Individualizing drug therapy: a potential role of pharmacogenomics in AED-induced hyponatremia

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Abstract

Use of carbamazepine (CBZ) and oxcarbazepine (OXC) as first line antiepileptic drugs in the treatment of focal epilepsy is limited by hyponatremia, a known adverse effect. Hyponatremia occurs in up to half of people taking CBZ or OXC and, although often assumed to be asymptomatic, it can lead to symptoms ranging from unsteadiness and mild confusion to seizures and coma. Hyponatremia is probably due to the antidiuretic properties of CBZ and OXC that are, at least partly, explained by stimulation of the vasopressin 2 receptor (V2R)/Aquaporin 2 (AQP2) pathway. No known genetic risk variants for hyponatremia exist, but likely candidate genes are part of the vasopressin water reabsorption pathway.

Introduction

Trial and error in drug choice is still an important aspect of pharmacotherapy in epilepsy. Finding an effective anti-epileptic treatment without significant adverse reactions (ADRs) for an individual may take months to years. Persistent seizures (in up to one-third of people) and ADRs lead to severe burdens in people with epilepsy, limiting their quality of life and prospects. The challenge for future pharmacotherapy is to find optimal treatment with minimal delay.

Pharmacogenomics may be a valuable tool for this, as it aims to uncover genetic variants that influence drug response in order to individualize a person's therapy and improve outcome. The clinical use of pharmacogenomics in epilepsy is well demonstrated by carbamazepine (CBZ)-induced severe cutaneous reactions. CBZ causes hypersensitivity reactions in up to 10% of people, ranging from mild to the life-threatening Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). In 2004 it was found that *HLA-B*1502* was strongly associated with CBZ-induced SJS/TEN in the Han-Chinese population, increasing the risk about 100 fold. (1) In Caucasian populations, in which the allele frequency of *HLA-B*1502* is very low (<0.1%), an association was found between carbamazepine hypersensitivity and *HLA-A*3103* (allele frequency 2-5%). (2) In the South-East Asian population screening for *HLA-B*1502* prior to CBZ prescription is now routinely performed due to the relatively high HLA carrier rate (17%). (3)

Another common adverse effect of CBZ and its keto-analogue oxcarbazepine (OXC) is hyponatremia. Here we review the clinical importance of hyponatremia related to CBZ and OXC use, the mechanism of the antidiuretic effect and the potential role for pharmacogenomics in uncovering the genetic predisposing factors.

ANTIEPILEPTIC DRUGS

Carbamazepine was first introduced in 1962. (4) In the central nervous system, CBZ reduces neuronal hyperexcitability and exerts its action mainly by inhibition of voltage-gated sodium channels. (5) Fifty years later it is still recommended as a drug of first choice for treating focal epilepsy despite recent concerns about its potential to induce liver enzymatic systems. (6-8) Indeed, CBZ is losing ground to the newer antiepileptic drugs (AEDs) due to these concerns. CBZ is also prescribed in the treatment of trigeminal neuralgia and bipolar disorders. Frequent ADRs of CBZ include drowsiness, loss of coordination, vertigo, rash, leucopenia, osteoporosis, hepatotoxicity and hyponatremia.

OXC, introduced in 1990, was developed as keto-analogue of CBZ to avoid formation of the epoxide metabolite of CBZ. (9) OXC and CBZ appear to be similarly effective. In a double-blind study comparing OXC and CBZ in people with newly diagnosed epilepsy, complete seizure control was achieved in 52% with OXC treatment and in 60% with CBZ treatment, a non-significant difference. (9) Similarly, a 50% reduction in seizure frequency was seen in 80% of people taking OXC and 81% taking CBZ. (9, 10) Subsequent studies showed better tolerability of OXC, apart from hyponatremia. Several studies have demonstrated that CBZ induces hyponatremia in 5-40 % of individuals. (11, 12) For OXC the incidence appears to be even higher at

30–51%. (12, 13) This serious ADR sometimes results in partial or complete withdrawal, seriously limiting the use of CBZ and OXC. (14)

THE ADVERSE DRUG RESPONSE

Hyponatremia is defined as a serum sodium level < 136 mEq/l resulting in excess total body water relative to total solute. It is considered mild when sodium levels are between 131 and 135 mEq/l, moderate when 125-130 mEq/l and severe when < 125mEq/l. (15, 16) Acute severe hyponatremia is associated with neurological symptoms such as seizures and coma and should be treated urgently to prevent life-threatening complications such as cerebral edema and encephalopathy. (15, 17, 18) Chronic hyponatremia causes more subtle neurological symptoms such as unsteadiness, difficulty concentrating, reduced attention span, mild confusion and personality changes. (19, 20) These symptoms are often mistakenly attributed to the underlying disorder, personality or direct drug toxicity without considering hyponatremia as a potential cause. The underestimation of symptoms was demonstrated by a study in 122 individuals with “asymptomatic” chronic hyponatremia with various causes; 12% were admitted to hospital for falls compared with 5% in matched controls. (19)

Several risk factors exist for hyponatremia associated with CBZ use, including age > 40 years, concomitant use of other medications associated with hyponatremia (21) (table 1), menstruation, psychiatric conditions, surgery, (psychogenic) polydipsia and female gender. (22, 23) Similar risk factors exist for OXC, but age> 40 years is correlated more strongly, as shown by the higher rate of hyponatremia in people

over 40 years of age taking either OXC (60%) or CBZ (20%). (12) A study of OXC-induced severe hyponatremia in a large cohort (n=1009) provided further support for age, concomitant use of diuretics and AED polytherapy as independent risk factors. (24) There is no clear dose-effect relationship between OXC and occurrence of hyponatremia. (12) In contrast, for CBZ a negative relationship between plasma sodium concentration and CBZ serum concentration, as well as the cumulative daily dose, has been described (25, 26); this could not be confirmed in another study. (27)

Case

An individual with epilepsy attending our Centre was successfully treated with OXC for over 10 years. Serum sodium levels were chronically low (121-129 mEq/l) and mild dizziness was accepted as the cost for complete seizure control. Due to hypertension, a combination of the ACE-inhibitor perindopril and the thiazide-like diuretic indapamide was added and the sodium level dropped to 114 mEq/l within a few days of the start, causing falls, cognitive slowness and hospitalization. Indapamide was stopped, the sodium level increased to 123 mEq/l and the symptoms disappeared. This case is an illustration of the care needed when adding medication associated with hyponatremia in people using CBZ/OXC.

Drugs affecting sodium and water homeostasis		
Diuretics	**incidence hyponatremia**	**cause**
Thiazides and related substances (indapamide)	11%	extracellular volume depletion and syndro inappropriate antidiuretic hormone secreti (SIADH)
Other (amiloride)		sodium loss
Drugs affecting water homeostasis		
Increased hypothalamic production of vasopressin		
Antidepressants Tricyclic antidepressants (amitryptiline, protriptyline, desipramine) Selective serotonin reuptake inhibitors (SSRIs) Monoamine oxidase inhibitors (MAOs)	0.5-32%	
Antipsychotic drugs Phenothiazines (chlorpromazine, fluphenazine) Butyrophenones (haloperidol)		SIADH and polydipsia dry mouth
Antiepileptic drugs sodium valproate		
Anticancer agents Vinca alkaloids (vincristine, vinblastine) Platinum compounds (cisplatin, carboplatin) Alkylating agents (cyclophosphamide, melphalan, ifosfamide) Miscellaneous (methotrexate, interferon α and ϒ, levamisole, pentostatin, monoclonal antibodies)	43%	neurohypophysis toxicity SIADH and renal salt wasting Nausea-induced vasopressin production
Opiates		
Potentiation of vasopressin effect		
Antiepileptic drugs Lamotrigine		
Antidiabetic drugs Sulfonylurea derivatives (chlorpropamide, tolbutamide)	4-6%	
Anticancer agents Alkylating agents (cyclophosphamide)		impaired water secretion
Nonsteroidal anti-inflammatory drugs	rare	↓renal prostaglandin synthesis (vasopress inhibitor)
'Reset osmostat' (SIADH variant)		
Antidepressants Venlafaxine		

Table 1 Other drugs associated with hyponatremia (21).

THE MECHANISM

There are several different biological mechanisms that can lead to hyponatremia. Simplified, there is either too much water (polydipsia, inappropriate antidiuresis) or too little salt (low intake or salt wasting) present. (16) Hyponatremia related to drugs is mainly caused by the syndrome of inappropriate antidiuresis (SIAD)(16). An antidiuretic effect of CBZ was first reported in 1966 when it was found to be beneficial in people with diabetes insipidus, a disorder characterized by polydipsia and polyuria caused by a lack of pituitary vasopressin production. (28, 29). In early case reports of CBZ-induced hyponatremia both elevated (30, 31) and lowered (32) levels of vasopressin (also called antidiuretic hormone, ADH) were found. These findings suggested that CBZ either stimulates vasopressin secretion from the posterior pituitary gland or has a direct renal effect itself. According to the renal effect theory, CBZ is thought to increase the sensitivity of osmoreceptors to vasopressin in the renal distal convoluted tubules and collecting ducts or to exert a direct effect on these receptors leading to water retention. (11) (Fig 1)

A combined central and renal effect has been suggested. (33) In a cross-over study, water loading tests were performed in 12 healthy volunteers before and after receiving 600 mg/day CBZ for seven days. With CBZ, vasopressin levels increased less during water deprivation and decreased less during water loading, without affecting plasma sodium concentration and plasma osmolality. It was concluded that

osmoreceptors were less responsive as a result of CBZ. (33) Impaired diuresis during CBZ use was also observed, despite similar vasopressin concentration at peak diuresis when on and of CBZ. (33) It could be argued that this is a direct effect of CBZ on receptors in the renal tubules.

For OXC a similar cross-over design study was performed in a group of people with epilepsy and a group of healthy controls. Exposure to OXC for 3 weeks resulted in significant reduction in serum osmolality (i.e. hypotonicity) and serum sodium concentration after a water loading test in both groups. Hypotonic hyponatremia was not associated with a significant change in serum vasopressin levels, but was the result of both a relative inability to dilute the urine and a reduction of over 50% in water excreted after the water loading test. (34)

Vasopressin exerts its antidiuretic action by binding and activating the arginine vasopressin receptor 2 (V2R), resulting in an increase in intracellular cyclic adenosine monophosphate (cAMP). cAMP promotes shuttling of intracellular vesicles, containing Aquaporin 2 (AQP2) water channels, to the apical membrane of the collecting-duct cells. Water permeability is thereby increased, inducing anti-diuresis.(35) (36) A rodent study suggested that CBZ could activate the vasopressin receptor in the renal medulla and that CBZ can induce renal water absorption by acting directly on the V2R -protein G complex and increasing the AQP2 expression.

In vitro microperfusion experiments showed that CBZ was able to increase water (re)-absorption in the absence of vasopressin. Tests with selective cAMP and V2R inhibitors showed that the CBZ effect on water absorption is cAMP-dependent and acts in the V2R-protein G-complex. In vivo tests were done in 3 groups: controls; rats on a CBZ diet; and rats initially taking lithium, subsequently taking lithium and CBZ. The CBZ diet alone did not increase AQP2 expression compared with controls. CBZ was, however, able to correct nephrogenic diabetes insipidus (NDI) in rats receiving lithium. Lithium decreases AQP2 expression since it blocks vasopressin action. Addition of CBZ reversed 20% of the decrease in AQP2 expression. (35)

Paradoxical effects were observed in another rodent study in which CBZ therapy increased diuresis and electrolyte loss. After rats received the V2R antagonist savaptan, urinary flow and natriuresis were further increased by CBZ. (37) Thus even though CBZ has a comparable pharmacological effect to a V2R agonist, some findings in *rat* studies suggest that other pathways also play a role.

One pathway of interest is the influence of prostaglandins on water transport. Prostaglandin E2 (PGE2), a product of arachidonic acid (AA) metabolism by cyclooxygenase (COX), inhibits vasopressin-induced water permeability by reducing cAMP levels. (38, 39) (fig 1) Inhibition of PGE2 synthesis potentiates antidiuresis. Nonsteroidal anti-inflammatory drug-induced hyponatremia has been associated with the inhibition of synthesis of renal prostaglandins due to COX inhibition. (40)

As well as COX, other enzymes are involved in AA metabolism; lipoxygenase and cytochrome P450 (CYP450) also metabolize AA. Induction of the CYP450 pathway results in less AA being available for metabolism by COX, resulting in less renal prostaglandin synthesis. (41) It is conceivable that CBZ, a major P450-enzyme inducer, potentiates natriuresis through this mechanism. It is unlikely that this is the only mechanism as OXC is a weaker CYP450 inducer than CBZ, whereas the incidence of hyponatremia associated with OXC use seems higher.

Lithium (Li)-induced polyuria due to resistance to vasopressin is mediated by increased PGE2 signalling acting via P2Y receptors. For CBZ/OXC-induced hyponatremia this pathway has not yet been assessed. (42, 43)

GENETICS AND PHARMACOGENOMICS

The antidiuretic property of CBZ and OXC seems to be a physiological effect of these drugs. The fact that hyponatremia is not clearly dose-dependent and is not an extension of the therapeutic effect suggests an idiosyncratic effect. It is likely that the severity of the hyponatremia depends on the genetic constitution of the individual, making subgroups more susceptible. Here we review what is known about the genetics of the V2R/AQP2 pathway and discuss how this could help us to learn more about susceptibility to hyponatremia associated with CBZ/OXC use.

X-linked, inactivating mutations in the arginine vasopressin receptor 2 gene (*AVPR2)* and autosomal mutations in *AQP2* cause nephrogenic diabetes insipidus. (44) From a pathophysiological perspective the opposite of nephrogenic diabetes insipidus is nephrogenic syndrome of inappropriate antidiuresis (NSIAD). This was first described in two unrelated infants and was characterized by excess hypotonic fluid and undetectable vasopressin levels. (45) Both were hemizygous for an *AVPR2* mutation presented with seizures, hyponatremia (123 and 118 mEq/l respectively), and serum hypo-osmolality with inappropriately elevated urinary osmolality and sodium levels. Functional studies showed that basal levels of cAMP production in cells expressing the mutated V2R were four times the levels in cells expressing wild-type V2R (P=0.01). These *AVPR2* mutations created a constitutively active V2R explaining the hyponatremia with increased urinary osmolality. (45)

After this first NSIAD report, two more families and several sporadic cases have been described. These families show great variability in phenotype, and NSIAD may go unrecognized for years. (46, 47) In another described family with five members, two hemizygous and three heterozygous, were assessed. One hemizygous male exhibited all the typical NSIAD features. The other four appeared totally asymptomatic under normal conditions, but all had an abnormal response (including hyponatremia) when challenged by a mild water load. Persistent excretion of AQP2 independent of vasopressin in four of these five individuals with NSIAD was consistent with a constitutive V2R activation. (47)

The condition in people with NSIAD is clinically similar to SIAD associated with CBZ/OXC use. Key characteristics in both are hyponatremia, serum hypo-osmolality, urine hyper-osmolality, low levels of vasopressin and an abnormal response to a water loading test. The fact that this genetic condition resembles the effect of CBZ and OXC use provides some additional support to the findings of a direct action of these drugs on one of the V2R-dependent pathways. The great variability in phenotype in people with NSIAD may be explained by interactions with variants in other genes from these renal pathways. These same variants may also play a role in the susceptibility to severe hyponatremia during use of CBZ or OXC.

CONCLUSION

Hyponatremia should no longer be considered an asymptomatic condition. (19) Symptoms such as unsteadiness, dizziness, difficulty concentrating, reduced attention span, mild confusion, and lethargy in people taking CBZ or OXC should alert the physician to check the serum sodium level. In people with multiple risk factors, hyponatremia might occur much faster with more severe, even life threatening, symptoms. Preventive fluid restriction can be of great value in these situations.

The mechanism of CBZ/OXC-induced hyponatremia remains incompletely understood but there is evidence that the antidiuretic effect is, at least partly, caused by stimulation, direct or via PGE2, of the V2R/AQP2 pathway. In people with NSIAD serum sodium levels and serum and urine osmolality are changed in the same direction as that caused by the use of CBZ and OXC. It is possible that other variants in *AVPR2* with influence on the activation state of V2R make people more susceptible to the antidiuretic effect of CBZ and OXC. Future research should investigate whether pharmacogenomic risk factors, such as variants in genes from the vasopressin water reabsorption and the arachidonic acid metabolism pathways, can identify people at risk of developing clinically relevant hyponatremia induced by CBZ or OXC. In these people CBZ and OXC should be gradually withdrawn and alternative antiepileptic drugs should be prescribed. When the person at risk is

dependent on CBZ or OXC for seizure control, electrolytes should be intensively monitored.

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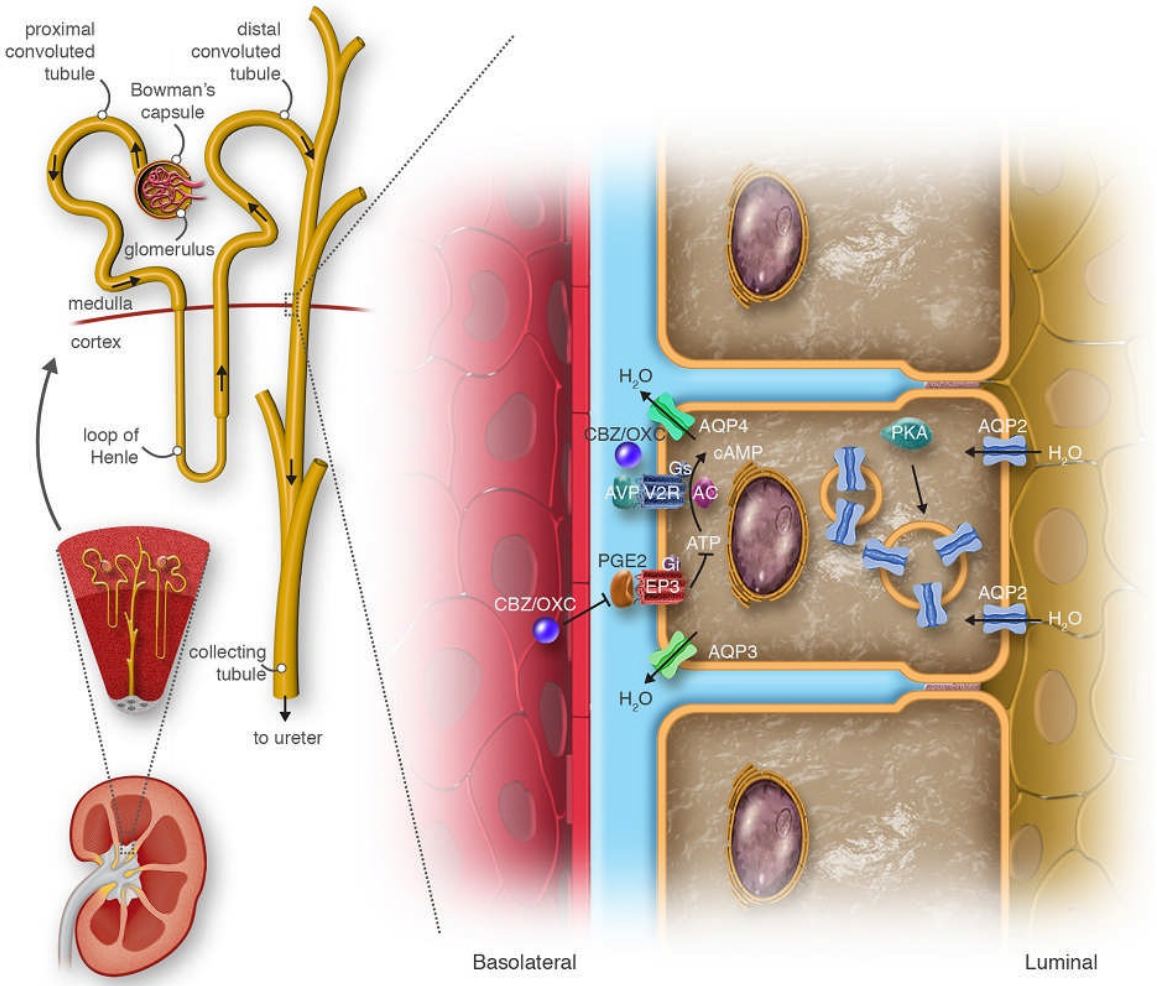

Fig 1. Vasopressin dependent water regulation. Vasopressin (AVP) acts on V2 receptors (V2R) in the basolateral plasma membrane. Through the GTP-binding protein Gs, adenylyl cyclase (A.C.) is activated, stimulating the production of cAMP from ATP. cAMP binds and activates protein kinase A (PKA), which than phosphorylates AQP2 in intracellular vesicles. AQP2 moves to the apical plasma membrane to increase water permeability. PGE2 inhibits this process by binding to the Prostaglandin receptor E3 (EP3)and reducing the production of cAMP. CBZ/OXC influences the water regulation by activating the V2R/AC complex and/or by inhibiting PGE2 formation.

Appendix

Water loading test: Participants are deprived of water for at least the previous 9 hours (up to 24 hours). The bladder is emptied. A standard water load of 20 ml/kg is given within a period of 30 minutes and urine collected every 15–60 minutes until peak diuresis, usually within 3–4 hours. The percentage of water load excreted, plasma vasopressin concentration, plasma and urine osmolality, and serum and urine sodium are measured before and after the water loading test.

In vitro microperfusion: Tubules are dissected from the renal medullas from normal rats and immersed in a dish of chilled Ringer–HCO3 buffer. After isolation, the segment is transferred to a temperature-regulated chamber (37°C). The perfusion solution used is a 295±5 mOsmol/kgH2O Ringer–HCO3, and the bath solution is made hypertonic (510±5 mOsmol/kgH2O) by the addition of NaCl. FD&C green dye is added to the perfusate as a visual marker. Net water absorption was measured with [14C]inulin dialyzed immediately before the experiments. Isolated inner medullary collecting ducts were perfused in absence of vasopressin and in the presence of CBZ, in order to determine the osmotic water permeability. Subsequently, the water permeability was determined in the presence of CBZ + V2R inhibitor and CBZ + cAMP inhibitor.