

Efficacy and tolerability of zonisamide in juvenile myoclonic epilepsy

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ABSTRACT – The recommended treatment for juvenile myoclonic epilepsy (JME) is valproate (VPA). Recently, topiramate and lamotrigine have also been shown to be effective. The objective of this study was to evaluate the efficacy and tolerability of zonisamide (ZNS) in the treatment of JME. We retrospectively analyzed the records of 15 patients (three M, 12 F, ages 11-20 years) diagnosed with JME at our institution during 2001-2003, and treated with ZNS. Generalized tonic-clonic (GTC), myoclonic and absence seizure response was assessed. The ZNS dose range was 200-500 mg/day (2.0-8.5 mg/kg/day). ZNS was started as the first drug, and as monotherapy, in 13 and was added to VPA in two patients. Follow-up range was 2-24 months (mean 12 months). Overall, 80% of patients on ZNS monotherapy showed good control ($\geq 50\%$ seizure reduction). Sixty-nine, 62 and 38% of patients were free of GTC, myoclonic, and absence seizures, respectively. Seizure control was achieved within four to eight weeks of attaining the maintenance dose. One patient on polytherapy had a 75% reduction in seizure frequency, whereas the other patient showed no response. There were no ZNS-VPA interactions. One patient stopped ZNS and was switched to VPA because of poor seizure control. Three patients (20%) experienced side effects (weight loss, headache, dizziness) during escalation, which resolved during maintenance. In this open-label, retrospective study, ZNS was shown to be an effective and well-tolerated drug in the treatment of patients with JME. The ease of titration, good safety profile, once-a-day dosing, lack of significant drug interaction, and short latency for onset of efficacy make ZNS an attractive therapeutic alternative for the treatment of JME.

KEYWORDS: zonisamide, juvenile myoclonic epilepsy, treatment

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Juvenile myoclonic epilepsy (JME) is a idiopathic, generalized epilepsy syndrome found in 5-11% of patients with epilepsy [1]. It is characterized by myoclonic jerks in 100% of patients, generalized tonic-clonic (GTC) seizures in 80%, absence seizures in 25%, and an abnormal photo-paroxysmal

response in 40%. The recommended drug of choice in the treatment of JME is valproate (VPA), although recently topiramate and lamotrigine have been demonstrated to be effective therapeutic alternatives [2]. Zonisamide (ZNS) is a new anti-epileptic drug (AED), with multiple mechanisms of action,

including an effect upon voltage-dependent T-type Ca channels. In the Japanese literature, there are data showing that ZNS is efficacious in primary generalized epilepsy [3]. No formal study has been done as yet in the US to assess the efficacy of ZNS in JME. We retrospectively analyzed our patient records to assess the efficacy and tolerability of ZNS as an option in the treatment of JME.

Design and methods

We retrospectively reviewed the records of patients with the diagnosis of JME between the years 2001 and 2003, and further distinguished between those who were on ZNS as monotherapy or polytherapy. The diagnosis of JME was based on the criteria of the International Classification of Epilepsies [1]. The response as regards to GTC, myoclonic and absence seizures was quantified. The baseline and on-treatment seizure count was assessed by patient diaries for the generalized tonic-clonic seizures and early morning myoclonus, and by periodic 24-hour ambulatory EEGs on ZNS treatment to assess residual frequency or complete remission of absences.

This study was approved by the IRB of St Christopher's Hospital for Children / Drexel University College of Medicine. No intramural (institutional) or extramural (public or industry) funding was used to develop this study.

Results

Fifteen patients with JME receiving treatment with ZNS were identified. Their age varied from 11 to 20 years; 12 were girls and three were boys. The ZNS dose ranged from 200 to 500 mg/day (2.0-8.5 mg/kg/day). Dose escalation was 50 to 100 mg every two weeks. Thirteen patients were on ZNS monotherapy, in whom ZNS was started as the first drug, while two patients were on polytherapy with ZNS and VPA, where ZNS was added after VPA failed to control their seizures.

Patients were followed in the clinic every six to eight weeks. Follow-up ranged from two months to two years, with a mean of 12 months. Only one patient was followed for two months; in all others, follow-up was over six months, and in the group of patients who were seizure-free (69%), follow-up was over one year.

Of the 13 patients on monotherapy, one had to stop ZNS and was switched to valproate because of poor seizure control (7.7%). Three patients (20%) experienced side effects: weight loss, dizziness, and headache during the escalation phase, which resolved during the maintenance of the medication.

The degree of seizure reduction on ZNS-monotherapy is shown in (figure 1) and summarized in (table 1). Overall, 80% of patients on ZNS monotherapy showed good control ($\geq 50\%$ seizure reduction). Sixty-nine, 62 and 38% of patients were free of GTC, myoclonic, and absence seizures, respectively. Seizure control was achieved within four to eight weeks of attaining the maintenance dose.

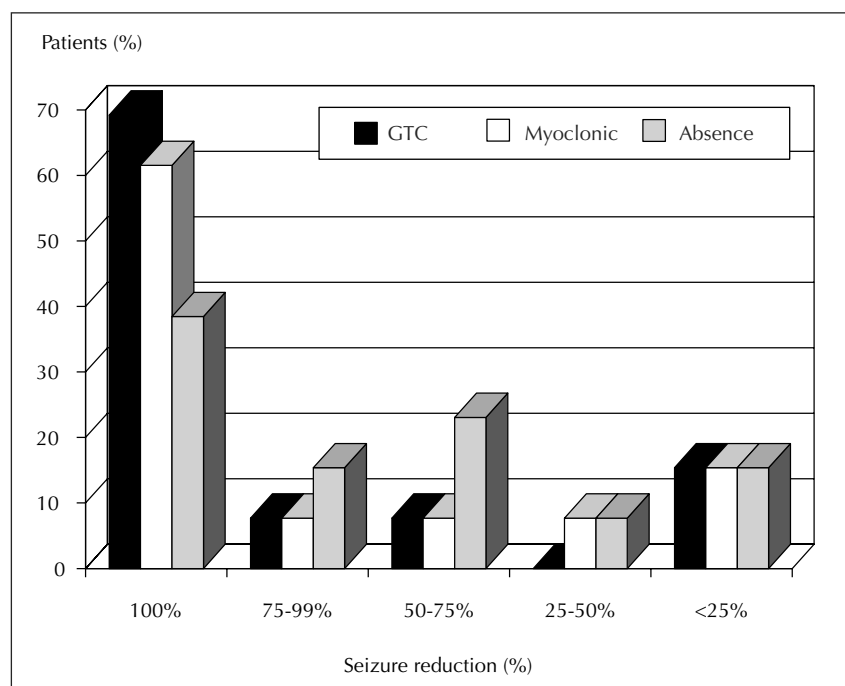


Figure 1. Zonisamide monotherapy: efficacy data (N=13).

Table 1. Efficacy of zonisamide-monotherapy in patients with JME (n = 13)

	% Seizure reduction				
	100%	75-99%	50-74%	25-49%	< 25%
Generalized Tonic-clonic seizures	69.5% (n = 9)	7.5% (n = 1)	7.5% (n = 1)	0% (n = 0)	15.5% (n = 2)
Myoclonic seizures	62% (n = 8)	7.5% (n = 1)	7.5% (n = 1)	7.5% (n = 1)	15.5% (n = 2)
Absence seizures	38.5% (n = 5)	15.5% (n = 2)	23% (n = 3)	7.5% (n = 1)	15.5% (n = 2)

One patient on polytherapy had a 75% reduction in seizure frequency for all three subtypes, whereas the other patient showed inadequate response. There were no ZNS-VPA interactions.

Discussion

ZNS is a novel antiepileptic drug (AED) classified as a sulfonamide, and having multiple mechanisms of action. It has been available in South Korea and Japan since 1989, and has been extensively used in children, with good efficacy and tolerability, to treat partial and generalized-onset seizures [3]. It was approved in the United States in the year 2002 as adjunctive therapy for partial onset seizures in adults. No controlled studies of zonisamide in children have been completed in the US. Eighty five to 90% of patients with JME become seizure-free with VPA monotherapy [4]. Most patients with JME, however, require lifelong treatment because seizures invariably return after withdrawal of therapy. JME is difficult to treat in about 15% of cases. The predictors of pharmaco-resistance include 1) co-existence of all three seizure types, and 2) existence of associated psychiatric problems [5]. Even though VPA has been shown to be effective in JME, the side-effect profile may make some patients non-compliant, with inadequate seizure control. Nonrandomized trials suggest that lamotrigine and topiramate may also have efficacy in the treatment of JME, however as yet, there are no definitive studies available [2].

The mechanisms of action of ZNS include blocking the low-threshold, T-type calcium channels, which may provide an explanation of its efficacy against absence seizures and JME [6]. It is not highly protein bound (40%), has a long half-life ($t_{1/2} = 49.7$ to 68.2 hours), and steady-state conditions may be achieved within two weeks of reaching a stable dose [7]. Children may require higher doses, but the average dose ranged from 6-12 mg/kg/day, starting at 1 mg/kg/day and increasing by 1 to 2 mg/kg/day every two weeks.

We chose ZNS in our patients with JME for several reasons. ZNS has a long half-life, thus requiring once a day dosing, with ease of titration of doses. There were more females (12) in our series than males, and this may be related to the side-effect profile of valproate (weight-gain, tremors, and alopecia) [8]. Adequate seizure control in this group was achieved within four to eight weeks of attaining an average maintenance dose of ZNS. Overall, 80% of JME patients treated with ZNS showed good control ($\geq 50\%$ seizure reduction). In addition, better seizure control was observed as regards to GTC and myoclonic seizures (69% and 62% respectively becoming seizure-free), and to a lesser extent against absence seizures (38% becoming seizure-free) (figure 1). Side effects of ZNS in children include somnolence, anorexia, exanthema, cognitive impairment, ataxia, renal calculi, etc, and are encountered in about 5% of patients [3]. In our series, 20% experienced side effects during the escalation phase, which resolved after attaining the maintenance dose. As seen in the Japanese data, ZNS was ineffective in controlling seizures in 7% cases of JME, requiring a switch to a different medication [3]. Of our 13 patients on ZNS monotherapy, one (7.7%) did not respond and was switched to VPA. Of our two patients on polytherapy (ZNS and VPA), one (50%) experienced less than 50% reduction in seizure frequency). ZNS-VPA polytherapy was well tolerated without any pharmacological interaction.

Although there is extensive Japanese literature on efficacy of ZNS in generalized epilepsies, we believe that this is the first series in the English literature documenting the efficacy, safety, and tolerability of ZNS in JME.

In conclusion, in our open-label, small series of JME patients, ZNS demonstrated to be an effective and well-tolerated therapeutic option. The ease of titration, good safety profile, once a day dosing, lack of significant drug interaction, and short latency for onset of efficacy makes ZNS an attractive alternative choice in the treatment of JME. Additional, prospective, randomized, double-blind, multi-center studies need to be performed to confirm our observations. □

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