Original Article

A 12-Year Observational Study of Stiripentol Efficacy and Safety in Dravet Syndrome

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Abstract

Aim: To assess long-term safety and efficacy of stiripentol as an anti-epileptic medication for people with Dravet syndrome (DS).

Method: A prospective, observational open label study (2003-2015) of the efficacy and long-term safety of stiripentol in patients with DS and ongoing seizures. Frequency of generalized tonic-clonic seizures, focal seizures, status epilepticus and adverse events were recorded.

Results: Forty-one patients started stiripentol, with median age at enrolment 5.6 years (range 11 months-22 years) and median duration of treatment 37 months (range 2-141 months). 20/41 (49%) patients had ≥ 50% long-term reduction in frequency of generalized tonic-clonic seizures. Frequency of focal seizures was decreased by ≥ 50% in 11/23 (48%) patients over the long term. Frequency of status epilepticus was decreased by 50% or more in 11/26 (42%) of patients.

The most common adverse events were anorexia, weight loss, sedation, and behavioural changes. One patient had worsening of absence and myoclonic seizures. Another developed recurrent pancreatitis on concurrent valproate.

Interpretation: Stiripentol improves long-term seizure frequency in approximately 50% of patients with DS, when used as part of unrestricted polytherapy. Long-term use appears safe. In > 40% patients, episodes of status epilepticus markedly decrease following stiripentol initiation.

What This Paper Adds

- Stiripentol reduces frequency of status epilepticus in 40% of patients with Dravet syndrome.
- Stiripentol is effective for generalized tonic-clonic and focal seizures
- Stiripentol can be safely used with a range of anti-epileptic drugs.

Dravet syndrome (DS) is an infantile-onset developmental and epileptic encephalopathy characterized by febrile seizures beginning around six months, commonly including hemiclonic status epilepticus. Other seizure types develop later, including afebrile generalized tonic-clonic, focal impaired awareness, absence, and myoclonic seizures. Although development is initially normal, regression or plateau occurs, usually between 12 and 24 months of age.[1] More than 80% of patients with DS have *SCN1A* mutations, almost all of which occur *de novo*.[2]

Individuals with DS often have monthly, or sometimes daily, seizures and frequent episodes of status epilepticus, often provoked by hyperthermia. Epilepsy is almost always refractory to medical therapy, with most patients having ongoing seizures despite two or three concurrent anti-epileptic drugs. The medication with the best evidence for positive therapeutic effect is stiripentol.[3] This drug is thought to reduce seizure frequency by directly modulating GABA-A receptors;[4] however, stiripentol has also been shown to increase plasma concentrations of other co-administered anti-epileptic drugs, including clobazam.[5]

We studied the longitudinal efficacy and safety of open label stiripentol in a cohort of patients with DS with regard to seizure frequency, episodes of status epilepticus and adverse events.

Method

This prospective, open label observational study examined the long-term efficacy and safety of stiripentol in people with DS. All patients had a clinical diagnosis of DS and were followed at a paediatric epilepsy clinic in Australia or the United Kingdom. Between 2003 and 2015, patients who had ongoing seizures were offered treatment with stiripentol. Dosage was gradually titrated up to 67 mg/kg/day or a maximum of 4 g per day, depending on seizure control and development of adverse events. If patients were concurrently taking clobazam or sodium valproate, the doses of these medications were kept below 0.5 mg/kg/day and 30 mg/kg/day respectively, whenever possible.

Participants were reviewed in clinic within 3 months of stiripentol initiation to assess initial therapeutic effect and ask about adverse events. Patients were reviewed regularly thereafter while on stiripentol therapy. Throughout the period of observation, frequency of focal seizures, generalized tonic-clonic seizures, status epilepticus and adverse events were recorded. Screening blood work, including complete blood count and liver enzymes, was collected at least once during the first month of therapy and repeated every six months per recommended guidelines.[6] Data was added and accrued at consecutive clinic and ward visits.

For this study, the clinical data was reviewed based on each patient's most recent clinic visit. Percentage improvement in frequency of seizure types and status epilepticus was determined based on seizure diaries. In order to capture only those patients with ongoing frequent episodes of status epilepticus, we only included patients in the status epilepticus analysis if they had experienced at least one episode of status in the three months prior to stiripentol initiation. Patients were defined as responders if they had $\geq$ 50% improvement in seizure frequency for a defined seizure type or status epilepticus.

The study was approved by the Human Research Ethics Committee of Austin Health (Project No. H2007/02961), and informed written consent was obtained from all Australian patients or their guardians. The United Kingdom data was collected in anonymized form as an audit, registered with the Great Ormond Street Hospital Research and Development Office.

Results

Forty-one patients took stiripentol during the study period 2003-2015 (demographic data in Table 1). All patients received at least two other anti-epileptic medications during the study period. The most commonly co-administered agents were clobazam and valproate; however, 10 other anti-epileptic medications were used during the study period (Table 2).

Data regarding frequency of seizures and status epilepticus at three months and most recent follow-up, are summarized in Table 3. Adverse events are also documented. All but two of the 41 patients were still taking stiripentol at the three-month timepoint. The first patient who discontinued developed streptococcus-induced toxic shock syndrome 2.5 months after starting the medication; stiripentol was held during the severe illness and was not re-started following recovery as she became seizure-free. The toxic shock syndrome was not thought to be related to stiripentol. The second patient had a good clinical response to stiripentol for one month but seizures returned and the medication was discontinued one month later; he then suffered sudden unexplained death in epilepsy (SUDEP) just before the three-month point.

Median duration of treatment was 37 months (interquartile range 13.5-66 months, absolute range 2-141 months) with 29/41 patients (71%) still on therapy at the time of most recent follow-up (Figure). Of the remaining 12 patients, ten discontinued stiripentol due to adverse events and/or lack of efficacy after median treatment duration 7 months (interquartile range 3-12 months, absolute range 2-81 months). Three patients died, two with SUDEP (patients #12 and #14 in Cooper et al (2017)[7]) and another from cerebral oedema following convulsive status epilepticus (patient #3 in Myers et al (2017)[8] and #13 in Cooper et al (2017)[7]). This includes the patient mentioned in the previous paragraph, who died weeks after discontinuing stiripentol but was still considered to be involved in the study.

With respect to generalized tonic-clonic seizures, 23/41 (56%) patients were responders with ≥ 50% reduction in seizure frequency at three months. At the point of final data collection, 12 of these 23 patients remained responders, and an additional eight were now classified as responders, resulting in 20/41 (49%) being long-term responders. One patient was seizure-free and a second had been seizure-free for 18 months before suffering status epilepticus and subsequent fatal cerebral oedema (previously mentioned).

Of the 20 patients with focal seizures, 11 (55%) had ≥ 50% seizure frequency reduction at three months. Four of these failed to maintain long-term control, but four more came under late control, such that 11/20 (55%) were classified as long-term responders.

Of the 27 patients with status epilepticus in the three months prior to commencing stiripentol (age at initiation of stiripentol: 0.9 y to 22.3 y), 11 (41%) had ≥ 50% reduction in frequency of

SE. Of these, nine (33%) had at least 90% reduction in SE events, with seven having no further SE after initiation of stiripentol.

With respect to adverse events, 30/41 (73%) patients had reported adverse events after starting stiripentol (Table 3). The most common were anorexia, weight loss, drowsiness, sedation and behavioural changes. One patient reported transient worsening of absence seizures and myoclonus with dose increases, but stayed on the medication because of a beneficial effect on generalized tonic-clonic seizures. One patient developed hypoalbuminemia with limb oedema at 22 years of age (eight years after starting stiripentol) due to a protein-losing enteropathy of unknown cause (endoscopy and intestinal biopsies were normal).

One patient developed recurrent pancreatitis, having at least 10 episodes over a two-year period. The episodes involved abdominal pain and vomiting, with serum lipase rising as high as 7000 U/L and returning to normal between attacks. The patient had been taking valproate since age eight months but did not have the first episode of pancreatitis until three years of age, two months after initiation of stiripentol. Valproate levels were therapeutic throughout the period of recurrent pancreatitis (542-677 μmol/L; reference range 350-700). A magnetic resonance cholangiopancreatography scan was normal and there was no other apparent cause for the recurrent pancreatitis. Stiripentol was first weaned; however, the patient had an additional episode of pancreatitis. Stiripentol was then re-started, and valproate weaned, after which there were no further episodes of pancreatitis, implicating valproate in its causation.

Interpretation

The best evidence for the use of stiripentol in DS comes from two randomized controlled European trials, which included a total of 41 patients in one study and 11 in the other who received stiripentol.[9,10] These studies used a relatively short double-blind treatment period of two months (though Chiron et al had a median open label follow-up period of 25 months), and employed stiripentol as add on medication to patients already on valproate and clobazam (no other concomitant medications were allowed). This triple therapy protocol was also employed in retrospective open label and cross-sectional European studies.[11,12] The only long-term prospective open label trial in which stiripentol was used for up to 56 weeks also allowed concomitant bromide in addition to the required valproate and clobazam.[13] The only data on stiripentol efficacy when not used in combination with valproate and clobazam comes from a retrospective multicentre survey conducted in the United States, where stiripentol is not currently approved and must be obtained through special access.[14] We present an open label, prospective, long-term study of stiripentol safety and efficacy in 41 patients with DS. Stiripentol was added in an unrestricted manner to the patients' baseline anti-epileptic medications, reflecting routine clinical practice.

Stiripentol maintained a ≥ 50% reduction in generalized tonic-clonic and focal seizures in 49% and 55% of patients long-term, respectively. Our responder rates are less than the short-term responder rates reported of 67-71%,[15,10,9] but similar to the long-term responder rate of 54% reported by Inoue and Ohtsuka (2015), reflecting the honeymoon period often seen in refractory epilepsies. In Wirrell et al's retrospective USA study, they defined the change in seizure frequency differently, reporting 68/103 (66%) of patients having "mild or marked reduction" in

seizure frequency overall, with variable periods of follow up. Our responder rate would not have captured patients with a mild reduction in seizure frequency.

One of the most frightening issues for families facing DS is the risk of status epilepticus which can be fatal.[8] The incidence of status epilepticus in this cohort was clearly decreased in 41% of those for whom we could reasonably assess a change as they had experienced status epilepticus in the three months prior to stiripentol initiation. Unfortunately, changes in the frequency of status epilepticus are difficult to assess, even with long-term studies, since the frequency varies considerably in and between patients with DS. There is, however, a growing body of evidence supporting the efficacy of stiripentol in status epilepticus.[14,11] Experimental evidence for this has been shown *in vitro* with the demonstration that stiripentol has ongoing GABA-A modulation during prolonged seizures when the modulatory effects of diazepam are no longer present.[16]

Anorexia and weight loss were the most common adverse events with stiripentol, occurring in 49% patients. Somnolence and sedation were the second most frequent group, occurring in 34% of individuals, and may be partially related to potentiation of concurrently administered clobazam or valproate. Although rare, recurrent pancreatitis can be associated with stiripentol therapy when added to valproate, thus clinicians should consider this previously undescribed adverse event and adjust management accordingly if it occurs by weaning valproate if possible.

We note that our methodology allowed for adjustments of other anti-epileptic medications during the period of stiripentol treatment. Such adjustments could have affected both seizure control and occurrence of adverse events, a point which should be considered when evaluating our data.

In summary, this study demonstrates that stiripentol is an effective anti-epileptic medication in DS, when used as part of unrestricted polytherapy. Roughly half of patients can be expected to have at least 50% reduction in frequency of both generalized tonic-clonic and focal seizures long-term. Most notable was that some patients have a dramatic improvement in frequency of status epilepticus, so we advocate earlier institution of stiripentol in an infant or child experiencing frequent episodes of life-threatening status epilepticus.

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Figure Legend

Figure: Outcomes of patients initiated on stiripentol treatment. * One patient discontinued stiripentol ~2 months after initiation and suffered SUDEP before the 3-month timepoint. Abbreviations: STP = Stiripentol.

Tables

Table 1: Characteristics of Patients

Variable	
Male (%)	23/41 (56)
Median age, years, at stiripentol initiation (interquartile range; absolute range)	5.6 (4.0-9.6; 0.9-22)
SCN1A mutation present (%)	39/41 (95)
Median duration, months, of stiripentol therapy (interquartile range; absolute range)	37 (13.5-66; 2-141)
Mean number of co-administered anti-epileptic drugs during stiripentol therapy (range)	2.8 (2-5)

Table 2: Medications Received in Conjunction with Stiripentol

Medication	**# Receiving (%)**
Clobazam	33 (80)
Valproate	29 (71)
Topiramate	25 (61)
Levetiracetam	7 (17)
Clonazepam	6 (15)
Ethosuximide	3 (7)
Lamotrigine	3 (7)
Phenobarbital	2 (5)
Phenytoin	2 (5)
Acetazolamide	1 (2)
Lacosamide	1 (2)
Piracetam	1 (2)

Table 3: Clinical Response to Stiripentol

Outcome	
3 months – number still taking stiripentol (%)	39/41 (95)
3 months - ≥ 50% reduction in generalized tonic-clonic seizures (%)	23/41 (56)
3 months - ≥ 50% reduction in focal seizures (%)	11/20 (55)
Last follow-up - ≥ 50% reduction in generalized tonic-clonic seizures (%)	20/41 (49)
Last follow-up - ≥ 50% reduction in focal seizures (%)	11/20 (55)
Last follow-up - ≥ 50% reduction in status epilepticus (%)	11/27 (41)
AE – Anorexia/Weight Loss (%)	20 (49)
AE – Drowsiness/Sedation (%)	14 (34)
AE – Behavioural Change (%)	9 (22)
AE – Neutropenia (%)	5 (12)
AE – Abdominal Pain (%)	4 (10)
AE – Insomnia (%)	4 (10)
AE – Ataxia/Unsteadiness (%)	3 (7)
AE – Drooling (%)	3 (7)
AE – Tremor/Myoclonus (%)	3 (7)
AE – Vomiting (%)	2 (5)
AE – Absence seizure increase (%)	1 (2)
AE – GGT elevation (%)	1 (2)
AE – Hypoalbuminemia and Oedema (%)	1 (2)
AE – Nightmares (%)	1 (2)
AE – Recurrent Pancreatitis (%)	1 (2)
AE – Streptococcus-Induced Toxic Shock Syndrome (%)	1 (2)

Abbreviation: AE = adverse event.