

A review of safety and efficacy of zonisamide for treatment of pediatric partial epilepsy

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Introduction: Zonisamide is one of the most promising antiepileptic drugs that was first approved in Europe as add-on therapy in adult patients with partial seizures and recently approved as monotherapy. More recently, zonisamide has been approved for pediatric use in the UK and can now be prescribed for partial epilepsy in adolescents and children aged 6 years and above.

Aim: This paper systematically reviews the current evidence on the efficacy and tolerability of zonisamide as monotherapy and adjunctive therapy for pediatric partial epilepsy.

Methods: Relevant randomized clinical trials and open-label studies were identified by a structured PubMed search, supplemented by an additional hand search of reference lists and authors' files.

Results: PubMed database search yielded 12 (four double-blind randomized, eight open-label) clinical trials published over the last 10 years (January 2004 to September 2014) and the pooled analysis included a total of 1,555 patients treated with zonisamide.

Conclusion: Zonisamide currently represents a robust option in the treatment of children with partial epilepsy, based on its multiple mechanism of action and efficacy in different situations.

Keywords: children, clinical trial, partial seizures, tolerability

Introduction

Zonisamide is a benzisoxazole derivative chemically unrelated to other anticonvulsant agents. It shows a broad spectrum of mechanistic actions that, in part, overlap the actions of phenytoin, carbamazepine, and valproate.¹ These include reduction of sustained high-frequency repetitive firing of sodium-dependent action potentials, inhibition of low-threshold T-type calcium currents, a modulatory effect on GABA-mediated neuronal inhibition, inhibition of glutamate release, and weak inhibition of carbonic anhydrase. The latter may contribute to some of the side effects of this drug. Zonisamide also alters the metabolism of dopamine, 5-hydroxytryptamine, and acetylcholine.^{2,3} There is also evidence from in vitro studies that zonisamide may have neuroprotective properties.⁴

Zonisamide is completely absorbed, with a bioavailability of 100% and reaching maximum plasma concentration in 2–5 hours of oral ingestion of a dose of 200–400 mg. This rate of absorption is slightly slower with food intake. Zonisamide is primarily excreted through the urinary tract, with a half-life of 63–69 hours. The half-life is decreased with coadministration of other isoenzyme-inducing antiepileptic drugs (AEDs), such as phenytoin, phenobarbital, carbamazepine, and sodium valproate, but still remains above 24 hours.² Zonisamide is metabolized by the action of isoenzyme

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3A4 in the liver, via the cytochrome P450 pathway. Since this process may be affected by other AEDs if used concomitantly, zonisamide dose adjustment may be required when used as an adjunctive treatment.⁵ In particular, zonisamide metabolism is affected by other AEDs, namely, hepatic enzyme inducers such as phenytoin and carbamazepine, which significantly reduce zonisamide serum levels.^{6–8}

Zonisamide is a viable first-line and adjunctive therapy for a wide range of seizures. In particular, ZNS may be effective in generalized forms of epilepsies, featuring myoclonic and/or absence seizures, such as in patients with juvenile myoclonic epilepsy and progressive myoclonic epilepsy, although studies of these included a heterogeneous group of patients.^{9–11}

Zonisamide is indicated in the EU as monotherapy in the treatment of partial seizures with or without secondary generalization in adults with newly diagnosed epilepsy, and as adjunctive therapy to other AEDs in the treatment of adults with partial seizures with or without secondary generalization.¹² More recently, zonisamide has been approved for pediatric use in the UK and can now be prescribed for partial epilepsy in adolescents and children aged 6 years and above.^{13–16} Phase II studies in pediatric patients indicate that adjunctive zonisamide has an acceptable safety profile in this population and a pharmacokinetic profile similar to that observed in adult patients.¹⁷ However, there is a need for studies to determine the safety, efficacy, and tolerability of newer AEDs, such as zonisamide, in children of varying ages.

This paper systematically reviews the current evidence on the efficacy and tolerability of zonisamide as monotherapy and adjunctive therapy for the treatment of pediatric partial epilepsy.

Methods

Relevant randomized clinical trials and open-label studies in add-on or monotherapy including pediatric patients were identified by a structured PubMed search, supplemented by an additional hand search of reference lists and authors' (MSV, PS) files. Keywords for the database search included "epilepsy", "pediatric", "zonisamide", "clinical trial", "placebo-controlled", "open-label", and "therapy".

Results

PubMed database search yielded 12 (four double-blind randomized, eight open-label) clinical trials published over the last 10 years (January 2004 to September 2014) and the pooled analysis included a total of 1,555 patients treated

with zonisamide (Table 1). In the large majority of studies, zonisamide was administered in patients with drug-resistant epilepsy, refractory to at least two AEDs.

Zonisamide as adjunctive therapy

The efficacy of zonisamide as add-on treatment in drug-resistant pediatric patients with focal seizures has been investigated in a large double-blind, placebo-controlled randomized trials in Europe and India.¹⁸ The authors recruited 207 (aged 6–17 years) patients who were taking one to two AEDs for focal seizures with or without secondary generalization. Dose adjustments were made during a titration phase, to a target dose of 8 mg/kg/day (maximum 500 mg/day). Responder rate was assessed during the 12-week maintenance phase, and 50% of the zonisamide group had achieved a $\geq 50\%$ reduction in partial seizure frequency, compared to 31% in the placebo group. The median decrease in seizure frequency from baseline was 50% for zonisamide, compared to 24.5% for placebo, a difference that reached statistical significance. The authors concluded that adjunctive zonisamide treatment was shown to be effective and well tolerated in pediatric patients with partial epilepsy. There were three open-label studies involved mixed cohorts of both children and young adults.^{19–21} Coppola et al²⁰ reported seizure freedom in 10.9% of their sample, and a responder rate in 37.8%, at a mean dose of 5.7 mg/kg/day as an add-on therapy in refractory partial epilepsy. Kluger et al¹⁹ assessed the use of zonisamide in 24 patients with partial epilepsy. Responder rates were 58.3% at 8 weeks and 41.7% at 18 months. Guerrini et al's²¹ extension study reported seizure freedom in 16% and a responder rate in 56.3% at dose of 8 mg/kg/day as an add-on therapy in refractory epilepsy. Another study looking at the use of zonisamide as an adjunctive therapy in pediatric populations reported a median decrease in seizure frequency of 1.3% per week, which approached statistical significance ($P=0.056$). Responder rate was not reported in this study.²²

Furthermore, a retrospective case-notes review of pediatric patients treated with adjunctive zonisamide found a low responder rate of 23.5% whereas the incidence of adverse effects was lower than other studies.²³ Two retrospective studies were undertaken in patients with intractable epilepsy.^{24,25} In the first study, 35 children (age: 8 months to 22 years; mean: 9 years) showed good to excellent seizure control (50%–100% reduction) in 42.8% of the all treated patients. Adverse effects were not associated with a higher mean dose. In the second retrospective study, 48.5% of 163 patients experienced a reduction in seizure frequency of more than

Table 1 Clinical trials of zonisamide in pediatric patients with partial epilepsy

Authors	Nationality	Population (age)	Dose	Monotherapy/ add-on	Efficacy	Adverse events (% of patients)
Randomized, placebo-controlled trials						
Guerrini et al ¹⁸	Europe, India	207 patients (aged 6–17 years), refractory partial-onset epilepsy	8 mg/kg/day (max: 500 mg/day)	Add-on	Responder rate =50.0% Seizure freedom =14.0%	55.1
Lu et al ⁴²	People's Republic of China	102 patients (aged 18–70 years), refractory partial-onset epilepsy	300 or 400 mg/day	Add-on	300 mg responder rate =55.2% Seizure freedom = NA 400 mg responder rate =56.5% Seizure freedom = NA	78.9
Brodie et al ³⁹	Europe, South Africa	351 patients (aged 12–77 years), refractory partial-onset epilepsy	100, 300, or 500 mg/day	Add-on	Seizure freedom = NA 100 mg responder rate =29.6% Seizure freedom = NA 300 mg responder rate =42.2% Seizure freedom = NA 500 mg responder rate =52.5% Seizure freedom = NA	100 mg group =67.9 300 mg group =70.9 500 mg group =81.4
Sackellares et al ⁴¹	USA	152 patients (aged 17–67 years), refractory partial epilepsy	400–600 mg/day	Add-on	Responder rate =26.9% Seizure freedom = NA	70.5
Open-label trials						
Guerrini et al ²¹	Europe, India	144 patients (aged 6–18 years) refractory partial epilepsy	8 mg/kg/day (max: 500 mg/day)	Add-on	Responder rate =56.3% Seizure freedom =16.0%	55.1
Wallander et al ⁴³	Sweden	75 patients (aged 0–17 years) with refractory partial or generalized epilepsy	6–8 mg/kg/day	Add-on	Responder rate =35% Seizure-freedom = NA	44.0
Eun et al ³¹	Korea	125 patients (aged 3–15 years) with newly diagnosed partial or generalized epilepsy	3–4 to 6–8 mg/kg/day	Monotherapy	Responder rate = NA Seizure freedom =63.1% (low dose); 57.6% (high-dose)	NA
Shinnar et al ²²	Europe, USA	109 patients (aged 3–15 years), partial and generalized refractory epilepsy	8.5 mg/kg/day (mean dose)	Add-on	Median decrease in seizure frequency =1.3% per week	NA
Coppola et al ²⁰	Italy	82 patients (aged 3–34 years), partial and generalized refractory epilepsy	5.7 mg/kg/day	Add-on	Responder rate =37.8% Seizure freedom =10.9%	NA
Kluger et al ¹⁹	Germany	24 patients (aged 2–40 years), 75% focal, 12.5% generalized, 12.5% refractory status epilepticus	7.7 mg/kg/day	Add-on	Responder rate =58.3% Seizure freedom =4.2%	46.0
Kothare et al ³⁰	USA	69 patients (mean age 13.2 years), 61% idiopathic generalized epilepsy, 4% symptomatic generalized epilepsy, 35% partial-onset epilepsy	4.9 mg/kg/day (range 2–13 mg/kg/day)	Monotherapy	Responder rate =75.4% Seizure freedom =67%	26.1
Kim HL et al ³³	USA	62 patients (aged 1–18 years), partial and generalized refractory epilepsy	5–10 mg/kg/day	Monotherapy and add-on	Responder rate =21% Seizure freedom =25.8%	61.8

(Continued)

Table 1 (Continued)

Authors	Nationality	Population (age)	Dose	Monotherapy/ add-on	Efficacy	Adverse events (% of patients)
Wifong ²²	USA	131 patients (aged 1–22) Partial and generalized refractory epilepsy	100–800 mg/day (max: 54 mg/kg/day)	Monotherapy	Responder rate =77.1% Seizure freedom =29.8%	2.3
Seki et al ²⁹	Japan	77 patients (aged 8 months–15 years): – 44 patients with cryptogenic/symptomatic partial epilepsy – 11 patients with cryptogenic/symptomatic generalized epilepsy – 4 patients with idiopathic partial epilepsy – 9 patients with idiopathic generalized epilepsy	12 mg/kg/day	Monotherapy	Responder rate = NA Seizure freedom =79%	39.0

Abbreviation: NA, not available.

50% after ZNS adjunctive therapy, with 25 patients (15.3%) being seizure-free.

Zonisamide as monotherapy

There have been multiple retrospective chart-review studies suggesting the potential efficacy and safety of zonisamide as monotherapy in refractory partial seizures in adults and across the lifespan.^{26–28} Overall, the evidence to support the use of zonisamide in pediatric populations, particularly as monotherapy, is still limited. The available studies are summarized in Table 1.

Three open-label studies considered the use of zonisamide as monotherapy in children.^{29–31} In these studies, seizure freedom ranged from 57% to 79% of patients; no significant differences in seizure-freedom rates were found between low- or high-dose zonisamide. Another open-label trial, including both pediatric and young adult population (aged 1–22 years), reported a lower rate of seizure freedom (29.8%) whereas a total of 101 patients (77.1%) achieved a 50% or greater decrease in seizure frequency (ie, responders).³²

An additional two open-label studies evaluated the efficacy of zonisamide in children with epilepsy, but did not report separated results for patients on monotherapy or polytherapy.^{33,34}

The large variability among the rate of seizure-free patients between the different trials can be explained by different factors, including their open-label nature and, mostly, the recruitment of adult patients in some studies.

In summary, the available literature suggests that zonisamide can be useful as monotherapy in pediatric patients who had received no previous treatment and in newly diagnosed partial epilepsy. However, further evaluation is needed with respect to efficacy, safety, and effectiveness in this population.

Safety and tolerability data

The pharmacokinetic profile of zonisamide has a number of advantages. First, the long half-life allows once-daily dosing, improves patient compliance, and suggests a low impact of missed doses on seizure control. However, it has to be acknowledged that the long half-life may represent a limitation when a rapid onset of action is required. In general, the majority of the reviewed trials suggest that zonisamide is an effective and well tolerated treatment option for pediatric patients with focal epilepsy. The occurrence of side effects in the different trials ranged from 26% to 81.4%.^{18–20} Side effects were usually mild in severity and resolved shortly after

discontinuation of the drug. The most frequently reported side effects included decreased appetite, decreased weight, somnolence, nausea/vomiting, and diarrhea; additionally, both psychiatric (eg, psychosis and suicidal ideation) or cognitive adverse effects were reported, and the high-dose group was significantly worse than that in the low-dose group, but that is in line with other new-generation AEDs.^{29,35} In many studies, patients experienced side effects during the escalation phase, of which the majority resolved during the maintenance of the medication.³⁰

Teratogenic effects of zonisamide were not clearly defined from these studies even if the present data do not indicate that the risk of teratogenicity is greater than that of other conventional AEDs.³⁶ However, such risk cannot be neglected even at therapeutic dosages or concentrations of ZNS, especially in patients receiving polytherapy. In addition, postmarketing studies conducted in Japan revealed that pediatric patients on zonisamide have an increased risk for oligohydrosis and hyperthermia. Therefore, it is advisable that patients would be monitored closely for signs of decreased sweating and increased body temperature, especially in warm or hot weather.³⁷

Discussion

Zonisamide (3-sulfamoylmethyl-1, 2-benzisoxazole) is an AED with a broad spectrum of mechanistic action that has demonstrated good efficacy in controlling seizures as an add-on therapy in adult and pediatric epilepsy.^{25,38–40} Despite some methodological drawbacks, our review of available literature supports the view that adjunctive zonisamide therapy is effective and well tolerated in pediatric patients with refractory partial epilepsy, and could therefore prove to be a useful new treatment option for this patient population. The evidence in support of the use of zonisamide in pediatric populations, as monotherapy, is still limited, indicating the need for further investigation in randomized, controlled trials. In the available clinical trials, the titration schedule of the drug varied but, in general, the recommended dosage escalation starts at 1 mg/kg/day and increases at weekly intervals in increments of 1 mg/kg to the target dose of 6–8 mg/kg/day up to a maximum dose of 300–500 mg/day in two daily doses. Of note, Sackellares et al showed that a slower (or 2-weekly) titration of zonisamide was associated with fewer adverse effects.⁴¹

The tolerability profile of zonisamide was high in the large majority of the studies, both in add-on and monotherapy. From the review of the literature (Table 1), the risk of significant side effects is higher in patients in polytherapy.

Notably, there are very limited data from clinical studies in patients with a body weight of less than 20 kg. Therefore, children aged 6 years and above and with a body weight less than 20 kg should be treated with caution.

In conclusion, zonisamide, as adjunctive therapy, and potentially as monotherapy, is successful in treating pediatric patients with refractory partial seizures because of its structural and mechanistic profile, safety, tolerability, and wide spectrum of antiseizure activity. The challenge for new more-efficacious, more-specific, and better-tolerated drugs is also continuing. However, the ultimate goal should be to not only render the patients seizure-free, but also to allow for improvement of quality of life of individuals and to reduce the costs of medical care.

Disclosure

The authors report no conflict of interest in this work.

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