the US and the UK, in large part owing to the lack of general availability for a preparation approved for human use. Also, it is worth recognising the general paucity of available randomised controlled trials with clinical outcome measures for most of the available therapies, leading to generation of recommendations which are based, to large extent, on expert opinion. Finally, on the one hand, the European guideline development group downgraded the quality of evidence of tolvaptan clinical trials based largely on the fact that they

were industry sponsored, and they relied upon existing meta-analyses of combined clinical trials of multiple vaptans, including those not licensed for use anywhere in the world. On the other hand, the authors of other guidelines focused on Phase III pivotal studies of tolvaptan only, based on which tolvaptan gained regulatory approval in the US and the EU[274].

Reviewing conflicting different guidelines, four published guidelines have recognised tolvaptan as a valuable pharmacological therapy for the treatment of SIADH[152 245 253]. An expert multidisciplinary panel led by Verbalis published in 2013 detailed recommendations, suggesting the use of tolvaptan as second line therapy after fluid restriction for SIADH in mild to moderate biochemical hyponatraemia (serum Na ≥ 125 mmol/l) and in mildly symptomatic, severe biochemical hyponatraemia (serum Na < 125 mmol/l)[152]. Also, it prompted clinicians to consider tolvaptan use as the first line treatment for SIADH in cases when fluid restriction is highly likely to fail or could not be adhered to. Finally, the expert panel, recognising the limited data for the use of tolvaptan in patients with serum Na < 120 mmol/l, recommended tolvaptan use with caution and more frequent monitoring in this subgroup[152]. Verbalis et al reviewed also alternative pharmacological agents for SIADH, such as demeclocycline and urea, which they did not rate as highly as vaptans, but still proposed considering their use in selected cases. The main reasons were the limited evidence base about their efficacy and safety and the fact that they have not undergone rigorous review by the regulatory authorities since they are not widely licensed agents; their documented side-effects and uncertainty about their true extent; their lack of availability in some countries[152]. In 2014, a Spanish multidisciplinary group worked under the auspices of the European Hyponatraemia Network and Spanish Medical Societies in order to publish algorithms for the

treatment of SIADH[253]. They recommended the use of tolvaptan in patients with SIADH and mild to moderate symptoms, either as second line treatment after failure to respond to 48-hour fluid restriction or as first line therapy when fluid restriction is unlikely to be effective or is not feasible. With respect to patients with baseline serum Na < 120 mmol/l, they made a statement that they preferred not to start tolvaptan in these patients since, in their experience, they seem to be at a higher risk for too rapid correction[253]. In 2015, a multidisciplinary group of senior UK clinicians with a special interest in hyponatraemia published an algorithm for the assessment and management of hyponatraemia[245]. In agreement with recommendations by Verbalis et al[152] and Runkle et al[253], they suggested using tolvaptan for the treatment of SIADH as a second line therapy in patients not responding to fluid restriction and as a first line therapy in cases when fluid restriction is predicted to fail, for example when urine/plasma electrolyte ratio is >1[245]. In 2012, Hoorn et al published Dutch guidelines on electrolyte disorders under the auspices of the Dutch Society of Internal Medicine[260]. Dutch guidelines did not recommend tolvaptan as a first-line treatment of hyponatraemia secondary to SIADH. They stated that the main reasons for this decision were that tolvaptan has not been shown to reduce hard outcomes such as mortality, can result to overly rapid correction, and is costly to use. However, tolvaptan is stated amongst possible second-line pharmacological options for SIADH, across demeclocycline and urea[260].

Contrary to these recommendations, a clinical practice guideline on treatment of hyponatraemia, developed as a joint venture of the European Society of Endocrinology (ESE), the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), and the European Society of Intensive Care Medicine (ESICM), did not recommend the use of tolvaptan for treatment of

SIADH[154]. The rationale behind this decision was that they considered the risk benefit ratio as being negative since vaptans have no proven hard clinical outcome benefit aside from increase in serum sodium concentrations, while there are increasing concerns on safety with respect to the risk of too rapid hyponatraemia correction and potential hepatotoxicity. Instead, they recommended as second-line treatment for SIADH either urea or a combination of low-dose loop diuretics and oral sodium chloride. In fact, the guideline development group recommended against the use of vaptans in patients with serum Na < 125 mmol/l, as the risk of overly rapid correction of hyponatraemia is greatest in this patient group[154]. The overarching principle on which these guidelines were based on was the lack of evidence that correcting hyponatraemia itself improves patient-important outcomes, while unduly rapid correction is well known to expose patients at the risk of ODS with potentially devastating neurological sequelae[154].

These European guidelines have prompted discussion over their decision to not recommend a place for use of vaptans in the treatment of hyponatraemia secondary to SIADH. Otsuka Pharmaceutical Europe, the pharmaceutical company manufacturing tolvaptan, argued against the exclusion of tolvaptan from the European guidelines, despite being the only licensed medication in the US and the EU for hyponatraemia due to SIADH and the sole agent with its efficacy and safety proven in randomised clinical trials[380]. By contrast, therapeutic modalities were recommended, for example urea or the combination of loop diuretics with oral sodium chloride, which have not been subjected to the rigors of a regulatory process requiring randomised controlled trials nor have they received the approval of any regulatory agencies. In a response letter to the European guidelines, Otsuka also stated that the European recommendations were mainly based on a meta-analysis of

four different vaptans, including vaptans not used in clinical practice and also including data from tolvaptan use in hypervolaemic hyponatraemia, rather than focusing on tolvaptan use in SIADH[380]. Replying to a letter from Otsuka, the European guideline development group emphasised that they considered only patient-relevant hard outcomes[389]. Thus, they did not recommend tolvaptan since, despite its great efficacy in increasing serum sodium concentration, it is not proven that it results in a meaningful change in hard clinical outcomes, for example mortality or quality of life[389]. The European guidelines were also criticised by a group of Endocrinologists who argued that the lack of recommendation for tolvaptan in SIADH removes the most evidence-based treatment option from the armamentarium of physicians and, by default, moves alternative therapies with very limited evidence base into prime consideration[274]. Therefore, the exclusion of tolvaptan, a drug widely approved by regulatory authorities on the basis of critical review of efficacy and safety data, from consideration for the treatment of SIADH may constitute a disservice to patients[274].

Future studies

Despite the divergence in recommendations between various guidelines, there has been unanimous agreement between authors of all guidelines on the lack of high quality evidence in the field of hyponatraemia, and especially regarding therapeutic choices for SIADH. For example, in accordance to GRADE, all recommendations about therapy for SIADH in European guidelines were based on low (C) or very low (D) level of evidence, while none were based on high quality of evidence[154 390]. The expert panel led by Verbalis acknowledged the paucity of available randomised controlled trials with clinical outcome measures to support evidence-based recommendations for most available therapies[152]. For this reason, they decided against the use of a quality-of-evidence scoring system to grade the strength of supporting data for each recommendation and they recognised the need for expert guidance in hyponatraemia management[152]. In agreement with other guideline development groups, the Spanish group recognised that their proposed algorithms were mainly based on widely-accepted recommendations, expert opinion, and authors' personal experience, rather than high quality evidence[253]. As a result, because of the widely recognised lack of high quality evidence base, personal opinion and experience inevitably are, to large extent, the basis of all guidelines, explaining important variations in their recommendations.

Given the dearth of evidence in many aspects of the management of hyponatraemia, our priority should be to undertake randomised controlled trials exploring the key hypothesis that correction of hyponatraemia in the acute setting translates into improvement of patient-important outcomes, such as mortality, length of hospital stay, and symptomatology. Only if we prove that correcting hyponatraemia improves

patient-relevant hard outcomes, we will have demonstrated the necessity to administer therapies increasing serum sodium concentration. Similarly, in the outpatient setting, we need to evaluate whether long-term treatment of chronic hyponatraemia will result in improved neurocognitive function, quality of life, functional status and whether correction of chronic hyponatraemia can improve bone mineral density, prevent falls and reduce fracture rates. In order to generate high quality evidence which can inform our clinical decision-making, we need to design and conduct studies with clinical endpoints, instead of the surrogate endpoint of increase in serum sodium concentration. Regulatory authorities, such as FDA and EMA, should reinforce a transformation of pharmaceutical studies in the field of SIADH, by approving drugs based on their ability to improve hard clinical outcomes rather than just increasing serum sodium. Further studies are also warranted to evaluate the therapeutic role of tolvaptan in homogeneous cohorts, for example in paraneoplastic SIADH or in neurosurgical cohorts, since its efficacy and safety may differ depending on the aetiology of SIADH. In addition to its clinical value, we should assess the cost-effectiveness of tolvaptan, taking into account potential benefits such as reduction in length of stay as well as additional resource implications arising from close monitoring in addition to the high cost of the drug. Subsequently, randomised head-to-head studies of tolvaptan versus other therapies, such as fluid restriction, demeclocycline and urea, are warranted to compare their clinical efficacy, not only in correcting hyponatraemia, but also to alter clinical outcomes and safety. These comparative studies also need to include real-life cost/benefit analysis.

The high rate of overly rapid correction in tolvaptan-treated patients with severe hyponatraemia, which was observed in our case series, highlights the need to evaluate the safety of tolvaptan use under appropriate monitoring in individuals with

serum Na < 125 mmol/l, and especially < 120 mmol/l. Our ‘’real-world’’ data add also urgency to the need for prospective studies examining the efficacy and safety of lower tolvaptan doses, such as 7.5 mg and 3.75 mg. The optimal vaptan regimen (dose and timing) to treat SIADH as well as the procedure to be recommended in a too rapid correction rate of chronic hyponatraemia need also to be addressed by future studies. In the era of personalised medicine, studies are urgently needed to identify which parameters can predict the likelihood and magnitude of response to tolvaptan. Therefore, individualising the dose, timing and monitoring of use of vaptans will deliver great efficacy and minimise the risk for adverse events.

Future role of tolvaptan

There is high quality evidence that vaptans are highly efficacious agents in increasing serum sodium levels. Vaptans are an elegant and attractive approach to treatment of SIADH, but elegance is not enough[304]. In an excellent review of vasopressin antagonists published in 2015, Tomas Berl highlighted the great challenge for the next decade in the field of hyponatraemia which will be to ascertain whether such increases in the plasma sodium level have an effect on mortality and morbidity associated with hyponatraemia[305]. Therefore, the magnitude of impact of tolvaptan on patient outcomes and the potential benefits, ranging from changes in mortality and quality of life to improvement in neurocognitive function and prevention of falls and fractures, will determine to large extent the future tole of vaptans. Also their safety profile, mainly their risk for overly rapid correction and new data about hepatotoxicity, will inform clinicians' decisions about the extent of tolvaptan use. In an review of vaptans published in 2011, Gross, Wagner and Decaux summarised the key unresolved questions which have not been answered yet[307]. Can vaptans save lives? Can vaptans improve quality of life? Can vaptans shorten the duration of hospitalisation? Can vaptans save money? What is their safety profile regarding risk for overly rapid correction of hyponatraemia and hepatotoxicity? Which symptoms and which degree of hyponatraemia should serve as indications for vaptans? Can we justify short-term or long-term use, based on clinical and cost-effectiveness analysis? Additionally, there is significant uncertainty at this time concerning when, how, and for how long to use vaptans. These issues should be resolved in future randomised controlled trials. Since the high cost of tolvaptan has been a barrier to its widespread use, a more attractive price of tolvaptan is essential in order to mitigate the substantial financial burden related with the care of hyponatraemic patients[305]. In

total, all these factors as well as their effect on length of hospital stay and its cost-effectiveness will, broadly, define the futurer role of vaptans in the treatment of hyponatraemia. For now, clinicians must rely on good judgment rather than unequivocal evidence to decide which patients with chronic hyponatremia should be given tolvaptan. The availability of an effective treatment for chronic hyponatraemia makes the need for data to inform that decision even more acute.

Our recommendations about tolvaptan use

Taking into consideration the low quality evidence base for most therapeutic modalities and the failure of treatment guidelines to reach a consensus on the appropriate SIADH management, the role of clinical acumen is becoming even more important than in other aspects of medicine. We disagree with the exclusion of any effective therapeutic options for hyponatraemia and we support that the caring physicians should be given access to all effective treatment options. For example, we oppose the European guideline development group which did not recommend pharmacotherapies, such as tolvaptan and demeclocycline, for the treatment of SIADH. In our opinion, the European guideline development group did not apply the same rigour to the analysis of risk-benefit profile for all therapeutic modalities. We recommend individualising treatment of SIADH, based on a benefit-risk analysis for each patient. Importantly, our goals and limits for hyponatraemia correction should vary according to each patient's characteristics and risk for ODS. Also several factors, including duration and aetiology of SIADH, biochemical parameters, urine output, sense of thirst, should impact on the choice of therapy for each individual.

Having acquired extensive experience in the use of tolvaptan, tolvaptan has become the main pharmacotherapy for SIADH in our practice. We prefer tolvaptan to other modalities, such as demeclocycline, urea and combination of loop diuretics with oral salt, because it is the only medication which is licensed for the treatment of SIADH in the US and Europe and which has undergone stringent review of risk-benefit balance by the regulatory authorities. Tolvaptan is also the sole treatment modality for SIADH with its efficacy and safety having been proven in randomised controlled trials, while data for other agents are of low quality, derived primarily from retrospective

uncontrolled studies and case series. Evidence that tolvaptan improves hard clinical outcomes is currently lacking, but this applies to all treatment options for SIADH. Regarding concerns about tolvaptan-related too rapid hyponatraemia correction, this risk exists as for any effective therapy of hyponatraemia. However, this risk can be substantially reduced, provided patients undergo rigorous electrolyte and fluid monitoring at frequent intervals and, if needed, clinicians implement promptly specific measures to prevent, or even reverse, overly rapid correction.

Therefore, we recommend tolvaptan as second-line therapy for the treatment of SIADH, after failure of patient to respond to, at least 48-hour, fluid restriction. In light of its high efficacy in correcting hyponatraemia, we recommend using tolvaptan as first line therapy in selected SIADH cases when there is a clinical need for prompt correction of hyponatraemia, such as to render a patient fit for chemotherapy or for surgery. In specific, we strongly recommend utilising tolvaptan as first-line treatment in cancer patients with SIADH who are waiting to start chemotherapy with drugs which either can worsen hyponatraemia by themselves, such as platinum-based agents or cyclophosphamide, or require infusion of large volume of fluids. Our recommendation is also supported by the, published in summer 2017, analysis of the management of 358 cancer patients with euvolaemic hyponatraemia as part of the Hyponatraemia Registry[391]. This report showed that tolvaptan showed significantly greater effectiveness than other therapies which were often ineffective and sometimes even aggravated hyponatraemia[391]. We also propose using tolvaptan as first-line therapy for SIADH in patients with urine osmolality > 500 mOsm/kg or urine/plasma electrolyte ratio > 1, since fluid restriction is unlikely to be effective. On outpatient long-term basis, we do not routinely use tolvaptan, mainly because of its high cost, with the exception of selected cases of paraneoplastic SIADH, refractory

to all other treatment modalities, which would otherwise result in recurrent hospitalisation and poor quality of life. Finally, taking into consideration the high rate of overly rapid correction in patients with starting serum Na < 125 mmol/l in our cohort, we have continued using tolvaptan in these patients, but at a lower initiation dose of 7.5 mg and under very stringent monitoring.

Our protocol of safe tolvaptan use

We have developed a specific local algorithm for the safe use of tolvaptan and we are aiming to audit our practice against this stringent protocol on annual basis. According to our local policy, tolvaptan is prescribed only by Consultant Endocrinologists with special interest in the field and is initiated only in hospitalised patients. Tolvaptan therapy is provided under the supervision of a named dedicated Consultant Endocrinologist, who is accessible 24 hours per day for specialist input. We exclusively use it as monotherapy, while in cases it follows hypertonic saline, the minimum interval between therapies is 6 hours. We do not use tolvaptan in patients treated with strong CYP3A4 inhibitors, such as ketoconazole, clarithromycin, and protease inhibitors, while we use a lower dose of 7.5 mg in case of concomitant administration of moderate CYP3A4 inhibitors, such as grapefruit juice, erythromycin, fluconazole, diltiazem or verapamil. We initiate tolvaptan at a dose of 15 mg for baseline serum Na ≥ 125 mmol/l and at a lower ‘’off label’’ dose of 7.5 mg for serum Na < 125 mmol/l. We prescribe it only as single stat doses and we start its administration in the early morning (6-9 am) to allow face-to-face review by caring Endocrinologist within the first 6-8 hours of initiation. During treatment with tolvaptan, patients are advised to maintain ad libitum fluid intake. It is of paramount importance to measure serum electrolytes, at least, 6-hourly (0, + 6 hours post administration, + 12 hours, + 18 hours, + 24 hours) during the first 24 hours. Also we should keep accurate fluid balance chart, recording fluid input and urine output at 2-hour intervals.

If serum Na increase exceeds 6 mmol/l at 6 hours or 8 mmol/l at any time point between 7 and 18 hours following tolvaptan initiation or 10 mmol/l in 24 hours, then free water losses are replaced with administration of 5% dextrose in water at a volume equal to urine output in order to prevent further correction. In cases when

reversal of overly rapid correction is warranted, larger volumes of hypotonic fluids are prescribed. In cases urine output exceeds 200 ml/hour for 2 consecutive hours, serum sodium should be measured urgently and we strongly consider replacing further free water loses with 5% dextrose in water. In all cases when specific safe limits are exceeded, closer electrolyte monitoring, initially 2-hourly, is warranted. If the daily serum Na increase is ≥ 10 mmol/l, further tolvaptan dose is withheld, while if it is 5-9 mmol/l, administration of another tolvaptan dose is considered. Finally, the dose can be titrated to 30 mg and 60 mg at 24-hour intervals if the increase in serum Na has been < 5 mmol/l in the previous 24 hours and serum Na is < 135 mmol/l.

It is worth mentioning that point of care testing with direct ISE plasma Na measurement by a blood gas analyser is often utilised in clinical practice to allow close electrolyte monitoring during the first 24 hours of tolvaptan therapy. The main reason is that quick decision making based on electrolyte values can be delayed by an average turnaround time for laboratory measurement of sodium of longer than 30 minutes. As many as 8% of indirect ISE plasma sodium measurements in a general hospital population and 25% in an Intensive Care Unit setting differ from corresponding direct ISE values by at least 4 mmol/l[148], with the dominant factors being indirect ISE overestimation driven by hypoproteinaemia and hypoalbuminaemia. Several studies have found that sodium values, measured by central laboratory auto-analyser employing indirect ISE, tend to be significantly higher, by an average of 5 mmol/l in critically ill patients[392], compared to those derived from blood gas analyser. The main reason is the low protein levels in critical illness, making direct ISE measurement more accurate and consistent than indirect ISE. This disagreement seems to be sufficient to jeopardise safe interchangeable interpretation in situations with a low tolerance for imprecision, such as

hyponatraemia correction[393]. Therefore, the results of electrolytes on blood gas analysis and indirect ISE measurement in the laboratory should not be used in inter-exchangeable manner and should be interpreted with caution[394]. In conclusion, we should consistently use the same analyte and method for all measurements in the active phase of hyponatraemia correction in order to evaluate the effectiveness and safety of therapeutic measures and guide our treatment decisions.

Conclusions

In conclusion, tolvaptan is highly effective in increasing serum sodium concentration. However tolvaptan-treated patients, especially with low baseline serum Na < 125 mmol/l, are exposed at a high risk of overly rapid correction of hyponatraemia. This observation reinforces the need for vigilant monitoring of tolvaptan therapy to minimise risk of overly rapid correction. Finally, studies are needed to evaluate the impact of tolvaptan on hard clinical outcomes as well as its safety when used for severe hyponatraemia under rigorous monitoring.

7.6 An intervention study demonstrating that intensive endocrine input shortens time for hyponatraemia correction and reduces length of hospitalisation

How can specialised input result in better outcomes?

Our study, described in detail in Chapter 6, demonstrated for the first time that expert input for SIADH achieved meaningful increase in serum sodium more quickly and resulted in shorter hospitalisation in comparison with ‘routine care’. Since we utilised various therapeutic modalities and implemented individualised treatment pathways tailored to patients’ characteristics, these benefits of expert care seem to be multifactorial. Patient receiving specialised care were characterised by prompt initiation of treatment, more frequent use of fluid restriction, higher effectiveness of fluid restriction, and administration of a higher number of different therapies than those receiving non-specialised care. To what extent each of these, or even other unrecognised, factors contributed to better outcomes is not clear and remains to be seen in future studies. This fact was also highlighted in a recent Editorial with a title ‘’Syndrome of inappropriate antidiuresis should be managed by specialised endocrinologists?’’, stating that the use of multiple therapies in our study, in a non-randomised way and without consistency in mode or dose or length of treatment, does not allow us to attribute the success of expert input to a specific therapy[395].

Serum urate as a diagnostic test to differentiate euvolaemia from hypovolaemia

In our cohort, serum urate levels were ≤ 0.25 mmol/l in all 28 SIADH patients, with 96% of patients with SIADH having serum urate values ≤ 0.19 mmol/l, including 54% with very low values ≤ 0.12 mmol/l[396]. Our data confirmed the findings of previous studies which suggested that serum uric acid levels can accurately differentiate euvolaemic from hypovolaemic hyponatraemia, with SIADH patients having depressed levels < 0.24 mmol/l in contrast to hypovolaemic patients exhibiting elevated levels > 0.30 mmol/l[397 398 206 212]. Measurement of serum uric acid concentration is a greatly underutilised biochemical test in day-to-day clinical practice despite the fact that Beck firstly reported in 1979 hypouricaemia as being present in virtually every patient with SIADH[397] and since then several authors have suggested serum urate < 0.24 mmol/l as a supporting diagnostic criterion for SIADH[168 162 163 154]. A recent study by Fenske et al, evaluating the utility of various biochemical parameters in diagnosis of SIADH, found a statistically significant difference ($P < 0.05$) between mean (± SD) serum urate of 0.20 ± 0.06 mmol/l in SIADH patients vs 0.38 ± 0.12 mmol/l in hypovolaemic patients[204]. Serum urate at a cut-off value of 0.24 mmol/l had high sensitivity and specificity of 83% for the diagnosis of SIADH with a positive and negative predictive value of 87% and 79% respectively[204]. Contrary to these studies, a study of biochemical parameters in the evaluation of hyponatraemia in an elderly population did not find a high discriminative value of serum urate levels with a significant overlap between volume-depleted and SIADH patients. Hypouricaemia < 0.24 mmol/l was observed in 73% of SIADH patients. This, lower than widely reported, sensitivity was attributed to a significant proportion of SIADH patients in this cohort having COPD (Chronic

Obstructive Pulmonary Disease) since tissue hypoxia increases uric acid plasma levels[399]. Also, as many as 41% of patients with hypovolaemic hyponatraemia had serum uric acid levels < 0.24 mmol/l[399].

In conclusion, we strongly recommend measurement of serum urate levels as part of routine evaluation of hyponatraemic patients since it combines relatively high sensitivity and specificity with high reliability and precision; it has low cost; it is easy to perform; its result is quickly accessible to the clinician within less than 60 minutes in most laboratories, while spot urine samples for sodium and osmolality measurement are often not timely collected. Additionally, we have been using serum urate as a longitudinal marker for effective volume status during treatment of SIADH with fluid restriction or tolvaptan. This use of serum urate is based on data from Beck et al who firstly showed that mean levels rose from 0.17 to 0.31 mmol/l after fluid restriction with these changes being consistent and occurring in every patient after restoration of normonatraemia[397]. Therefore, serum urate levels > 0.30 mmol/l should prompt us to consider discontinuation of treatment.

Role of isotonic saline in the diagnosis and treatment of SIADH

Another interesting observation in our study was that, amongst 9 individuals who were administered a diagnostic/therapeutic challenge of isotonic saline, 8 (88.9%) increased serum sodium by 1-4 mmol/l with only one patient (11.1%) experiencing aggravation of hyponatraemia[396]. In contrast to a 29% response rate to isotonic saline, defined as a serum sodium rise ≥ 5 mmol/l, in the laboratory-diagnosed SIADH subgroup of Hyponatraemia Registry[164], our study did not include a single case showing sodium rise ≥ 5 mmol/l. This might be attributed to our study protocol, according to which a 24-hour infusion of 2000 ml isotonic saline was administered and subsequently discontinued regardless of initial response, contrary to the Registry where often patients had continuation of isotonic saline infusion until sodium reached a plateau. Also all our SIADH patients had urine osmolality ≥ 438 mOsm/kg, while high response to isotonic saline is expected with urine osmolality ≤ 300 mOsm/kg[206]. No clear correlation was observed between response to isotonic saline and parameters such as urine osmolality and Furst ratio, but the sample size was very small with a narrow range of urine osmolality across subjects. Noteworthy, isotonic saline infusion resulted in lowering of serum sodium only in 1 case despite the fact that almost all individuals had urine osmolality ranging between 438–604 mOsm/kg. In fact, all but one patients with urine osmolality > 530 mOsm/kg and Furst ratio > 1.0 increased, rather than decreased as expected from previous studies[213], their serum sodium concentration after isotonic saline. Apparently, all these parameters do not always accurately predict response to isotonic saline for a variety of reasons. Urine osmolality is not fixed and can vary substantially; time can elapse between measurement of biochemical parameters and isotonic saline challenge; other factors such as treatment of underlying condition or discontinuation

of drugs can alter serum sodium. In conclusion, isotonic saline infusion which is underutilised as a diagnostic challenge in routine clinical practice can be a useful adjunct in the differentiation between euvolaemic and hypovolaemic hyponatraemia and is usually safe, provided urine osmolality is not very high and renal electrolyte free water clearance is not negative.

Effectiveness of fluid restriction

Our intervention study found a much higher success rate of fluid restriction, defined as total rise of serum sodium by ≥ 5 mmol/l, in the intervention (71%) than in the control arm (31%). This unprecedentedly high response rate to fluid restriction exceeded a 20% response rate observed in our recent multicentre real-world study[325] and a 48% response rate in the Hyponatraemia Registry, the largest real-life observational study of hyponatraemia management[164]. The increased effectiveness of fluid restriction in the intervention arm of our study may be explained by a variety of factors. In our intervention study, fluid intake was rigorously restricted in all our subjects to a maximum volume of 1000 ml/day with the mean volume being around 800 ml/day and, more importantly, we actively and systematically promoted patient adherence to fluid restriction through regular patient encouragement and explanation of its benefits in combination with bedside notices, detailed fluid balance charts and removal of excess bedside fluids. Our study findings provide some evidence against the increasingly popular notion that fluid restriction should not be the mainstay treatment for SIADH because it is either ineffective or, at best, modestly effective[167], with recent results from Hyponatraemia Registry suggesting that it is not superior to no active treatment for SIADH[164]. However, our high success rate was based on a small sample of 18 individuals who were intensively monitored. Thus, the questions remaining to be answered are; whether our data could be reproduced in larger samples and different healthcare settings, and whether it would be achievable as well as cost-effective to increase patient adherence in real-world settings and outside the context of an intervention study.

In our study, the large majority, around 80%, of non-responders had parameters which predicted failure to respond to fluid restriction, such as elevated urine osmolality > 500 mOsm/kg and Furst equation > 1.0. However, at the same time, 27% and 36% of ‘great responders’ with sodium rise ≥ 7 mmol/l had high urine osmolality and Furst ratio respectively, predictive of non-response. Of note, these data, based on a small sample of patients, might reflect in some cases resolution of SIADH, either spontaneous or due to treatment of underlying aetiology. Interestingly, a recent prospective study of 183 well-defined, consecutive SIADH patients in two different hospitals demonstrated that almost two thirds of SIADH patients had at least one baseline parameter at the time of diagnosis predicting failure of fluid restriction[374]. In conclusion, a randomised controlled trial of fluid restriction in SIADH, incorporating measurement of potential predictors of fluid restriction, is urgently warranted in order to inform the clinicians about whether and when fluid restriction should be used as first line therapy for SIADH.

Association of correction of hyponatraemia with length of hospital stay

Our prospective intervention study found that intensive specialist input, resulting in more effective and timely hyponatraemia correction, significantly reduced length of hospitalisation by an average of 3.6 days[396]. Although hyponatraemia is a well-established risk factor for prolonged hospital length of stay and increased risk for readmission[138], there is a paucity of prospective data that hyponatraemia correction can improve these outcomes. SALT studies, which were neither designed nor powered to study length of hospital stay, showed a nominally greater shortening of hospital stay in the tolvaptan-treated patients which reached statistical significance only in a subgroup analysis[285]. In addition, subgroup analysis of SIADH patients recruited in Europe as part of the Hyponatraemia Registry showed that the median length of hospital stay was significantly shorter by 3 days in tolvaptan-treated patients than fluid restricted patients[164]. This observation suggested that shorter hospitalisation of tolvaptan-administered subjects than fluid restricted ones is likely to be attributed to timely hyponatraemia correction. A recently published retrospective study of 412 patients admitted with serum Na < 120 mmol/l suggested that undercorrection of hyponatraemia was associated with an increase in length of hospital stay[400]. Regarding the potential impact of intensive input and rate of hyponatraemia correction on readmission rate, our study did not find any difference between intervention and control group. However, a large retrospective cohort study of 4295 patients with hyponatraemia and heart failure found that absence of correction of hyponatraemia during hospitalisation was independently associated with a 45% increase in the odds of having a 30-day planned readmission or death[401]. This association was independent of heart failure severity[401]. In total, additional

clinical studies are needed in order to provide definite proof that effective sodium correction can shorten hospitalisation and reduce the readmission rate.

Association between correction of hyponatraemia and mortality rate

Our study found a low inpatient mortality rate of 5.5% in the intervention group, almost a third of the 17.4% death rate in the control group. Nevertheless, this difference did not reach statistical significance, either because this study was not powered to detect difference in mortality or because our intervention did not have a true effect on mortality. Despite the well-known association between hyponatraemia and increased risk of inpatient mortality, it has not been clearly established, so far, whether an improvement of hyponatraemia is able to revert or decrease the increased risk of death associated with hyponatraemia. The best quality evidence to date originates from observational studies with generally short duration, none of which were originally designed to address clinical outcomes after serum sodium improvement. A recently published meta-analysis, including all studies until June 2014 that compared the mortality rate with and without interval improvement of hyponatraemia, finally included 15 studies yielding a total of 13,816 hyponatraemic patients with a mean follow-up of 33.6 months[316]. Amongst those 15 studies, most of them, 7, evaluated the effect of hyponatraemia improvement on mortality rate in subjects with heart failure, 3 in hospitalised series of patients, 1 in intensive care unit, and the remaining in specific patient populations (1 in patients undergoing liver transplantation, 1 in patients with small-cell lung cancer, 1 in patients with myocardial infarction, and 1 in patients with pulmonary embolism)[316]. This meta-analysis showed that patients with any increase in serum sodium compared to those with no serum sodium correction at all had a significant reduction of overall mortality (OR = 0.57, 95% CI 0.40 - 0.81; P = 0.002). The association between improvement of hyponatraemia and reduced mortality was even stronger by performing a sensitivity analysis which considered only the 8 studies reporting a threshold for serum sodium

improvement > 130 mmol/l (RR = 0.51, 95% CI 0.31-0.86, P < 0.001). The reduced risk of mortality associated with hyponatraemia improvement appeared to last during prolonged follow-up, at least for 12 months of follow-up. Also the same meta-analysis reported that the beneficial effect of hyponatraemia improvement on mortality rate was more evident at patients of older age and with lower baseline serum sodium levels[316]. Thus, our study findings in combination with evidence from this meta-analysis highlight the need for well-designed prospective studies exploring a possible cause-effect relationship between hyponatraemia correction and reduction of mortality.

Role of automated electronic alerts

In total, our study showed that improving clinical practice led to more effective hyponatraemia correction and better patient outcomes. It could be argued that the better standard of care achieved through regular endocrine input might be also met by ‘generalists’. However, the consistently suboptimal management of SIADH in clinical practice, recorded in numerous contemporary observation studies[325 164], indicated that wider provision of expert input should be strongly considered. To effectively deliver this service, multidisciplinary hyponatraemia teams should be developed and led by specialists with expertise in the management of hyponatraemia. Specialised care was provided in our studies by Endocrinologists, but it may also be delivered by other Specialists such as Nephrologists, depending on local expertise and resources. In view of the high prevalence of hyponatraemia, we may need to consider a 2-tier model of care and to incorporate electronic alert systems, recently tested with variable results in acute kidney injury (AKI).

Lessons should be learnt from the variety of automated electronic alerts for AKI introduced at various hospital settings since 2010. On the basis that the prompt and reliable identification of AKI cases to clinicians may trigger improved care, NHS England issued in June 2014 a national Patient Safety Alert entitled “Standardising the Early Identification of Acute Kidney Injury”. The aim of this initiative has been to embed an automated AKI detection system in the biochemistry laboratories of all acute hospitals in order to deliver direct clinical benefits that may come from earlier and more systematic recognition of AKI and to feed a national AKI registry, a potent tool for future measurement and improvement initiatives[402]. Hyponatraemia and AKI share a lot of characteristics such as a high prevalence in hospitalised patients, a

strong association with increased mortality rate, being a predictor for longer hospitalisation, and being frequently suboptimally cared for. Both conditions are also defined by specific values in serum sodium and creatinine for hyponatraemia and AKI respectively, allowing implementation of prompting systems depending on biochemical values. The questions then arises with regards to how these automated real-time systems could not only be used as early detection tools, but also they could alter physicians' behaviour and trigger earlier and more effective intervention[403]. The results with respect to the effect of e-alert systems on patient outcomes have been variable so far. The first randomised controlled trial of its kind evaluated an intervention which was a single text message informing the responsible clinician and pharmacist of the diagnosis of AKI without providing treatment recommendations for AKI care or being supported by educational programmes[404]. This study did not show any improvement in clinical outcomes[404]. In contrast, other studies found that implementing an AKI care bundle, linked to electronic recognition of AKI, can decrease fatalities and progression to higher AKI stage[405 406]. Two recent systematic reviews have also generated conflicting evidence about the effect of e-alerts on patient outcomes. On the one hand, according to a systematic literature search of several controlled non-randomised trials, AKI alerts which were linked to concrete treatment recommendations to the treating ward physicians or with the introduction of specialist support led to more frequent implementation of diagnostic or therapeutic measures, less loss of renal function, lower inpatient mortality, and lower mortality after discharge compared to control groups without an electronic alert for AKI[407]. On the other hand, a systematic review of 6 studies concluded that e-alerts for AKI did not improve survival or reduce utilisation of renal replacement therapy[408]. Thus, there is still an important gap in knowledge about the effectiveness of e-alerts in AKI and

their potential to improve patient-related outcomes. In total, it seems that simply alerting a clinican to the presence of a possible AKI incident may be insufficient to improve outcomes[404], with all the positive studies so far having included interventions which combined detection systems with specific care bundles. Therefore, in 2016, a dedicated workgroup from the 15th Acute Dialysis Quality Initiative (ADQI) Conference published a consensus statement, recommending that AKI alerting systems should be linked to context specific treatment recommendations[409]. The National Institute for Health and Care Excellence (NICE) guidelines on AKI management suggest that patients with more severe AKI may benefit from care delivery by suitably expert clinicians, for example as part of a 'rapid referral' nephrology service. An example of a local initiative in the Royal Free Hospital is the introduction and implementation of a digitally-enabled AKI care pathway as a core service to hospital inpatients. A mobile software application (Streams-AKI) provides real-time alerts of potential AKI cases to a clinical response team comprising nephrologists and critical care nurses. This response team will assess the data, prioritise cases and then deliver investigations and therapies according to current best practice guidelines. Considering data from studies evaluating AKI electronic alerts and taking into consideration current AKI initiatives, we should develop and test e-alert hyponatraemia systems which should not be limited to detecting patients with low sodium, but they should incorporate sophisticated investigation and treatment algorithms.

Our recommendations about the optimal management of SIADH

We recommend an individualised approach to SIADH management, based on several factors, including duration and degree of hyponatraemia, severity of symptoms, the capacity of the nephron to excrete free water, the safety and efficacy of each treatment modality, cost implications of each therapy, and patient's compliance[410]. Especially in light of divergent approved indications and guideline recommendations for pharmacotherapies such as tolvaptan, we are strong advocates that clinical judgment must continue to play a primary role in individual decision-making about the management of hyponatraemia. As suggested by various world experts in the field of hyponatraemia[274 163], clinical judgment and application of clinical acumen rather than guidelines, especially when they are based on low quality evidence such as in this area, should ultimately dictate the choices physicians make for their patients with respect to hyponatraemia just as for all aspects of medicine.

Prompt and accurate ascertainment of the aetiology of hyponatraemia is essential to guide effective treatment for hyponatraemia. We are in favour of applying diagnostic algorithms in which biochemical parameters are prioritised over, often unreliable[201 200], clinical assessment of volume status, as they have been shown to have a better diagnostic performance[202 203], in agreement with recommendations by the authors of European guidelines on hyponatraemia[154]. In addition to the use of urinary sodium as the primary discriminating factor between hypovolaemic and euvolaemic hyponatraemia, we suggest routine measurement of serum uric acid, an underutilised test with high sensitivity and specificity at values < 0.24 mmol/l in confirming SIADH[204 163]. Furthermore, we apply a very low threshold for a diagnostic challenge of infusing 2000 ml isotonic saline over 12-24 hours to distinguish between mild hypovolaemia and SIADH as the cause of hyponatraemia. In total, we should

confirm the diagnosis of SIADH only if all essential, or, at least, almost all essential in combination with at least one supplemental, criteria are met. Following confirmation of SIADH diagnosis, we propose thorough work-up to establish its aetiology, including detailed drug history, physical examination and in selected cases investigations such as CT thorax–abdomen–pelvis and MRI brain.

Patients with severe symptoms related to hyponatraemia, such as seizures, reduced Glasgow Coma Scale (GCS) and coma, constitute a medical emergency and should be treated with infusion of hypertonic saline[245 152 154] . Treatment with hypertonic saline should commence with 100 ml of 3% NaCl infused intravenously over 10-15 minutes, which should be repeated up to twice if there is no clinical or biochemical improvement in order to achieve a target of 4-5 mmol/l increase in serum sodium[152]. Susbsequent treatment should be in the form of continuous intravenous infusion of hypertonic saline under close clinical and biochemical monitoring in an HDU/ICU environment.

In the absence of severe hyponatraemic encephalopathy, we aim for an increase in serum Na concentration by 4-6 mmol/l/day and not exceeding the limit of 8 or 10 mmol/l/day, depending on the presence or not of risk factos for ODS[152 245], with first line therapy encompassing treatment of the underlying cause of SIADH and fluid restriction. Restriction of all fluid intake should be titrated according to the Furst formula using the urine/plasma electrolyte ratio (U/P) = $(U_{Na}+U_K) / (P_{Na}+P_K)$, for example 500 ml/day if U/P is 0.5-1.0 and 1000 ml/day if U/P is < 0.5[254]. If urine electrolytes are not readily available, we impose fluid restriction at 750-1,000 ml/day. In order to enforce adherence to fluid restriction, which can often prove challenging, we take a variety of measures, such as explaining the rationale and benefits of treatment to patients and those close to them, regular patient encouragement by

medical and nursing staff, use of bedside signs to remind patients and healthcare professionals, and use of bedside charts to keep detailed record of fluid balance. We recommend tolvaptan use as 1st line treatment in 2 groups of SIADH patients; first, if there is a clinical need for prompt correction of hyponatraemia, for example to render a patient fit for chemotherapy or surgery, and second, in cases when fluid restriction is highly unlikely to be effective, evidenced by U/P > 1.0 or urine osmolality > 500 mOsm/kg H2O[152]. As 2nd line therapy, tolvaptan should be strongly considered if a patient has not responded to fluid restriction, defined as serum Na increase of ≤ 3 mmol/l over 48 hours. We recommend tolvaptan use only under the supervision of an Endocrinologist or Nephrologist with patients on tolvaptan maintaining ad libitum fluid intake and not receiving any other concomitant treatment for hyponatraemia. At our institution, we start tolvaptan at a dose of 15 mg for baseline serum Na ≥125 mmol/l and at an 'off-label' dose of 7.5 mg, half the recommended initiating dose, for serum Na < 125 mmol/l, since this low starting dose may be associated with lower risk of overly rapid correction, while it retains its efficacy[297 379 386]. Serum Na concentration should be closely monitored no later than 4-6 hours after treatment initiation and at regular 6-hour intervals, at least, during the first 24 hours of therapy. If serum Na increase exceeds 6 mmol/l at 6 hours or 8 mmol/l at any time point between 7 and 18 hours following tolvaptan initiation or 10 mmol/l in 24 hours, then free water losses are replaced with administration of 5% dextrose in water at a volume equal to urine output in order to prevent further correction. In cases when reversal of overly rapid correction is warranted, larger volumes of hypotonic fluids are prescribed. Finally and in light of the high cost associated with long-term tolvaptan use, we prescribe demeclocycline at a starting dose of 300 mg three times

per day in selected cases with likely long duration of SIADH, such as malignant SIADH.

Future studies

As far as suggestions for future research are concerned, there has already been a wealth of evidence about the strong independent association of hyponatraemia with a variety of adverse clinical outcomes. Despite that, the authors of both European and US guidelines highlight the lack of high quality evidence about whether hyponatraemia correction can improve patient-related outcomes[152 154]. This key question in the field of hyponatraemia remains unanswered, prompting clinicians and researchers at a worldwide level to consider this to be of highest priority and concentrate their efforts on addressing it. Our prospective intervention study, which showed that timely hyponatraemia correction could significantly shorten length of hospital stay and might reduce fatalities, highlights the need for multicentre prospective controlled studies to evaluate whether more effective hyponatraemia correction can improve 'hard' clinical outcomes such as mortality rate, length of stay and readmission rate. So it is the time for a major paradigm shift, changing the end points of hyponatraemia studies. As a clinical research community in the field of hyponatraemia, we should shift from surrogate outcomes, such as magnitudes of increase in serum sodium concentration and time required to achieve them, to real clinical outcomes, such as mortality and length of hospitalisation. In addition to 'hard' clinical outcomes, it is also essential to assess the impact of hyponatraemia correction on 'soft' outcomes such as neurocognitive symptomatology. While, in cases of severe hyponatraemic encephalopathy hyponatraemia correction can improve neurological symptoms, we need to study if this also applies to the majority of patients who have non-severe symptoms associated with hyponatraemia. These studies will be further complicated by the absence of validated tools measuring symptoms related to hyponatraemia as well as by the fact that most hyponatraemic

patients are elderly who sometimes have varying degrees of cognitive impairment and other comorbidities such as psychiatric disease, malignancies, lung disease, and liver disease that can also contribute to neurocognitive deficits. This topical question has become an even higher priority following recently published INSIGHT trial which showed that tolvaptan-related reversal of hyponatraemia in patients without overt neurological symptoms correlated with improvements in results of various neurocognition tests, especially rapid motor movements[292].

In light of the paucity of comparative studies between different available SIADH treatments, another area of high priority is undertaking well-designed head-to-head studies comparing efficacy and safety, including patient-related outcomes, of various SIADH therapies. These studies will inform clinicians' decision making about optimal use of different pharmacotherapies such as vaptans, demeclocycline and urea, depending on their risk-benefit profile. Since the mainstay of SIADH treatment, fluid restriction, has no high quality evidence basis about its efficacy and safety, it is of paramount importance to include fluid restriction in randomised head-to-head studies. Our observation in a small cohort that well-adhered rigorous fluid restriction was much more effective than in routine clinical practice raises the question of whether implementing our steps to improve compliance in different healthcare settings could result in equally high effectiveness rates. With regards to the potential scope for expanding the provision of expert input to hyponatraemic inpatients, incorporating a diagnostic and therapeutic algorithm similar with our intervention study, further studies should take place to examine whether the benefits of our intervention, especially the significantly shorter hospitalisation time, are reproducible. The reproducibility of our improvement is in question, primarily, because Endocrinologists in our study were likely to have much higher level of expertise in the

field of hyponatraemia than Endocrinologists in other hospital settings without special research interest in this area. With respect to optimising the mode of care provision to inpatients with hyponatraemia, studies are warranted to test different systems at various healthcare settings. Whether ‘hard’ clinical outcomes can improve following implementation of different systems of care, including expert input to all hyponatraemic patients below a specific cut-off; e-alert systems prompting the responsible clinician of the diagnosis without treatment recommendations; hyponatraemia care bundle with concrete management recommendations linked to e-alert system; 2-tier model combining a hyponatraemia care bundle with expert review offered to selected cases, need to be evaluated in ‘before and after’ studies. Moreover, some of these studies could target subgroups of hyponatraemic hospital population who may benefit more such as elderly and the ones with more severe degree of biochemical hyponatraemia. It is also essential to test the cost-effectiveness of these systems since SIADH is highly prevalent in hospital population and represents a potential target for intervention to reduce healthcare expenditures, taking into account on the one hand potential reduction in length of hospitalisation and readmission rate and on the other hand additional cost related to clinical and nursing time, cost of pharmacological therapies, and cost of development and implementation of new systems of care.

Conclusions

In conclusion, these preliminary data demonstrated that intensive endocrine input not only was superior to ‘routine’ care in correcting hyponatraemia, but also improved patient-important outcomes such as length of hospital stay and symptoms. If these results could be generalised, provision of systematic endocrine care for patients with SIADH should be widely adopted to improve clinical outcomes and potentially reduce utilisation of hospital resources.

7.7 Key unanswered questions

The findings of these five studies in combination with an extensive literature review raise some key questions which need to be answered. First of all, the strong association between hyponatraemia and mortality does not equal causality. We need to design studies looking into the mechanistic aspects of hyponatraemia, exploring the posibilty of a causal relationship. These will include both in vitro and in vivo/ex vivo studies to explore the mechanisms, whereby hyponatraemic stress may cause maladaptive responses that may lead to excess mortality, such as the effects of acute osmotic stress in the immune system. Considering the adverse prognostic significance of hyponatraemia, the burning question for clinicians encountering so many hyponatraemic patients on day-to-day basis is whether correcting hyponatraemia could alter mortality rates. This issue needs to be resolved by undertaking prospective well-designed studies with primary end point mortality. Being aware of the difference in mortality rates between various types of hyponatraemia, it is time to conduct studies on more homogenous populations such as SIADH, and ideally even more specific groups like SIADH due to pneumonia or malignant SIADH.

As far as investigation of hyponatraemia is concerned, we need to take into account the findings of recent studies in order to develop new diagnostic algorithms, incorporating fractional excretions and, in some cases, copeptin measurements. Afterwards, prospective evaluation of performance of up-to-date algorithms in real-life clinical practice is required to inform future hospital protocols. In addition, further evidence is required to conclude on the threshold for serum cortisol below which dynamic testing of adrenocortical function or glucocorticoid replacement is indicated. Finally, the consistently suboptimal standards in diagnosing hyponatraemia urges

clincians, health policy makers and other key stakeholders to assess various initiatives with the potential to improve quality of care. Some of the future directions which need prospective multicentre assessment include systematic provision of undergraduate and postgraduate education in the field of hyponatraemia, biochemical reflex testing, and electronic alerts.

The key, still unresolved, question remains. Does hyponatraemia matter? If it does, can correction of hyponatraemia translate into clinical benefits? Until we answer these questions, many will argue that it is not worth, and it could be even detrimental, investigating and treating a ‘’number’’. We urgently need to design studies with endpoints being clinical outcomes, such as short-term and long-term mortality, length of hospitalisation, need for re-hospitalisation, neurocognitive performance, symptomatology, quality of life, bone mineral density, falls, and fractures. In light of the high prevalence of hyponatraemia, more data are also needed about cost-effectiveness of any intervention.

Vaptans, and in specific tolvaptan, remain subject of heated debate, dividing the scientific and medical community across the world. It’s time to coordinate efforts in order to generate, much needed, high quality data which will define the future role of vaptans. It’s time for the new generation of tolvaptan studies with primary end points being hard clinical outcomes rather than hyponatraemia correction. The same challenge was addressed during the last two decades in the field of lipid-lowering medications, when regulatory authorities and physicians focused on generating data with respect to reducing cardiovascular events rather than, just, lowering cholesterol values. These studies, looking into patient-important outcomes, will determine the future use of vaptans. Furthermore, we urgently need to assess the safety of tolvaptan. What is the risk for too rapid sodium increase in large studies with

baseline sodium < 125 mmol/l? What is this risk under appropriate electrolyte and fluid balance monitoring? Could we lower the risk and retain efficacy by using lower tolvaptan doses? Could we develop an algorithm, taking into consideration variables predicting natraemic response, in order to individualise tolvaptan dose with a view to combine maximal drug efficacy and safety? Also, very importantly, what is the truly safe limit of hyponatraemia correction that we should not exceed? What is the likelihood for neurological sequelae when we exceed it? What are the measures we should put in place if we correct too rapidly and can they reduce the clinical risks? For example, should we re-lower serum sodium, and if yes, when and how? The answers to these questions will allow us to undertake risk benefit analysis for vaptans.

With respect to treatment of SIADH, the limited evidence base behind the use of fluid restriction and its poor efficacy rate suggest that we need to generate high quality data for the use of fluid restriction in SIADH. In addition, prospective evaluation of possible predictors of response to fluid restriction is more topical than ever, informing clinicians about whether they should be incorporated in future treatment pathways and, even, determine first choice therapy. In light of the lack of high quality data with regards to the use of all SIADH therapies but vaptans, multicentre, prospective, randomised controlled trials are needed to evaluate the efficacy and safety of various treatment modalities such as urea. Subsequently, we need to conduct head-to-head trials to compare vaptans with fluid restriction and other therapies such as urea. With all the contemporary observational studies suggesting poor efficacy of hyponatraemia management, we need, firstly, to determine the best therapeutic options and, second, to test and put systems in place, allowing provision of best care in routine clinical care.

Our intervention study has shown for the first time that expert input for SIADH can shorten time for hyponatraemia correction and reduce length of hospital stay. The key question is whether these results could be replicated. We urge for replication studies since it is questionable whether additional input from ‘specialists’, not having our expertise and experience in the management of hyponatraemia, in other hospital settings could provide similar, or actually any, benefits compared to ‘routine care’. Depending on their findings, these multicentre prospective studies may change the landscape in the future care of hyponatraemia with a potential for widespread application of specialised care.

Finally, we need to find out what are the true consequences of hyponatraemia and to which extent, if any, are they fixed or could we alter them by restoring hyponatraemia? After numerous observational studies, we need to move into mechanistic ones since our knowledge of pathophysiology is still limited, and prospective intervention studies with hard clinical end points. Interestingly, regardless of each doctor’s opinion about therapeutic role of vaptans, they can allow us to undertake all these studies, expanding our knowledge about impact of hyponatraemia and its improvement.

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Appendix

Age/Gender	Admission sNa (mmol/l)	Median sNa (mmol/l)	Lowest sNa (mmol/l)	sNa at death (mmol/l)	Day of Death	Clinical Course	Cause of hyponatraemia
82/M	133	130	123	123	32	Presented with stroke. Developed recurrent hospital-acquired pneumonias. SNa>130 mmol/l until last 2 days before death.	SIADH due to pneumonia
64/M	126	136.5	126	143	6	Presented with cerebellar ataxia. Developed hospital-acquired pneumonia and type 1 respiratory failure. SNa 141-143 mmol/l last 2 days.	Hypovolaemia due to poor oral intake and GI losses
69/F	136	135	123	135	50	Presented with coma due to cerebral vasculitis. Developed recurrent hospital-acquired pneumonias. SNa 133-138 mmol/l last 20 days.	SIADH due to cerebral vasculitis
87/F	141	135	127	132	21	Decompensated heart failure, pleural effusion, acute on chronic renal failure. SNa 130-134 mmol/l last 8 days.	Diuretic-induced due to iv administration of loop diuretics
78/F	122	127	122	127	6	New diagnosis of pancreatic cancer with liver metastases. Rapid deterioration.	Unknown
75/F	134	137	124	140	36	Presented with recurrent embolic strokes. Developed recurrent hospital-acquired pneumonias. SNa >134 mmol/l last 27 days.	SIADH due to pneumonia

59/M	131	137	128	139	42	Presented with hepatic encephalopathy due to decompensated chronic alcoholic liver disease. Developed bilateral strokes. Hyponatraemia only for 1 day in view of poor oral intake.	Hypovolaemia due to poor oral intake (reduced consciousness level and impaired thirst)
50/M	128	135	126	137	24	New diagnosis of HIV and Castleman disease. 19-day ICU admission with severe sepsis, acute kidney injury, CMV (Cytomegalovirus) pneumonitis and respiratory failure. SNa 134-140 mmol/l last 16 days.	Unknown
80/M	128	162	123	162	17	Pneumonia, type 1 respiratory failure and decompensated heart failure. SNa 162-174 mmol/l last 10 days.	Hypovolaemia ± SIADH due to pneumonia
88/M	128	131.5	128	133	9	Presented with liver abscess. Advanced cholangiocarcinoma. After 1st day, sNa > 130 mmol/l.	Unknown
82/F	126	123.5	114	135	13	Presented with acute coronary syndrome and arrhythmia. Died after 24-hour ICU admission with bradycardia, acute oliguric kidney injury, and severe metabolic acidosis. SNa <125 mmol/l until 2 days before death when she received renal replacement and sNa normalised.	Diuretic-induced due to iv administration of loop diuretics
53/M	131	129	125	128	51	Decompensated chronic alcoholic liver disease; large volume ascites; acute kidney injury.	Cirrhosis
60/F	122	124.5	112	112	7	Acute liver failure, metastatic breast cancer with liver metastases. Rapid deterioration.	Hypovolaemia

73/M	137	130	127	128	12	Presented with ST segment elevation myocardial infarction, managed conservatively. Metastatic non-small cell lung cancer.	Probable malignant SIADH
90/F	127	130	125	130	10	Presented with large, malignant pleural effusion. New diagnosis of disseminated adenocarcinoma of unknown primary. Rapid deterioration.	SIADH due to malignancy / pneumonia
83/F	123	126.5	121	151	11	Presented with multiorgan failure (acute kidney injury, type I respiratory failure, heart failure).	Heart failure
55/M	136	145	122	141	31	Presented with multi-system inflammatory disease (skin, joints, liver). New onset of cirrhosis due to autoimmune hepatitis. Died after 4-day ICU admission with duodenal perforation. SNa 135-143 mmol/l last 4 days.	Hypovolaemia due to poor oral intake
98/F	134	136.5	124	127	29	Presented with severe community-acquired pneumonia and recurrent non-convulsive seizures. Had seizures prior to development of hyponatraemia.	Hypovolaemia due to poor oral intake
61/M	138	136	125	138	97	Presented with intra-abdominal collection with enterocutaneous fistula. Developed recurrent hospital-acquired pneumonias. Died after 55-day ICU admission from septic shock and multi-organ failure. SNa within normal range last 22 days.	SIADH due to pneumonia

49/F	129	138	119	143	24	Pneumonia, ARDS (Acute Respiratory Distress Syndrome), severe type 1 respiratory failure, decompensated cirrhosis, acute kidney injury. After 18-day ICU admission, she developed disseminated intravascular coagulation and gastrointestinal bleeding. SNa within normal range last 14 days.	SIADH due to pneumonia
76/M	135	142.5	122	145	17	Hypothermia, bradycardia, coma and type 2 respiratory failure. Died from visceral perforation and septic shock. SNa 143-152 mmol/l last 12 days.	Hypovolaemia due to poor oral intake and GI losses
66/F	134	133.5	128	136	22	Cirrhosis due to alcoholic liver disease. Developed large hepatohydrothorax. SNa within normal range last 7 days.	Cirrhosis
78/M	138	132.5	128	128	10	Presented with anterior ST segment elevation myocardial infarction. Rapid deterioration in renal function with anuria and hyperkalaemia; decided not suitable for renal replacement therapy.	Unknown
94/M	137	137	123	146	35	Presented with fracture of humerus. Developed aspiration pneumonia. SNa 139-146 mmol/l last 7 days.	SIADH due to pneumonia

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Multicentre study of investigation and management of inpatient hyponatraemia in the UK

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ABSTRACT

Purpose Hyponatraemia is associated with significant morbidity and mortality. The objectives of this study were to evaluate the investigation and management of hyponatraemia and to assess the use of different therapeutic modalities and their effectiveness in routine practice.

Study design This multicentre, retrospective, observational study was conducted at three acute NHS Trusts in March 2013. A retrospective chart review was performed on the first 100 inpatients with serum sodium (sNa) ≤128 mmol/L during hospitalisation.

Results One hundred patients (47 male, 53 female) with a mean±SD age of 71.3±15.4 years and nadir sNa of 123.4±4.3 mmol/L were included. Only 23/100 (23%) had measurements of paired serum and urine osmolality and sodium, while 31% had an assessment of adrenal reserve. The aetiology of hyponatraemia was unrecorded in 58% of cases. The mean length of hospital stay was 17.5 days with an inpatient mortality rate of 16%. At hospital discharge, 53/84 (63.1%) patients had persistent hyponatraemia, including 20/84 (23.8%) with sNa <130 mmol/L. Overall 37/100 (37%) patients did not have any treatment for hyponatraemia. Among 76 therapeutic episodes, the most commonly used treatment modalities were isotonic saline in 38/76 cases (50%) and fluid restriction in 16/76 (21.1%). Fluid restriction failed to increase sNa by >1 mmol/L/day in 8/10 (80%) cases compared with 4/26 (15.4%) for isotonic saline.

Conclusions Underinvestigation and undertreatment of hyponatraemia is a common occurrence in UK clinical practice. Therefore, development of UK guidelines and introduction of electronic alerts for hyponatraemia should be considered to improve clinical practice.

INTRODUCTION

Hyponatraemia, defined as serum sodium (sNa) concentration below 135 mmol/L, is the most common electrolyte abnormality encountered in hospitalised patients, with a reported incidence of 30–42%.[1 2] Hyponatraemia is an independent risk factor for mortality[3 4] and is associated with an increase in length of hospital stay[5] and hospital resource utilisation.[6]

Accurate diagnosis of hyponatraemia is necessary to guide effective treatment. However, numerous single-centre studies in the UK have consistently reported underutilisation of appropriate biochemical tests in the investigation of hyponatraemia.[7–13] It is unclear to what extent inadequate investigation of hyponatraemia reflects UK clinical practice in general. There is also a paucity of data about the utilisation of different therapeutic modalities for hyponatraemia and their efficacy in a real world setting.

This study describes current clinical practice in three acute UK hospitals. The objectives were to evaluate the investigation and management of inpatient hyponatraemia and to assess the use of different therapeutic modalities and their effectiveness.

METHODS

Study design

This was a multicentre, retrospective, observational study examining the investigation and management of 100 consecutive inpatients with serum sodium (sNa) ≤128 mmol/L.

Recruitment started on 1 March 2013 and ended on 28 March 2013 when a total of 100 patients were reached. It was conducted simultaneously at three acute NHS Trusts in London: centre 1, an 850-bed teaching hospital; centre 2, including 850 beds across two teaching hospitals; and centre 3, a 450-bed district general hospital. None of the three institutions had local guidelines for the management of hyponatraemia.

Patient selection

We defined inpatient hyponatraemia as an sNa concentration ≤128 mmol/L at any point during hospital admission. Patients were identified through an automated laboratory database search. A cut-off of 128 mmol/L was selected because previous data from this hospital cohort showed an upward inflection in inpatient mortality below that threshold.[3] Subjects with hyperglycaemia were included only if their corrected sNa was ≤128 mmol/L. If venous glucose was 15–24.4 mmol/L, sNa was corrected by 1.6 mmol/L for every 5.6 mmol/L increase in glucose concentration above 7 mmol/L; if glucose was >24.4 mmol/L, a correction factor of 2.4 mmol/L was used.[14]

Data collection

Hospital case notes, laboratory results, drug prescription charts and discharge letters were retrospectively reviewed for each patient after hospital discharge. Data were collected on age, gender, speciality responsible for each patient, drug history, admission to the intensive care unit, length of hospital stay, outcome of admission, investigations and documented cause of hyponatraemia, sNa levels at various time points, use of therapeutic modalities, sNa 24 and 72 h after initiation of treatment, and sNa at hospital discharge.

Adequate investigation of hyponatraemia should include clinical assessment of volume status, measurement of paired serum and urine osmolality and Na, thyroid function tests and serum cortisol measurement. The effectiveness of treatment of hyponatraemia was assessed by sNa concentration at hospital discharge. For the purpose of evaluating the effectiveness of different treatment modalities, 'clear failure' of treatment was defined as a total sNa increase of ≤3 mmol/L after the 72 h period after initiation of therapy. Over-rapid correction of hyponatraemia, known to risk osmotic demyelination syndrome,[15 16] was defined as an sNa increase of >12 mmol/L in 24 h.

Data analysis

All data were recorded on an Access database and then transferred into an Excel spreadsheet. Data were analysed separately for each hospital and for all three hospitals together. Data were summarised using descriptive statistics, with continuous variables being expressed as mean±SD, and categorical variables as percentages.

Adequacy of investigation was assessed by the percentage of patients who underwent each of the recommended tests. The proportion of patients with normonatraemia and different degrees of hyponatraemia (mild/moderate/severe) was used to determine the effectiveness of management of hyponatraemia. The percentage of patients who had 'clear failure' and 'over-rapid correction' determined the effectiveness of each therapeutic modality.

RESULTS

Demographic characteristics

Across three hospitals in London, 100 patients (47 male, 53 female) were included with a mean±SD age of 71.3±15.4 years. Centre 1 included 38 patients (19 male, 19 female with a mean age of 73.6±15.1 years), centre 2 contributed 30 patients (13 male, 17 female aged 68.5±15.5 years) and centre 3 contributed 32 patients (15 male, 17 female with a mean age of 70.4±15.4 years).

The mean sNa on admission was 128.1±7.1 mmol/L, and the lowest sNa during hospitalisation was 123.4±4.3 mmol/L. In terms of the time point of onset of hyponatraemia, 58/100 (58%) patients presented on admission with sNa ≤128 mmol/L in comparison with 42/100 (42%) who developed sNa ≤128 mmol/L during hospitalisation.

Speciality distribution

There was a wide distribution of patients within different specialities: 81/100 (81%) patients were under the care of medical specialities including geriatrics (18%), general medicine (11%), respiratory (9%), gastroenterology (9%), oncology (6%), hepatology (6%), cardiology (5%), infectious diseases (5%), endocrinology (4%), nephrology (3%), neurology (3%) and rheumatology (2%); 19/100 (19%) patients were under the care of surgical specialities including general surgery (5%), urology (5%), orthopaedics (4%), cardiothoracic surgery (3%) and gynaecology (2%).

Drug history

Of the 100 patients, 35 were taking ACE inhibitors, 23 loop diuretics, 22 thiazide diuretics, 15 selective serotonin reuptake inhibitors (SSRIs), 14 potassium-sparing diuretics, 12 angiotensin-II receptor antagonists, and 6 tricyclic antidepressants.

Outcome of admission

The inpatient mortality rate in our cohort was 16%. The mean length of hospital stay was 17.5±14.8 days with 9/100 (9%) of patients requiring admission to the intensive care unit.

Diagnostic work-up

Clinical assessment of volume status was documented in 62/100 (62%) cases, while paired serum and urine osmolality and Na were measured in 23/100 (23%). Complete work-up was undertaken in 18/100 (18%) patients, as shown in table 1.

Aetiology of hyponatraemia

The aetiology of hyponatraemia was unrecorded in the notes of 58/100 (58%) patients. Review of case notes was used to ascertain the aetiology of hyponatraemia in the remaining 42/100 (42%) patients, as summarised in table 2. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) was attributed to drugs in three cases (SSRIs in two cases and mirtazapine in one case), to malignancy in two cases (small cell lung cancer in one case and chronic lymphocytic leukaemia in one case) and to miscellaneous causes in two cases (SIADH after transsphenoidal surgery and SIADH of unknown cause).

Only 6/11 (54%) patients diagnosed with SIADH had all the essential tests performed, including clinical assessment of volume status, measurement of paired serum and urine osmolality and Na, and assessment of thyroid and adrenal function.[17 18]

Effectiveness of treatment of hyponatraemia

Correction of sNa ≥130 mmol/L was observed in 70/84 (83.3%) patients at some point during admission, but hyponatraemia with sNa <130 mmol/L recurred in 6/84 (7.1%). A significant proportion of patients (53/84 equal to 63.1%) had persistent hyponatraemia at discharge from hospital, as shown in table 3.

Utilisation of treatment modalities

Overall, 37/100 (37%) patients did not have any treatment for hyponatraemia. Of the 63 patients treated for hyponatraemia, 53 received one therapeutic modality, 7 received two modalities, and 3 received three treatment modalities. First-line therapy was isotonic saline in 34/63 (54%) cases, discontinuation of potentially offending drugs in 16/63 (25.4%), fluid restriction in 10/63 (15.9%), infusion of human albumin solution in 2/63 (3.2%), and initiation of hydrocortisone replacement in 1/63 (1.5%) cases. Second-line therapy was isotonic saline in 4/10 (40%) cases, fluid restriction in 4/10 (40%), and hypertonic saline in 2/10 (20%). Only three patients received third-line treatment, including two cases of fluid restriction and one case of demeclocycline.

Potentially offending drugs were discontinued in 36/100 (36%) patients, with the most common being ACE inhibitors or angiotensin-II receptor antagonists (18%), loop diuretics (15%),

Table 1 Investigation of patients with hyponatraemia

Investigation	Total (N=100) (%)	Centre 1 (N=38) (%)	Centre 2 (N=30) (%)	Centre 3 (N=32) (%)
Volume status	62	71.0	53.4	59.4
Serum osmolality	39	39.5	33.3	43.8
Urine osmolality	33	39.5	30.0	28.1
Urine Na	29	34.2	36.6	15.6
Paired osmolality–Na	23	26.3	26.7	15.6
Serum TSH	61	71.0	63.3	46.9
Serum cortisol	31	34.2	26.6	31.2
Full work-up	18	23.7	20.0	9.4
Expert input	16	13.1	13.3	21.8

TSH, thyroid-stimulating hormone.

Table 2 Classification of cases according to documented aetiology of hyponatraemia

Aetiology	Overall (N=42), n (%)
Hypovolaemic	23 (54.7)
Gastrointestinal Na losses	9 (21.4)
Poor oral intake	7 (16.6)
Diuretics	6 (14.3)
Adrenal insufficiency	1 (2.4)
Euvolaemic	11 (26.2)
SIADH due to pneumonia	4 (9.5)
Drug-induced SIADH	3 (7.1)
Malignant SIADH	2 (4.8)
Miscellaneous causes	2 (4.8)
Hypervolaemic	8 (19.1)
Decompensated cirrhosis	4 (9.5)
Heart failure	4 (9.5)

SIADH, Syndrome of inappropriate antidiuretic hormone secretion.

thiazide diuretics (10%), potassium-sparing diuretics (10%) and SSRIs (3%).

In total, 76 episodes of treatment were recorded, which included isotonic saline in 38/76 (50%) cases, drug discontinuation in 16/76 (21.1%), fluid restriction in 16/76 (21.1%), hypertonic saline in 2/76 (2.6%), human albumin solution in 2/76 (2.6%), hydrocortisone replacement in 1/76 (1.3%) and demeclocycline in 1/76 (1.3%) cases. Use of other drug therapies for SIADH, such as tolvaptan, urea or combination of loop diuretics with oral sodium chloride, was not recorded.

Effectiveness of isotonic saline and fluid restriction

'Clear failure' of treatment with a total sNa increase of ≤3 mmol/L after the 72 h period after initiation of therapy was recorded in 4/26 (15.4%) patients treated with isotonic saline compared with 8/10 (80%) individuals managed with fluid restriction, as illustrated in table 4. Fluid restriction was imposed on 16 patients with various volumes prescribed per 24 h (1500 mL in 4 cases, 1000 mL in 9 cases, 750 mL in 1 case and 500 mL in 2 cases). Hypertonic saline was used in two patients, with infusion of 1000 mL saline 1.8% over 18 h increasing sNa by 13 mmol/L, and 300 mL saline 1.8% over 8 h increasing sNa levels by 11 mmol/L.

DISCUSSION

We found that hyponatraemia was frequently underinvestigated, underdiagnosed and suboptimally managed in routine practice in three hospitals in London. Urine Na, the most important biochemical test[19 20] in investigation of hyponatraemia, was measured in less than one-third of cases. The underlying aetiology of hyponatraemia, despite being essential to guide appropriate treatment, was unrecorded in more than half of the cases. The limited effectiveness of current management, with 63.1% of patients being discharged with persistent hyponatraemia, was not surprising considering the lack of treatment for hyponatraemia in a substantial proportion of patients. Among patients receiving treatment for hyponatraemia, isotonic saline or fluid restriction were most commonly used, with fluid restriction being ineffective in the majority of cases.

Table 3 Serum sodium (sNa) concentration at hospital discharge

SNa at discharge	Overall N=84
Patients with sNa <125 mmol/L (%)	4.8
Patients with sNa 125–129 mmol/L (%)	19.0
Patients with sNa 130–134 mmol/L (%)	39.3
Patients with sNa ≥135 mmol/L (%)	36.9
Mean±SD sNa (mmol/L)	132.8±4.7

Table 4 Effectiveness of isotonic saline and fluid restriction in correcting hyponatraemia in first 72 h

SNa correction after treatment	Isotonic saline (N=26)	Fluid restriction (N=10)
Mean±SD change in sNa (mmol/L)	7.3±5.0	2.8±3.2
Percentage of patients		
sNa increase <2 mmol/L	7.7	30.0
sNa increase 2–3 mmol/L	7.7	50.0
sNa increase 4–8 mmol/L	50.0	10.0
sNa increase 9–12 mmol/L	19.2	10.0
sNa increase >12 mmol/L	15.4	0

Over-rapid correction of hyponatraemia (sNa increase of >12 mmol/L/day) was recorded in 3/76 (3.9%) therapeutic episodes. All three patients, two treated with isotonic saline and one with hypertonic saline, had an sNa increase of 13 mmol/L within 24 h without any adverse neurological sequelae.

Similar results from all three hospitals indicate that insufficient diagnostic work-up and ineffective treatment of hyponatraemia may reflect UK routine care in general. There are several possible barriers to good clinical practice in this field, such as the diminished provision of undergraduate and postgraduate education in clinical chemistry in recent times,[13 21] the lack of national guidelines, the absence of diagnostic algorithms and treatment pathways in most hospitals or their complexity where they exist, and the limited therapeutic options with little evidence basis for the treatment of SIADH. Besides demonstrating suboptimal standard of care for hyponatraemia, we found that fluid restriction, currently the first-line treatment for SIADH, does not correct hyponatraemia in most cases. Potential reasons are poor patient adherence because of thirst, inadequate rigour in the volume of fluid intake prescribed (which needs to be restricted to at least 500 mL/day less than urine output), and its questionable effectiveness per se given the limited evidence base behind its therapeutic value.[20 22] Therefore, clinicians should pay more attention to appropriate prescription and implementation of fluid restriction and should also have access to alternative therapeutic options such as vaptans and urea.

In comparison with previous UK studies, we recorded a higher frequency of performance of appropriate diagnostic tests. In the subgroup of our cohort with a nadir sNa ≤125 mmol/L, 40.7% of patients had urine Na and 40.7% had serum cortisol measured compared with 10–18.6%[7–10] and 8–15.2%,[7–9 11] respectively, reported in other UK series using the same cut-off. It is unclear whether these findings represent a widespread rather than a local improvement in the investigation of hyponatraemia in recent years. Regarding the aetiology of hyponatraemia, SIADH was reported in only a quarter of our cases, in contrast with most studies suggesting it as the most common cause;[18 23 24] therefore, SIADH was probably underdiagnosed.

This study has provided insight into the contemporary investigation and management of hyponatraemia in the UK. However, it had a number of limitations. First and foremost, it could not, by its design, test whether undertreatment of hyponatraemia

contributed to adverse patient outcomes and, more importantly, whether correcting hyponatraemia could improve clinical outcomes. Second, the small sample size and the fact that all three hospitals are in London raise the question whether the findings apply to UK clinical practice in general. Third, its retrospective nature made accurate identification of the cause of all cases of hyponatraemia impossible. As a result, its ability to evaluate the effectiveness of different therapeutic modalities was limited because failure of treatment might sometimes reflect misdiagnosis.

In conclusion, this study highlights the need to improve clinical practice. It is essential to develop tools such as electronic alert systems for severe hyponatraemia, similar to electronic alerts for acute kidney injury already introduced in several NHS hospitals.[25–27] By highlighting hyponatraemia and referring to intranet-based guidelines, electronic alerts could prompt optimal investigation and treatment in a timely manner. Another innovative model of care delivery with the potential to improve standard of care is the development of multidisciplinary hospital 'hyponatraemia teams' combining the expertise of endocrinologists, nephrologists, chemical pathologists and other physicians. In addition, UK guidelines on management of hyponatraemia are still needed despite the recent publication of clinical practice guidelines by an expert panel[22] and by a joint venture of the European Society of Endocrinology with the European Renal Association.[20] The reason is that clinical practice and experience in the UK differ from that in the USA[22] and continental Europe[20] with regard to the structure of the healthcare system and the availability of treatment options, such as urea and vaptans. Finally, we agree with the authors of both European and US guidelines on the urgent need for studies evaluating the effect of correction of hyponatraemia on patient-important outcomes such as symptoms, quality of life, mortality and length of hospital stay.[20 22]

Main messages

- Hyponatraemia is frequently underinvestigated and underdiagnosed in UK clinical practice.
- Most patients are discharged with persistent hyponatraemia, while a substantial proportion of them have not received any treatment for hyponatraemia.
- Fluid restriction is often ineffective in correcting hyponatraemia due to SIADH.

Current research questions

- Does correction of hyponatraemia improve patient outcomes such as length of hospital stay and mortality?
- What would be the impact of measures such as introduction of electronic alert systems or widespread provision of expert input on management of inpatient hyponatraemia and patient outcomes?
- What is the optimal treatment strategy for hyponatraemia due to SIADH with regard to sodium correction and patient outcomes?

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Contributors PT conceived and designed the study, monitored data collection for the whole study, cleaned and analysed the data, and drafted and revised the paper. PMB conceived and designed the study, and drafted and revised the paper. RE and AF were involved in data collection and data analysis. MB, TT, BK, MP and DN were involved in study design and patient recruitment, and drafted and revised the paper. EW, RL, NM, RE and RS were involved in patient recruitment, and drafted and revised the paper. KG designed the data collection tools, was involved in data analysis, and drafted and revised the paper. All authors approved the final version of the manuscript.

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Multicentre study of investigation and management of inpatient hyponatraemia in the UK

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ORIGINAL ARTICLE

Real-life experience of tolvaptan use in the treatment of severe hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion

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Summary

Objective European guidelines do not recommend tolvaptan for treatment of syndrome of inappropriate antidiuretic hormone secretion (SIADH), principally owing to concerns about risk of overly rapid correction of hyponatraemia. This study evaluated the real-life effectiveness and safety of tolvaptan.

Design Consecutive case series.

Patients Inpatients treated with tolvaptan for SIADH in 2 UK hospitals over a 3-year period.

Measurements The primary outcome measures were serum sodium (sNa) correction at 24 and 48 h after tolvaptan therapy.

Results This case series included 61 patients aged 74·4 ± 15·3 years with (mean ± SD) sNa 119·9 ± 5·5 mmol/l. The mean sNa increase 24 h after tolvaptan initiation was 9 ± 3·9 mmol/l. Excessive correction of hyponatraemia was observed in 23% of patients with all these patients having baseline sNa <125 mmol/l, but no cases of osmotic demyelination syndrome were recorded. At the end of tolvaptan therapy, sNa increase was 13·5 ± 5·9 mmol/l with 96·7% of patients having sNa increase ≥5 mmol/l in 48 h. There was a negative significant correlation ($P = 0·012$) between baseline sNa and 24-h change; for every 1 mmol/l reduction in baseline value, sNa increased by an additional 0·23 mmol/l (95% CI 0·05–0·41).

Conclusions Tolvaptan is effective in correcting hyponatraemia. Without rigorous electrolyte monitoring, tolvaptan carries a significant risk of overly rapid sodium correction, especially in patients with starting sNa <125 mmol/l. Tolvaptan should be used with great caution under close electrolyte monitoring.

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Introduction

Hyponatraemia, the most common electrolyte disorder in hospitalized patients, is associated with considerable morbidity and is an independent risk factor for mortality.[1,2] Hyponatraemia carries a substantial economic burden related to increased hospital resource utilization, length of stay and risk of readmission.[3] The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is one of the most common causes of hyponatraemia.[4] Several studies have shown that most patients with SIADH are inadequately treated and discharged from hospital with persistent hyponatraemia.[5,6]

Fluid restriction, currently the mainstay of treatment for SIADH, is often ineffective in correcting hyponatraemia, especially in patients with very little to no free water excretion by the kidneys.[7] Fluid restriction is often poorly implemented and tolerated, and rarely fully adhered because of thirst.[8,9] In cases of SIADH where fluid restriction is not successful in increasing sodium levels, pharmacological therapy should be considered. Pharmacological options include vasopressin receptor antagonists, hypertonic saline, urea, demeclocycline and a combination of low-dose loop diuretics and oral sodium chloride; no consensus as to the optimal second-line approach to the management of SIADH exists.[8,10]

Tolvaptan, an orally active competitive antagonist of the vasopressin V2-receptor, is the only agent currently licensed in Europe for the treatment of adults with hyponatraemia secondary to SIADH. Tolvaptan prevents free water reabsorption by blocking the binding of arginine vasopressin (AVP) to V2 receptors, located in renal collecting ducts.[9] Thus, it produces an 'aquaresis' by increasing renal water excretion without significantly affecting excretion of urine solutes such as sodium and potassium.[11]

Randomized controlled trials have shown that tolvaptan is a safe and effective agent for the treatment of hyponatraemia due to SIADH.[12–14] However, there are very limited real-world data and in particular there is a paucity of data about the effectiveness and safety of tolvaptan in patients with low baseline sNa. Patients with sNa <120 mmol/l, very few of whom were

included in randomized controlled trials,[12–14] are at the highest risk of developing osmotic demyelination syndrome (ODS) when overly rapid correction of hyponatraemia occurs.[15–17] Due to this concern and reports of hepatotoxicity associated with the chronic use of high tolvaptan doses,[18,19] recently published European guidelines on management of hyponatraemia do not recommend the use of tolvaptan in patients with SIADH.[10] Contrary to the European guidelines, tolvaptan has been recommended as a second-line treatment of SIADH after fluid restriction according to a US expert panel.[8]

The aim of this study was to evaluate the effectiveness and safety of tolvaptan use for treatment of SIADH in real-life clinical practice. We also tested the hypothesis that the magnitude of correction in serum sodium is correlated to the baseline value.

Materials and methods

Study design

This study was a retrospective case series of all consecutive hospitalized patients treated with tolvaptan for SIADH in 2 hospitals between November 2010 and February 2014. The study was registered with the Clinical Governance & Clinical Audit Department of both institutions, and ethics approval was not required.

Patient selection

The study was conducted in 2 acute hospitals in London and included 61 individuals (49 in Centre A and 12 in Centre B). Centre A (Royal Free Hospital) is a major teaching hospital with around 900 beds. Besides all branches of medicine and surgery, it is a major centre for neurosurgery and has a large oncology and haematology unit. Centre B (Barnet Hospital) is a 450-bed district general hospital.

All adult hospitalized patients with SIADH who were administered at least one dose of tolvaptan were included. The participants underwent full work-up and met all essential diagnostic criteria for SIADH, including euvolaemia, hyponatraemia and low serum osmolality with inappropriately raised urine osmolality and sodium, normal adrenocortical reserve and exclusion of hypothyroidism.[20,21] Patients with hypervolaemic or hypovolaemic hyponatraemia who were administered tolvaptan were excluded.

All tolvaptan prescriptions were directed by Consultants Endocrinologists. All patients were treated with tolvaptan as monotherapy, and all other therapeutic modalities had been withdrawn at least 12 h before initiation of tolvaptan. All patients administered tolvaptan were clearly advised to drink *ad libitum,* as documented in case notes. There were no specific local guidelines for tolvaptan initiation, frequency, mode of monitoring and timing of withdrawal. In a small number of patients, a lower initiation tolvaptan dose of 7·5 mg, instead of 15 mg, was used because of previous reports suggesting that 'off-label' starting dose of 7·5 mg may be associated with a reduced risk of sNa overly rapid correction.[22]

Data collection

Hospital case notes, drug prescription charts, discharge letters and laboratory results were reviewed retrospectively for each patient. Data were collected about: age, gender, ethnic origin, comorbidities, drug history, aetiology of SIADH, history of prior hyponatraemia, therapeutic modalities used for treatment of SIADH and sodium response, serum biochemistry (sodium, osmolality, urea, creatinine, potassium, urate, cortisol, free thyroxine, thyrotropin) and urine biochemistry (osmolality, sodium, potassium), initiation dose of tolvaptan, duration of tolvaptan therapy, length of hospitalization and inpatient mortality.

The primary outcome measures were sNa correction at 24 and 48 h after initiation of tolvaptan and at the end of treatment episode. Secondary outcome measures were sNa concentration 3 days and 5 days after tolvaptan withdrawal. For the purpose of evaluating the effectiveness of tolvaptan, response to treatment was defined as sNa increase by ≥5 mmol/l from baseline or sNa at the end of treatment episode >130 mmol/l.[6] Overly rapid correction of hyponatraemia was defined as a sNa increase of >12 mmol/l in 24 h or >18 mmol/l in 48 h.[15–17] Recurrence of hyponatraemia after withdrawal of therapy was defined as sNa decrease by ≥5 mmol/l within first 5 days after stopping tolvaptan.

Statistical analysis

Data from each hospital were first analysed individually, and then, the combined data from both hospitals were analysed. Data were summarized using descriptive statistics, with continuous variables being expressed as mean ± SD (standard deviation), and categorical variables as percentages. Linear regression models were applied to investigate the relationship of sNa change in first 24 h after tolvaptan therapy with various baseline biochemical parameters, such as baseline sNa, urine osmolality, urine Na and urine/plasma electrolyte ratio (calculated as urine Na + urine K/serum Na). Fisher's exact test was used to compare the incidence of overly rapid correction between patients with baseline sNa <125 and ≥125 mmol/l. An unpaired *t*-test was used to examine the treatment effect of different initiation doses of tolvaptan. A threshold P value <0·05 was chosen as significance level.

Results

Demographic characteristics

Data were collected on 61 consecutive patients (49 in Centre A and 12 in Centre B). Participants (33 females, 28 males) had a (mean ± SD) age of 74·4 ± 15·3 years. With respect to ethnic origin, the largest ethnic group was Caucasian accounting for 78·7%, while 18·0% of patients were of Asian origin and 3·3% Afro-Caribbean origin.

Speciality distribution

There was a wide distribution of patients within different specialities: 45 of 61 (73·7%) patients were under the care of

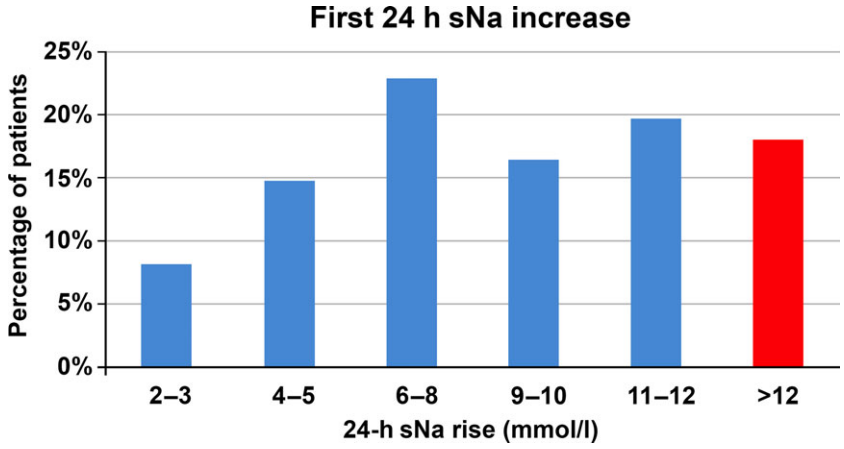

Fig. 1 Relative frequency distribution of sNa change in first 24 hours after tolvaptan therapy.

medical specialities, including geriatrics (26·2%), general medicine (18·0%), oncology (9·8%), endocrinology (6·6%), neurology (4·9%), respiratory (3·3%), haematology (3·3%) and infectious diseases (1·6%); 16 of 61 (26·3%) patients were under the care of surgical specialities, including neurosurgery (13·1%), orthopaedics (6·6%) and other surgical specialities (6·6%).

Aetiology of SIADH

Following detailed review of the medical case notes and laboratory results, the most likely cause of SIADH was identified. The aetiology of SIADH was malignancy (24·6%), unknown (24·6%), central nervous system (CNS) pathology/neurosurgery (16·4%), pulmonary illness (14·7%), drug-related (9·8%), postoperative (6·6%) and miscellaneous (3·3%).

Duration of SIADH

Hyponatraemia was newly diagnosed in 41 of 61 (67·2%) patients. The remaining 20 of 61 (32·8%) patients had hyponatraemia in the recent past as evidenced by at least one sNa value <135 mmol/l in the preceding 6 months.

Initial therapy of hyponatraemia

The mean time interval between sNa levels reaching ≤128 mmol/l and initiation of tolvaptan was 6·7 ± 6·5 days. Tolvaptan was used as first-line agent only in 9 of 61 cases (14·8%). In most cases, tolvaptan was used as second-line (37/61 patients; 60·6%) or third-line treatment (15/61 patients; 24·6%) after failure of other therapeutic modalities such as fluid restriction or demeclocycline. The duration of first-line therapy which preceded tolvaptan therapy was 3·4 ± 3·1 days with subsequent sNa change of − 0·1 ± 3·5 mmol/l at the end of therapy.

Baseline biochemical parameters

Prior to initiation of tolvaptan, the (mean ± SD) serum values were for Na 119·9 ± 5·5 mmol/l, K 4·3 ± 5·5 mmol/l, urea 4·8 ± 2·1 mmol/l, creatinine 64·6 ± 27·1 umol/l and osmolality 252·4 ± 12·4 mOsm/kg. Urine values were for Na 84·2 ± 43·0 mmol/l, K 38·3 ± 16·6 mmol/l and osmolality 468·6 ± 151·2 mOsm/kg.

Rate of serum sodium correction

Tolvaptan was initiated at a dose of 15 mg in 55 of 61 cases and 7·5 mg in 6 of 61 cases. The proportions of patients with differing magnitudes of sNa increase in the first 24 h of tolvaptan therapy are illustrated in Fig. 1.

Overly rapid correction of serum sodium, defined as sNa increase of >12 mmol/l within 24 h or >18 mmol/l within 48 h, was observed in 14/61 (23·0%) of patients, as shown in Table 1. However, none of those patients subsequently exhibited neurological symptoms or signs indicative of ODS, as evidenced by detailed review of medical charts.

Frequency of serum sodium monitoring and measures to prevent overly rapid correction

While sNa concentration was measured in all patients 24 h after initiation of tolvaptan, measurement at any time point during the first 24 h was recorded only in 13 of 61 (21·3%) of individuals. SNa was measured 6 h after administration of tolvaptan in 7 of 61 patients with increase of 5·3 ± 2·1 mmol/l and 12 h after in 11 of 61 patients with increase of 7·0 ± 3·9 mmol/l.

Table 1. Serum sodium changes in first 24 and 48 h of tolvaptan therapy

Correction of sNa over first 24 and 48 h	
Baseline sNa (mmol/l)*	119·9 ± 5·5
sNa change in first 24 h (mmol/l)*	9 ± 3·9
Percentage with over rapid 24-h correction†	18%
sNa change in first 48 h (mmol/l)*	11·4 ± 5·6
Percentage with over rapid 24-h or 48-h correction‡	23%

*Mean ± standard deviation.
†Over rapid 24-h correction defined as sNa increase of >12 mmol/l.
‡Over rapid 24-h or 48-h correction defined as sNa increase of >12 mmol/l in 24 h or >18 mmol/l in 48 h.

Despite sNa monitoring during the first 24 h, 5 of 13 patients (38·5%), who had 12-h sNa increase of 7, 8, 10, 10, 11 mmol/l, exceeded the safe rate of hyponatraemia correction. Only 1 patient received hypotonic fluid infusion but, despite that, sNa concentration increased further from 10 mmol/l in 12 h to 13 mmol/l in 24 h.

Measures to reverse overly rapid correction of sNa by infusing 5% dextrose in water were also taken in 2 patients 24 h after and in 1 patient 36 h after tolvaptan initiation. Desmopressin was not used in any patients.

Effectiveness of tolvaptan

After tolvaptan treatment, 59 of 61 (96·7%) of patients were responders and had increase of sNa of ≥5 mmol/l. In all cases, this increase was achieved within 48 h, as shown in Table 2. At the end of tolvaptan therapy, sNa was 133·5 ± 4·5 mmol/l, K 4·4 ± 0·5 mmol/l, urea 6·1 ± 3·9 mmol/l and creatinine 71·8 ± 31·1 umol/l. Among 61 patients, 27 (44·3%) received only 1 or 2 doses of tolvaptan.

Association of baseline biochemical values with rate of sodium correction

There was a negative significant correlation (coefficient – 0·23, *P* value 0·012) between baseline sNa and 24-h sNa change. For every 1 mmol/l reduction in baseline value, sNa increased by an additional 0·23 mmol/l (95% CI 0·05, 0·41) at 24 h after tolvaptan initiation, as shown in Fig. 2.

No statistically significant association was found between other biochemical parameters (urine osmolality, urine Na, urine/plasma electrolyte ratio) and 24-h sNa increase after tolvaptan initiation.

In patients with baseline sNa ≥125 mmol/l, the mean increase over first 24 h was lower at 5·5 ± 2·9 mmol/l compared to 9·7 ± 3·6 mmol/l in patients with baseline sNa <125 mmol/l. None among 12 patients with starting sNa ≥125 mmol/l exceeded the safe rate for sNa correction at any time point compared to 14/49 (28·6%) patients with sNa <125 mmol/l, as shown in Table 3. However, this difference did not reach statistical significance (*P* = 0·052). Of note, among patients exceeding the safe rate for sNa correction, the highest starting sNa was 122 mmol/l.

Table 2. Serum sodium correction at the completion of tolvaptan therapy

At the end of tolvaptan therapy	
Duration of therapy (days)*	4·2 ± 4
sNa rise (mmol/l)*	13·5 ± 5·9
Percentage of patients with sNa rise of ≥5 mmol/l	96·7%
sNa (mmol/l)*	133·5 ± 4·5
Percentage of patients with sNa >130 mmol/	80·3%

*Mean ± standard deviation.

Association of speciality and previous therapies for SIADH with rate of overly rapid correction

The rate of overly rapid correction in patients under the care of medical specialities was 20·0% (9/45) *vs* 31·2% (5/16) in surgical patients. The difference was not statistically significant (*P* = 0·490). In specific, 3 of 8 (37·5%) neurosurgical patients exceeded safe rate of correction.

With respect to previous therapeutic modalities for SIADH, none of 9 patients treated with demeclocycline prior to tolvaptan had overly rapid correction. Among 6 patients who had the offending drug withdrawn for drug-induced SIADH, 2 of 6 (33·0%) had overly rapid correction.

Effectiveness and safety of lower tolvaptan doses

Among patients with baseline sNa <125 mmol/l, 6 individuals were prescribed 7·5 mg as the initiation dose (half the recommended). The rise of sNa in first 24 h after tolvaptan dose of 7·5 mg was 9·8 ± 2·9 mmol/l (range 5–13 mmol/l) with one patient with baseline sNa 103 mmol/l exceeding the safe limit for correction. Among patients with sNa <125 mmol/l, patients initiated on 7·5 mg dose (mean starting sNa 115·3 mmol/l) had 24-h sNa increase of 9·8 ± 2·9 mmol/l *vs* 9·9 ± 3·9 mmol/l in

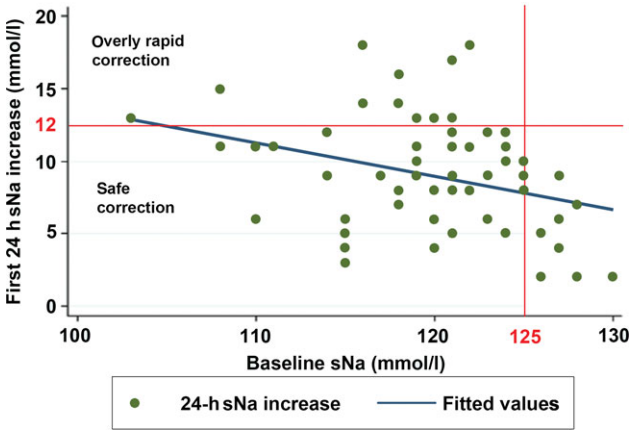

Fig. 2 Linear regression between baseline sNa (x axis) and sNa correction in first 24 h after initiation of tolvaptan (y axis). Red vertical line indicates baseline sNa of 125 mmol/l. Red horizontal line indicates sNa increase of 12 mmol/l in first 24 h. Correlation coefficient: – 0·23 (*P* value 0·012).

Table 3. Contingency table for rate of sNa correction with tolvaptan

		Number of patients (*N*) (%) as per rate of sNa correction	
Baseline sNa (mmol/l)	Total *N*	*N* (%) (within safe limits)	*N* (%) (overly rapid)
<125	49	35 (71·4%)	14 (28·6%)
≥125	12	12 (100%)	0 (0)

patients treated with 15 mg dose (mean starting sNa 118·7 mmol/l). The initiation dose did not affect the degree of sNa increase in 24 h ($P = 0{\cdot}989$), as shown in Fig. 3.

Serum sodium after discontinuation of tolvaptan

In 49 individuals, sNa was reassessed at 3 or 5 days after discontinuation of tolvaptan. Three days after discontinuation of tolvaptan, the mean change of sNa was $-3{\cdot}1 \pm 5{\cdot}0$ mmol/l and 5 days after was $-3{\cdot}9 \pm 6{\cdot}6$ mmol/l. Serum Na decrease of ≥5 mmol/within first 5 days after discontinuation of tolvaptan was observed in 21 of 49 (42·8%) patients with half of these (11/21) patients being administered another course of tolvaptan as inpatients.

Outcome of admission

The inpatient mortality rate in this cohort was 8·2%. The mean length of hospital stay was $22{\cdot}6 \pm 17{\cdot}2$ days with sNa of $132{\cdot}5 \pm 5{\cdot}0$ mmol/l at hospital discharge. A significant proportion of patients (17/56 or 30·3%) were discharged with sNa <130 mmol/l. In total, 20 of 56 (35·7%) patients were discharged on therapy for SIADH, including 11 patients on fluid restriction; 6 on tolvaptan (all of whom had SIADH due to malignancy); 3 on demeclocycline.

Discussion

This study confirmed that tolvaptan is an effective treatment modality for hyponatraemia due to SIADH with 96·7% of patients achieving sodium increase of ≥5 mmol/l after 48-h treatment. However, the safe rates of hyponatraemia correction were exceeded in a substantial proportion of patients (23%) with no cases of osmotic demyelination recorded.

Our data also highlighted the failure of real-life clinical practice at our institutions to meet the recommended standards for electrolyte monitoring during tolvaptan use. Less than 10% of patients had 6-hourly monitoring of serum sodium during the first day after tolvaptan initiation, as suggested in the drug label. This may explain the much higher incidence (23·0%) of overly rapid sodium correction in our experience compared to 5·9% in the SIADH subgroup of SALT-1 and SALT-2 studies[14] and 10·8% in the Hyponatraemia Registry,[6] the largest observational hyponatraemia study to date. In addition, the present study demonstrated greater effectiveness in correcting sNa by a mean rise of 11·4 mmol/l over a 2-day period in comparison to 5·3 mmol/l over a 4-day period in the subgroup of SIADH patients[14] in the landmark SALT-1 and SALT-2 studies. These findings may be explained by the lower median baseline sNa value of 121 mmol/l in our cohort compared to approximately 128·5 mmol/l in SALT studies[12,14] and 124 mmol/l in the Hyponatraemia Registry.[6] Among all biochemical parameters, starting sNa was the only predictor for the rate of sNa correction after tolvaptan administration. All cases with overly rapid correction of hyponatraemia had baseline sNa <125 mmol/l with the greatest increase in sNa occurring in patients with the lowest baseline sNa, as previously shown in the SALT studies.[12] A possible explanation is that patients with lower sNa have larger amount of excess total body water; as a result, higher volume of free water becomes available for renal excretion when tolvaptan decreases the number of aquaporin-2 channels in the renal collecting tubules, resulting in more pronounced 'aquaresis' and larger increase in sNa concentration.

Given our initial experience of using a starting tolvaptan dose of 15 mg, a small number of subjects with sNa <125 mmol/l were treated with an 'off-label' initiation dose of 7·5 mg. The sNa increase in 24 h of 9·8 mmol/l was not different from that seen in patients treated with the licensed initiation dose. These data suggest that lower doses of tolvaptan may be effective, but may still carry a risk of overcorrection. However, the sample size was too small to draw a firm conclusion about the safety and effectiveness of using lower doses.

This study, the largest UK observational study of tolvaptan use in 'real-life' clinical practice, allowed for the first time a comparison of monitoring in clinical practice against the standards set in the drug label. A novel aspect of our data was that half of the patients had a baseline sNa <120 mmol/l. This is a population for which safety data concerning tolvaptan therapy is lacking as highlighted by both the European[10] and US[8] guidelines.

Our study had a number of limitations, mainly because this was a retrospective observational study describing real-life clinical experience. Firstly, a case of ODS could not be categorically excluded. However, no neurological deterioration was recorded in medical notes, while manifestations of ODS, such as spastic quadriparesis, pseudobulbar palsy and impairment in the level of consciousness, would be unlikely to go unnoticed by healthcare professionals. They also typically occur within 7 days after correction[23] when most individuals in our cohort were still inpatients. Also such a 'real-life' retrospective study could not accurately assess clinical outcomes. Thus, it is unclear to what extent biochemical correction translated into clinically significant

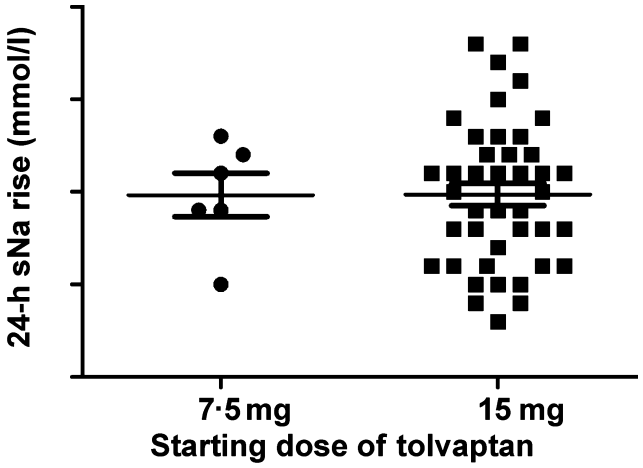

Fig. 3 Scatter plot of magnitude of sNa rise for different initiation doses (7·5 mg *vs* 15 mg). Horizontal lines indicate the mean 24-h sNa rise for each group.

improvement of symptoms, particularly as our cohort included many elderly patients with several chronic comorbidities who received active treatment for acute illnesses and might have symptomatology of multifactorial aetiology. A further inherent weakness of this 'real-world' study was its heterogeneity of SIADH aetiologies, ranging from self-limiting acute conditions, for example pneumonia, to chronic diseases of indefinite duration, such as advanced malignancies. In addition, parameters such as initiation dose of tolvaptan, frequency of monitoring and decision to withdraw therapy did not follow a specific protocol, but were based on the clinical judgement of the prescribing physician. Finally, frequent electrolyte monitoring after tolvaptan initiation was not systematically performed.

The high incidence of overly rapid sodium correction in our cohort raises concerns about the safety of tolvaptan use without adequate electrolyte monitoring in place, especially in patients with sNa <125 mmol/l. Our study reinforces the need to follow label instructions by European Medicines Agency (EMA) and US Food and Drug Administration (FDA) for mandatory electrolyte and fluid monitoring at frequent intervals and development of specific local protocols including specific measures to prevent or reverse overly rapid correction. Our experience suggests that tolvaptan should be used with great caution under the rigorous supervision of a Physician with expertise in treatment of SIADH. In addition, all patients treated with tolvaptan should maintain *ad libitum* fluid intake and should not receive any other concomitant treatments for hyponatraemia. Furthermore, clinicians should be mindful of co-administration of CYP3A4 inhibitors, such as grapefruit, macrolides, ketoconazole, diltiazem, verapamil and protease inhibitors, which can significantly increase serum concentration of tolvaptan and alter its pharmacokinetics.[9]

The authors of US guidelines,[8] recognizing the limited data for the use of tolvaptan in patients with sNa <120 mmol/l, recommend tolvaptan use with caution and more frequent monitoring in this subgroup. However, they anticipate that the use of tolvaptan under vigilant monitoring should be safe in more severe hyponatraemia. It is also worth mentioning that only one case of ODS in association with tolvaptan monotherapy has been reported thus far when inappropriate continuation of tolvaptan caused sNa correction to an extremely high concentration of 187 mmol/l over 3 days.[24] Contrary to the US guidelines, the European guideline development group recommends against the use of tolvaptan when starting sNa is <125 mmol/l in view of a greater risk of overly rapid sodium correction.[10]

In conclusion, this study confirmed the effectiveness of tolvaptan in correcting hyponatraemia in SIADH, but it also showed a significant risk of overly rapid sodium correction in real-life clinical practice when rigorous electrolyte monitoring was not in place. Our real-world data highlight the need for prospective studies examining the safety of tolvaptan use under appropriate monitoring in patients with sNa <125 mmol/l and also for studies evaluating the efficacy and safety of lower tolvaptan doses such as 7·5 and 3·75 mg.

Conflict of interest/financial disclosure

Nothing to declare.

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ORIGINAL ARTICLE

Improving care and outcomes of inpatients with syndrome of inappropriate antidiuresis (SIAD): a prospective intervention study of intensive endocrine input vs. routine care

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Abstract
Purpose: The syndrome of inappropriate antidiuresis is often undertreated with most patients discharged with persistent hyponatraemia. This study tested the hypothesis that an endocrine input is superior to routine care in correcting hyponatraemia and can improve patient outcomes.
Methods: This single-centre prospective-controlled intervention study included inpatients admitted at a UK teaching hospital, with serum sodium ≤ 127 mmol/l, due to syndrome of inappropriate antidiuresis over a 6-month period. The prospective intervention group (18 subjects with mean serum sodium 120.7 mmol/l) received prompt endocrine input, while the historical control group (23 patients with mean serum sodium 124.1 mmol/l) received routine care. The time needed for serum sodium increase ≥ 5 mmol/l was the primary endpoint.
Results: The intervention group achieved serum sodium rise by ≥5 mmol/l in 3.5 vs. 7.1 days in the control group ($P = 0.005$). In the intervention group, the mean total serum sodium increase was 12 mmol/l with only 5.8 % of patients discharged with serum sodium < 130 vs. 6.3 mmol/l increase ($P < 0.001$) and 42.1 % of the subjects discharged with serum sodium < 130 mmol/l in the control group ($P = 0.012$). The mean length of hospital stay in the intervention group (10.9 days) was significantly shorter than in the control group (14.5 days; $P = 0.004$).The inpatient mortality rate was 5.5 % in intervention arm vs. 17.4 % in control arm, but this difference was not statistically significant.
Conclusions: Since the endocrine input improved time for correction of hyponatraemia and shortened length of hospitalisation, widespread provision of endocrine input should be considered.

Keywords Hyponatraemia · Syndrome of inappropriate antidiuretic hormone secretion · Vasopressin · SIADH · Sodium

Introduction

Hyponatraemia is associated with considerable morbidity and mortality [1–4], and carries a substantial economic burden related to increased hospital resource utilisation, length of hospital stay and risk of readmission [5, 6]. Syndrome of inappropriate antidiuresis (SIAD), the commonest cause of hyponatraemia [7], is often undertreated with recent large observational studies showing that most patients are discharged with persistent hyponatraemia [8–10].

Despite suboptimal standards of care for SIAD, no prospective studies have examined the effect of widespread provision of endocrine input on its management. Also there is paucity of data about whether correcting hyponatraemia can improve patient-related outcomes, such as mortality, length of hospital stay, and readmission rate. The primary hypothesis of our study was that prompt and intensive endocrine input was superior to non-specialised 'standard' clinical care in correcting hyponatraemia with the primary endpoint being time to achieve an increase in serum sodium (sNa) by ≥5 mmol/l. Secondary objectives were:

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(1) to compare the total rise in sNa and the percentage of patients discharged with sNa < 130 mmol/l between intervention and control group
(2) to examine the effect of endocrine input on inpatient mortality and length of hospital stay
(3) to study whether correction of hyponatraemia improves cognitive function.

Materials and methods

Study design

This single-centre prospective-controlled intervention study was conducted in a UK teaching hospital over a 6-month period. During the first 3-month period (1st October 2014–31st December 2014), all patients underwent 'routine' care (control group), while in the following 3-month period (1st January 2015–31st March 2015), patients received intensive endocrine input (intervention group). The rationale behind the use of a historical control was that undertaking a randomised controlled trial in a real-life clinical setting was considered impractical since clinicians might often seek expert help from the investigators about patients allocated to the control arm, resulting in possible 'dilution' of the control group with patients receiving the intervention. The time required to achieve sNa increase of ≥5 mmol/l was chosen as the primary endpoint since this magnitude of correction can be sufficient to improve symptoms of hyponatraemia [11]. The study received ethical approval from the London-Camden & Islington Research Ethics Committee, and all subjects provided written informed consent before participation.

Patient selection

All adults with sNa concentration ≤ 127 mmol/l both on hospital admission and on the following day were identified through an automated laboratory system. This cut-off sNa value was selected because previous data from our cohort showed a significant upward inflection in inpatient mortality below that threshold [4]. Among these patients, only subjects who met all essential diagnostic criteria for SIAD, including euvolaemia, hyponatraemia and low serum osmolality with inappropriately raised urine osmolality and sodium, normal adrenocortical reserve, and exclusion of hypothyroidism [12, 13], participated in the study.

Subjects were excluded if they met any of the following exclusion criteria: (1) aged < 18 years old, (2) presence of hypervolaemic hyponatraemia, (3) hypovolaemic hyponatraemia, (4) decompensated chronic liver disease, (5) decompensated heart failure, (6) renal impairment with serum creatinine >200 umol/l or receiving renal replacement therapy, (7) uncontrolled hyperglycaemia with serum glucose >15 mmol/l, (8) pregnancy/breastfeeding, (9) receiving end-of-life care.

Taking into account preliminary data from our cohort indicating a mean time of 5.5 days to reach the primary endpoint of sNa rise ≥5 mmol/l and if standard deviation (SD) for each arm is 1, power sample size was estimated, as 18 patients in each arm, in order to show 20 % difference in the primary endpoint (1.1 day) with 90 % power and 5 % significance level.

Control group

In real-life clinical practice, the mainstay of SIAD treatment was fluid restriction in combination with discontinuation of offending drugs and treatment of underlying cause. When hyponatraemia was refractory to fluid restriction, some patients were referred to endocrinologists, usually after considerable delay, for consideration of pharmacological therapy. In addition to 'standard' clinical care, all patients had full biochemical work-up automatically performed with the attending physicians being notified of the results.

Intervention group

The investigators, two senior endocrinologists with special interest in hyponatraemia and a Research Nurse, provided regular input on daily basis throughout hospitalisation to the attending medical and nursing team under whose care the patients remained. The intervention reflected best clinical practice [14–16] without the utilisation of any novel diagnostic tests and therapeutic modalities.

Treatment options for SIAD included hypertonic saline, fluid restriction, demeclocycline and tolvaptan. First-line treatment was fluid restriction at a volume of 750–1000 ml/day, apart from cases of severe hyponatraemic encephalopathy requiring urgent correction with intravenous infusion of 1.8 % sodium chloride under close supervision in a high dependency or intensive care unit. In patients not responding to fluid restriction within 48–72 h,second-line treatment, tolvaptan or demeclocycline was prescribed, while urea was not utilised because of lack of availability and absence of local experience in its use. Tolvaptan at a starting dose of 15 mg once per day [17, 18] was used when there was a clinical need for prompt hyponatraemia correction, for example to render a patient fit for chemotherapy or surgery, and in cases with likely short duration of SIAD, for example pneumonia. Demeclocycline at a starting dose of 900 mg per day in divided doses [19] was prescribed in patients with high probability of requiring treatment for longer than 1–2 weeks, such as malignant SIAD.

Assessment of cognitive function

Taking into account the lack of validated tools to assess symptoms in association with hyponatraemia, Mini-Mental State Examination (MMSE), used extensively to follow the course of cognitive changes over time [20, 21], was performed in all participants of the intervention group at three different time points; on admission, when sNa increased by ≥5 mmol/l from baseline and when sNa was ≥132 mmol/l.

Statistical analysis

Data were analysed using SPSS (version 21.0, Chicago, IL). Continuous variables were expressed as mean ± SD or percentages. Analysis of variance and Pearson's χ^2 test were used to test differences between the intervention and the control group. *P*-values of <0.05 were considered significant.

Results

Demographic characteristics

The control group included 23 patients (11 males, 12 females) with a (mean ± SD) age of 77.6 ± 10.7 years compared to the intervention group of 18 subjects (12 males, 6 females) with a (mean ± SD) age of 72.7 ± 10.2 years. There was no statistically significant difference in age and gender distribution across groups.

Speciality distribution, duration and aetiology of SIAD

There was a wide distribution of patients within different specialities with most patients in both groups being under the care of medical specialities. Chronic hyponatraemia, defined as most recent sNa value measurement within previous 6 months ≤132 mmol/l, was recorded in 34.8 % of cases in the control arm and 44.5 % in the intervention arm ($P = 0.529$). Different aetiologies of SIAD had similar prevalence across groups, as shown in Table 1.

Baseline biochemical parameters

Serum Na concentration on admission was significantly lower in the intervention arm (120.7 ± 5.5 mmol/l) in comparison with the control arm (124.1 ± 3.1 mmol/l) with a *P* value of 0.017. All other biochemical parameters, apart from serum osmolality, did not differ between two groups, as shown in Table 2.

Table 1 Classification of cases according to aetiology of SIAD

Aetiology	Control group $N = 23$ (%)	Intervention group $N = 18$ (%)	*P* value
Pulmonary illness	8 (34.8 %)	6 (33.3 %)	0.923
Idiopathic	6 (26.1 %)	6 (33.3 %)	0.613
Malignancy	5 (21.8 %)	2 (11.1 %)	0.369
Drug-induced	1 (4.3 %)	2 (11.1 %)	0.573
CNS disorder[a]	2 (8.7 %)	1 (5.6 %)	0.702
Various	1 (4.3 %)	1 (5.6 %)	0.859

[a] Central nervous system pathology

Table 2 Baseline biochemical parameters in both study arms

Biochemical parameters	Control group $N = 23$	Intervention group $N = 18$	*P* value
Serum	Mean ± SD	Mean ± SD	
Na (mmol/l)	124.1 ± 3.1	120.7 ± 5.5	**0.017**
K (mmol/l)	4.4 ± 0.7	4.5 ± 0.7	0.643
Urea (mmol/l)	4.9 ± 2.1	4.3 ± 2.0	0.365
Creatinine (umol/l)	58.7 ± 18.5	59.4 ± 20.5	0.916
Osmolality (mOsm/kg)	259.1 ± 8.0	252 ± 10.2	**0.017**
Urine			
Na (mmol/l)	88.1 ± 48.8	65.3 ± 29.2	0.088
K (mmol/l)	36.6 ± 20.3	36.3 ± 20.2	0.968
Osmolality (mOsm/kg)	445.1 ± 138.0	401.6 ± 146.0	0.333

Endocrine input

All patients (100 %) in the intervention group received endocrine input compared with 12/23 patients (52.2 %) in the control group ($P = 0.001$). The mean time interval between admission and expert input in the intensive arm was 1.8 days, much shorter than in the 'routine' care arm (5.7 days; $P = 0.007$).

Treatment of SIAD

In the group receiving 'routine' clinical care, 26.1 % of patients had no specific treatment for SIAD vs. no untreated cases in the intervention group ($P = 0.027$). The mean number of therapeutic modalities used in the control arm was 1.2, significantly lower than in the intervention arm (1.9; $P = 0.041$). The frequency of utilisation of different therapeutic modalities is illustrated in Table 3.

Achievement of primary endpoint

The percentage of patients reaching the primary endpoint of sNa rise ≥5 mmol/l was similar in the intervention group (88.9 %) and in the control group (73.9 %; $P = 0.230$).

Table 3 Frequency of utilisation of different therapeutic modalities

Treatment modality	Control group $N = 23$ (%)	Intervention group $N = 18$ (%)	P value
Drug discontinuation	5 (21.7 %)	7 (38.9 %)	0.231
Fluid restriction	16 (69.6 %)	18 (100 %)	**0.010**
Tolvaptan	5 (21.7 %)	3 (16.7 %)	0.684
Demeclocycline	2 (8.7 %)	3 (16.7 %)	0.439
Hypertonic saline	1 (4.3 %)	2 (11.1 %)	0.409

However, subgroup analysis of control arm indicated that all patients who did not reach the primary endpoint belonged to the subgroup not receiving endocrine input.

The time interval needed for sNa rise ≥5 mmol/l was 3.5 days in the intervention group, almost half the time (7.1 days) required in the control group ($P = 0.005$).

Rate of hyponatraemia correction

Three days following admission, a further decrease from the baseline in sNa value was observed in 43.5 % of patients in the control arm vs. 5.6 % of subjects in the intervention arm ($P = 0.007$). The intervention group achieved significantly larger magnitudes of sNa correction than the control group, as illustrated in Table 4.

Overly rapid correction of hyponatraemia, defined as sNa increase >12 mmol/l during any 24 h-period or >18 mmol/l during any 48 h-period, was not recorded in the intervention group, while one patient in the control group exceeded the safe limits with sNa increase of 14 mmol/l in the first 24 h following tolvaptan initiation. No cases of osmotic demyelination syndrome were documented.

sNa at discharge and patient outcomes

As illustrated in Fig. 1, the proportion of patients discharged with moderate to severe hyponatraemia (sNa < 130 mmol/l) in the intervention group (5.8 %) was significantly lower than in the control group (42.1 %; $P = 0.012$). Subgroup analysis of the control arm demonstrated that 30 % of cases receiving endocrine input were discharged with moderate to severe hyponatraemia vs. 55.5 % of cases not receiving endocrine input.

The difference in the mean total sNa increase between intervention arm (12 mmol/l) and control arm (6.3 mmol/l) was statistically highly significant ($P < 0.001$). Further subgroup analysis of the control arm showed higher total sNa rise in patients with endocrine input (9 ± 3.8 mmol/l) compared to patients not receiving endocrine input (4.5 ± 4.8 mmol/l).

As shown in Table 5, the mean length of hospital stay in the intervention group was significantly shorter than in the control group by 3.6 days ($P = 0.004$). The inpatient mortality rate in the intervention group was 5.5 % in comparison

Table 4 Correction of sNa 2, 3 and 5 days following admission

Correction of sNa	Control group $N = 23$	Intervention group $N = 18$	P value
2 days			
Correction (mmol/l)[a]	0.3 ± 4.7	1.9 ± 3.5	0.234
Cases with sNa decrease (%)	12 (52.2 %)	4 (22.2 %)	0.051
3 days			
Correction (mmol/l)[a]	0.5 ± 4.7	4.5 ± 3.3	**0.004**
Cases with sNa decrease (%)	10 (43.5 %)	1 (5.6 %)	**0.007**
5 days			
Correction (mmol/l)[a]	1.9 ± 6.2	8.4 ± 3.3	**<0.001**
Cases with sNa decrease (%)	7 (31.8 %)	0	**0.015**

[a] Mean ± SD

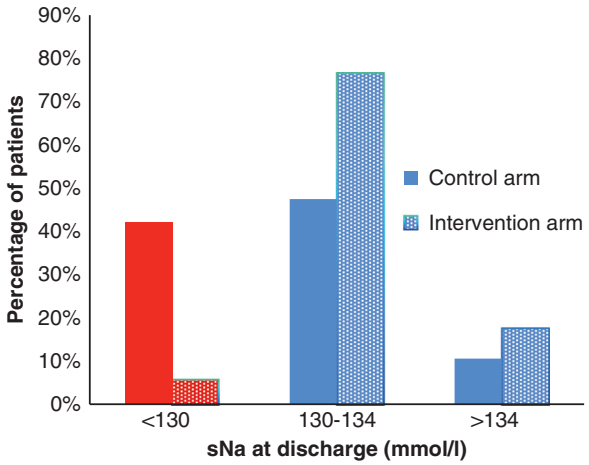

Fig. 1 Bar chart illustrating relative frequency distribution of sNa at hospital discharge in both groups. *Solid bars* represent control arm, while *dotted bars* represent intervention arm. *Red bars* show percentage of patients discharged with moderate to severe hyponatraemia (sNa < 130 mmol/l)

to 17.4 % in the control group, but this difference did not reach statistical significance. Among the five fatal cases, two patients, both in the 'routine' care group, had persistent severe hyponatraemia at the time of death. The first patient did not receive any specific therapy for SIADH and died with a sNa of 123 mmol/l, while the second patient was not given second-line treatment for SIADH despite failing to respond to fluid restriction and died with a sNa of 122 mmol/l.

Effect of hyponatraemia correction on cognitive function

Amongst 18 subjects in the intervention group, 4 patients exhibited severe neurological symptoms, such as acute changes in mental status and confusion, including 2 individuals with Glasgow Coma Score of 12. All these patients

Table 5 Patient outcomes at discharge

Outcomes	Control arm $N = 23$	Intervention arm $N = 18$	P value
Total sNa rise[a] (mmol/l)[b]	6.3 ± 0.3	12 ± 6.8	**<0.001**
Inpatient mortality rate	4/23 (17.4 %)	1/18 (5.5 %)	0.250
Length of stay (days)[b]	14.5 ± 7.9	10.9 ± 5.3	**0.004**
Cases discharged on therapy	3/19 (15.8 %)	10/17 (58.8 %)	**0.004**
Readmission rate	5/19 (26.3 %)	4/17 (23.5 %)	0.970

[a] calculated as [sNa at discharge or death−baseline sNa]

[b] Mean ± SD

showed marked improvement in symptomatology after sNa increase. The remaining patients either had non-specific mild symptoms (9 cases) or seemed asymptomatic (5 cases). Improvement in MMSE score by ≥3 points when sNa reached 132 mmol/l or increased by ≥5 mmol/l was recorded in 38.9 % of subjects in the intervention arm, including 22.2 % of patients with incremental rise of ≥10 points.

Discussion

This study demonstrated that prompt endocrine input reduced the time required to achieve clinically meaningful sNa increase and led to significantly shorter length of hospital stay.

Several factors may explain the superiority of regular endocrine input to 'routine' clinical care in correcting hyponatraemia despite the fact that endocrine input was also provided to almost half of patients in the 'routine' care arm. A key factor may be that in the control arm, the average time from presentation to referral for endocrine review was longer than 5 days. Also considerable delay in therapy was frequently observed in the control group, while patients in the intervention group had prompt diagnosis and timely initiation of appropriate treatment for SIAD. In the control arm, around a quarter of patients did not receive any specific treatment for SIAD, whereas there were no untreated cases in the intervention arm. Another main factor differentiating the treatment between groups was the frequency of using fluid restriction, being higher by 30 % in the intervention compared to control arm. Despite the fact that only half of all patients seem to respond to fluid restriction, as shown in Hyponatraemia Registry [10], its implementation in an additional 30 % of cases in the intervention arm might have resulted in significant correction in around 15 % of cases. The increased utilisation of fluid restriction might have made an even more significant contribution to hyponatraemia correction, taking into account that adherence to fluid restriction in the control group was often poor, while in the intervention group, fluid restriction was quite rigorous with a mean oral intake of 800 ml/day and, more importantly, regular patient encouragement in combination with bedside notices, detailed fluid balance charts and removal of excess bedside fluids was used to promote patient compliance. When fluid restriction was ineffective, it was often not followed with an additional therapy in the control arm in contrast to second-line treatment with tolvaptan or demeclocycline being administered in the intervention group, when indicated. Specialist care provision, apart from being effective, was safe without limits for sodium correction being exceeded in any cases and potentially cost-effective with costly pharmacological agents such as tolvaptan being utilised less often than in the control group.

In addition to superiority in correcting hyponatraemia, expert input reduced by 3.6 days of the mean length of hospitalisation. This finding becomes even more noteworthy in light of the unprecedentedly low percentage of patients (5.8 %) discharged with moderate or severe hyponatraemia, much lower than that observed in a recent multicentre UK observational study (23.8 %) [8] and in the Hyponatraemia Registry (43 %) [9]. Moreover, the intervention group had numerically lower inpatient mortality rate (5.5 %) than the control group (17.4 %), but this difference was not statistically significant. Finally, in a considerable proportion of patients, prompt correction of hyponatraemia resulted in rapid improvement of cognitive function.

The main strength of our study was being the first prospective study assessing the effect of expert endocrine input on correction of hyponatraemia and patient-related outcomes. Also this intervention could be readily applicable in everyday clinical practice since the investigators used only tests and therapeutic measures routinely available. Taking into account that 'routine' care at our institution included referral to endocrinologists in a large proportion of cases and that the subgroup of the control arm without specialist input achieved much lower sNa increase than the subgroup with endocrine input, our study might underestimate the positive impact of the intervention.

However, this study had a number of limitations. First and foremost, use of historical control instead of randomising subjects to two arms, introduced a potential confounding bias. To minimise the possibility of authors' bias resulting in shorter length of stay in the intervention group, caring clinical teams responsible for patient care took all clinical decisions such as when a patient should be discharged, with the exception for decisions related to hyponatraemia management. In fact, in a few cases, especially under surgical speciality, the investigators' input contributed to prolongation rather than shortening of hospitalisation by strongly recommending against hospital discharge, based on

high probability of hyponatraemia recurrence and continuing need for close electrolyte monitoring. Also the intervention arm was studied immediately after the control arm in order to ameliorate differences in standards of medical and nursing care, discharge policy, characteristics of hospital population, and clinicians' prescribing habits. Another possible confounder was the seasonal effect on the distribution of SIAD aetiologies. However, the frequency of pulmonary infection-related SIAD cases was similar across groups since the first arm of the study took place in late autumn and at the beginning of winter, while the second arm in late winter and at the beginning of spring. A further limitation of this study was the small sample size which had adequate power to detect differences in time for correction of hyponatraemia, but it was not powered to identify differences, unless large, in mortality rate and length of stay. The small sample size might also increase the probability of type II statistical error if it introduced confounding through significant differences in the underlying aetiology of SIAD. However the proportion of short duration SIAD cases with a high probability for prompt correction, such as pulmonary infection-related and drug-induced SIAD, was almost identical between intervention and control arm. Additionally, all cases in the intervention arm with drug-induced SIAD, a condition which usually responds very well to drug withdrawal, did not discontinue the, regarded as essential, offending drug, but were treated with fluid restriction. Finally, the generalisability of the positive impact of endocrine input was questionable since it might be highly dependent on the clinical acumen, knowledge and skills of the physicians providing expert input, especially since investigators had extensive experience and expertise in management of SIAD.

This study showed that improving clinical practice led to effective and safe hyponatraemia correction and better patient outcomes. It could be argued that the better standard of care achieved through regular endocrine input might be also met by 'generalists'. However the consistently suboptimal management of SIAD demonstrated in numerous contemporary studies [8–10] [22] indicated that wider provision of expert input should be considered. To effectively deliver this service, multidisciplinary hyponatraemia teams should be developed. These teams should be led by endocrinologists or other physicians with a special interest in hyponatraemia, such as nephrologists, depending on local expertise. In view of the high prevalence of hyponatraemia, we could consider a 2-tier model of care incorporating electronic alert systems, recently tested with promising results in acute kidney injury [23, 24], with regular involvement of hyponatraemia teams in selected cases.

Our proposed algorithm for optimal SIAD management includes various therapeutic options with individualised treatment decisions being based on several factors, including duration and degree of hyponatraemia, severity of symptoms, the capacity of the nephron to excrete free water, urine osmolality, the safety and efficacy of each treatment modality, cost implications of each therapy and patient compliance [25]. The only treatment modality indicated in patients with severe symptoms related to hyponatraemia, such as seizures, reduced Glasgow Coma Scale and coma, is infusion of hypertonic saline. Treatment with 3 % sodium chloride should commence as bolus of 100 ml over 10–15 min, which should be repeated, if needed, and be followed by intravenous continuous infusion [15]. In the absence of severe hyponatraemic encephalopathy, we aim for an increase in sNa concentration by 4–5 mmol/l/day and not exceeding the limit of 10 mmol/l/day [14] [16] . First-line therapy encompasses treatment of the underlying cause of SIAD and fluid restriction. Restriction of all fluid intake should be titrated according to the Furst[27] formula using the urine/plasma electrolyte ratio $(U/P) = (U_{Na} + U_K)/(P_{Na} + P_K)$, for example 500 ml/day if U/P is 0.5–1.0 and 1000 ml/day if U/P is <0.5 [26]. If urine electrolytes are not readily available, we impose fluid restriction at 750–1000 ml/day. We recommend tolvaptan use as first-line treatment in two groups of SIADH patients; first, if there is a clinical need for prompt correction of hyponatraemia, for example to render a patient fit for chemotherapy or surgery, and second, in cases when fluid restriction is highly unlikely to be effective, evidenced by U/P > 1.0 or urine osmolality > 500 mOsm/kg H_2O [15]. Tolvaptan should be strongly considered as second-line therapy if a patient has not responded to fluid restriction, defined as sNa increase of ≤3 mmol/l over 48 h. We recommend tolvaptan use only under the supervision of an endocrinologist or nephrologist with patients on tolvaptan maintaining ad libitum fluid intake and not receiving any other concomitant treatment for hyponatraemia. At our institution, we start tolvaptan at a dose of 15 mg for baseline sNa ≥ 125 mmol/l and at 7.5 mg, half the recommended initiating dose, for sNa < 125 mmol/l, since this low starting dose may be associated with lower risk of overly rapid correction, while it retains its efficacy [27–29]. Serum Na concentration should be closely monitored no later than 4–6 h after treatment initiation and at regular 6-h intervals, at least, during the first 24 h of therapy. If serum Na increase exceeds 6 mmol/l at 6 h or 8 mmol/l at any time point between 7 and 18 h following tolvaptan initiation or 10 mmol/l in 24 h, then free water losses are replaced with administration of 5 % dextrose in water at a volume equal to urine output in order to prevent further correction. In cases when reversal of overly rapid correction is warranted, larger volumes of hypotonic fluids are prescribed [16]. Finally and in light of the high cost associated with long-term tolvaptan use, we prescribe demeclocycline at a starting dose of 300 mg three times

per day in patients with likely long duration of SIAD, such as malignant SIAD.

Our findings highlight the need for multicentre prospective-controlled studies to examine the impact of specialist input on clinical endpoints such as mortality rate, length of stay, symptoms and readmission rate. Since SIAD represents a potential target for intervention to reduce healthcare expenditures for a large population of inpatients, it is also essential to test the cost-effectiveness of widespread provision of expert input, taking into account on the one hand potential reduction in length of hospitalisation and readmission rate, and on the other hand additional cost related to clinical and nursing time and cost of pharmacological therapies. Finally, studies are warranted to develop tools measuring hyponatraemia-specific symptoms which could be used longitudinally for assessment of symptoms and neurocognitive performance in response to any sodium-correcting therapy.

In conclusion, these preliminary data demonstrated that intensive endocrine input not only was superior to 'routine' care in correcting hyponatraemia, but also improved patient-important outcomes such as length of hospital stay and symptoms. If these results could be generalised, provision of systematic endocrine care for patients with SIAD should be widely adopted to improve clinical outcomes and potentially reduce utilisation of hospital resources.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

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