Original article

Epileptic Disord 2009; 11 (1): 61-6

Efficacy and tolerability of zonisamide in idiopathic generalized epilepsy

Ainhoa Marinas[1], Vicente Villanueva[2], Beatriz G. Giráldez[1], Albert Molins[3], Javier Salas-Puig[4], Jose M. Serratosa[1]

[1] Fundación Jiménez Díaz, Madrid
[2] Hospital La Fe, Valencia
[3] Hospital Josep Trueta, Girona
[4] Hospital Central de Asturias, Oviedo, Spain

Received August 14, 2008; Accepted December 22, 2008

ABSTRACT – *Objective*. The objective of this study is to evaluate the efficacy and safety of zonisamide (ZNS) for the treatment of idiopathic generalized epilepsies (IGEs). *Methods*. Thirteen patients with different types of IGEs who were treated with ZNS between the years 2006 and 2008 were identified. Efficacy and tolerability were assessed at months 6 and 12 post-treatment. Response was defined as a 50% or greater reduction in seizure frequency. *Results*. Twelve patients (92.3%) continued with ZNS at month 6, and 11 (84.6%) at month 12. Mean daily dose was 319 mg (range 100-500 mg/d). Response was achieved at month 6 in eight of the 12 patients that continued with ZNS (66.6%), of which 7 were seizure-free (58.3%). At month 12, eight of the 11 patients that continued with ZNS were responders (72.7%) and 6 were seizure-free (63.6%). For different types of seizures, better responses were observed for absences and generalized tonic-clonic seizures. Four out of 13 patients (30.7%) experienced adverse events and in two (15.3%), these led to withdrawal. *Conclusion*. In this retrospective study, ZNS showed efficacy and tolerability for the treatment of different types of IGEs. Limitations include a small sample size and a relatively short period of follow-up. Our results are promising and justify the need for prospective controlled trials in IGE.

Key words: zonisamide, idiopathic generalized epilepsy, generalized seizures, myoclonic, absence, tonic-clonic seizures

The idiopathic generalized epilepsies (IGEs) are a group of common epilepsies that affect mainly children and adolescents and have a significant impact on their quality of life. The idiopathic generalized epilepsies (IGEs) are estimated to account for 15-20% of all epilepsies (Jallon and Latour 2005). Response to antiepileptic drugs (AEDs) is usually good, but pharmacoresistance occurs in 10-20% of patients (Benbadis 2005). The classic choice of AEDs includes valproic acid (VPA), clonazepam (CZP) and ethosuximide. Recently, lamotrigine (LTG), topiramate (TPM) and levetiracetam (LEV) have been shown to also be effective in some

Correspondence:
Dr J.M. Serratosa
Epilepsy Unit,
Neurology Service,
Fundación Jiménez Díaz,
Avda Reyes Católicos, 2,
28040 Madrid, Spain
<serratosa@telefonica.net>

doi: 10.1684/epd.2009.0239

The work was presented as poster presentation at the 8th European Congress on Epileptology (Berlin, September 2008)

generalized seizures in patients with IGE. However, in case of lack of efficacy or of adverse events, new AEDs may be needed.

Zonisamide (ZNS) is an AED with proven efficacy as adjunctive therapy in patients with partial seizures (Brodie *et al.* 2005, Faught *et al.* 2001, Sackellares *et al.* 2004, Schmidt *et al.* 1993). To date, no double-blind, randomised, controlled trial has evaluated its efficacy in idiopathic generalized epilepsy (French *et al.* 2004a, b). However, evidence from long and extensive clinical use of ZNS in Japan, and data from trials conducted prior to registration, post-marketing surveillance studies and independent reports indicate that ZNS is also efficacious in treating generalized-onset seizures both in adult and paediatric patients, showing response rates of 66-78% in patients with IGEs and 58-87.5% for different types of generalized seizures (Ohtahara 2006, Yagi and Seino 1992, Yamauchi and Aikawa 2004). Better responses were found when ZNS was administered as monotherapy (Yagi and Seino 1992, Yamauchi and Aikawa 2004). There are also some case reports, observational studies and a few open-label studies that suggest that ZNS may be effective for the treatment of IGEs (Kothare *et al.* 2004, Wilfong and Schultz 2005, Kothare *et al.* 2006, O'Rourke *et al.* 2007).

One of the mechanisms of action of ZNS that supports its efficacy in generalized seizures is blockage of the low-threshold T-type calcium channel, which may confer efficacy against absence seizures (Suzuki *et al.* 1992, Kito *et al.* 1996, Futatsugi and Riviello 1998, Kim *et al.* 2001).

To advance our knowledge of the efficacy of ZNS for the treatment of IGEs, we retrospectively analyzed 13 patients with different types of idiopathic generalized epilepsy that were treated with ZNS. The objective of this study was to evaluate the efficacy and safety of ZNS for the treatment of IGEs.

Patients and methods

All patients with IGE from four hospitals in Spain who were treated with ZNS between the years 2006 and 2008 were identified. The accuracy of the diagnosis of IGE and subtypes was reviewed and assessed according to ILAE criteria (Commission 1989). Patient charts were reviewed for demographic characteristics, seizure types and frequency, date of onset for each type of seizure, electroencephalographic findings, reason for introducing ZNS (pharmacoresistancy or intolerance to other AEDs), previous and concomitant antiepileptic drug therapy, ZNS dosage, duration of ZNS therapy, subjective patient reports of ZNS efficacy and adverse events. Safety, efficacy and tolerability were assessed at months 6 and 12. Data were analysed using descriptive statistics. Efficacy was assessed by comparing monthly seizure frequency during the last 3 months (6 month follow-up group) and last 9 months (12 month follow-up group) with the seizure frequency during the first pre-ZNS year. Response was defined as a 50% or greater reduction in seizure frequency.

Results

The characteristics of the patients and follow-up data are summarized in *table 1*. Thirteen patients were identified (four males and nine females with a mean age of 28; ranging between 10-53 years). Three patients had childhood absence epilepsy (CAE), two had juvenile absence epilepsy (JAE), six had juvenile myoclonic epilepsy (JME) and two idiopathic generalized epilepsy (IGE) with generalized tonic-clonic (GTC) seizures only. Mean age at seizure onset was 12.4 years old (ranging between 7-19 years). Nine patients were pharmacoresistant and presented frequent seizures: one patient presented at least one seizure per day (absences), seven patients presented at least one seizure per month (two patients with absences, two with myoclonic seizures, one with generalized tonic-clonic seizures, one with generalized tonic-clonic and absence seizures, one with generalized tonic-clonic and myoclonic seizures), and one patient presented at least one seizure every two months (myoclonic seizures). Four patients were seizure free with VPA treatment. In these patients ZNS was added to replace VPA due to intolerable adverse events. One of these four patients was switched to ZNS. For the other three patients the dose of VPA was reduced with the objective of complete withdrawal.

ZNS was introduced at a starting daily dose of 25-100 mg/day. The mean daily dose was 319 mg (range 100-500 mg/day). ZNS was initially administered as add-on therapy in all patients. However, during follow-up two patients were switched to ZNS monotherapy. Concomitant AEDs included VPA, LTG, LEV, TPM and CZP. During ZNS therapy changes in patients' concomitant AED regimens were performed.

Patients were exposed to ZNS for two to 22 months (mean duration of exposure being 12 months). Twelve patients (92.3%) continued with ZNS at month 6 (one patient withdrew due to adverse events) and 11 (84.6%) at month 12 (two patients withdrew due to adverse events).

Efficacy

Response was achieved at month 6 in eight of the 12 patients (66.6%) that continued with ZNS, of which seven (58.3%) were seizure-free. At month 12, eight of the 11 (72.7%) patients that continued with ZNS were responders, of which six (63.6%) were seizure-free. Four patients were seizure-free at baseline with VPA monotherapy. Three of these four remained seizure-free after receiving ZNS (one switched to ZNS, and two continued to be

Table 1. Characteristics of the patients and follow-up data.

Pt	Sex	Age	Age at seizure onset	Type/s of epilepsy	Seizure type	Seizure frequency	EEG	Therapy at the onset	Current therapy	Current ZNS daily dose mg	Follow-up duration	Seizure reduction (%) 6 months	Seizure reduction (%) 12 months	Adverse events
1	F	10	9	CAE	Absence	Absence-daily	GSW	VPA	VPA + ZNS	100	16 months	Seizure free	Seizure free	
2	M	43	7	JAE	Absence, GTC	GTC-monthly Absence-monthly	GSW, PSW	LTG + LEV	LTG + LEV + ZNS	400	22 months	> 50% reduction	50% reduction GTC. >50% reduction absences	
3	F	53	17	JME	Myoclonic, GTC	Myoclonic-monthly. GTC-free	BFSW, PSW	VPA + LTG + TPM + CZP	VPA + LTG + CZP + ZNS	300	14 months	No change	No change	Yes
4	F	47	7	CAE	Absence, GTC	Absence-monthly GTC-free	PSW	VPA + LEV	VPA + LEV + ZNS	300	14 months	Seizure free	Seizure free	
5	F	32	17	JAE	Absence, GTC	Absence-monthly GTC-every two months	GSW, PSW	CBZ + CZP	ZNS + CZP	500	15 months	No change GTC. Worsening absences	Worsening GTC. >50% reduction absences	
6	M	15	13	JME	Myoclonic, GTC	Myoclonic every two months GTC-free	PSW	VPA	ZNS	300	12 months	Seizure free	Seizure free	
7	M	29	11	IGE	GTC-only	GTC-free	PSW	VPA	VPA + ZNS	300	12 months	Continued seizure free	Continued seizure free	Yes
8	F	48	12	IGE	GTC-only	GTC-free	Normal	VPA	VPA + ZNS	400	12 months	Continued seizure free	Continued seizure free	
9	F	18	14	JME	Myoclonic	Myoclonic-free	GSW, PSW	VPA	ZNS	400	12 months	Continued seizure free	Continued seizure free	
10	F	18	15	JME	Myoclonic	Myoclonic-free	GSW, PSW	VPA	VPA + ZNS	200	2 months. Withdrawal adverse events	_	_	Yes. Withdrawal
11	F	21	7	CAE	GTC, Absence	GTC-monthly Absence - annual	GSW	LTG + LEV	LTG + ZNS	400	16 months	GTC free. Worsening absences	GTC free. Absences no change	
12	F	26	19	JME	Myoclonic, GTC	Myoclonic-monthly. GTC-every two months	GSW, PSW	TPM + LEV	TPM + ZNS	300	12 months	Seizure free	Seizure free	
13	M	23	13	JME	Myoclonic, GTC	Myoclonic-weekly. GTC monthly	GSW, PSW	VPA + CZP	VPA + CZP + ZNS	150	8 months. Withdrawal adverse events and inefficacy	No change	_	Yes. Withdrawal

BFSW: bifrontal spike and wave discharge; CAE: childhood absence epilepsy; CZP: clonacepam; GSW: generalized spike-and-wave discharge; GTC: generalized tonic-clonic; IGE: idiopathic generalized epilepsy; JAE: juvenile absence epilepsy; JME: juvenile myoclonic epilepsy; LEV: levetiracetam; LTG: lamotrigine; PSW: polyspike-and-wave discharge; TPM: topiramate; VPA: valproate; ZNS: zonisamide.

seizure-free with less than half the dose of VPA). In one of the four patients ZNS was withdrawn at month 2 because of adverse events and efficacy was not assessed.

At the end of the study two patients with JME were on monotherapy with ZNS: one became seizure-free after switching to ZNS and the other one, previously seizure-free on VPA, remained seizure-free.

According to seizure types, response was observed for absences in 3/5 patients (60%) at month 6 and 4/5 (80%) at month 12. For generalized tonic-clonic seizures, response was obtained in 7/10 patients (70%) at months 6 and 12, and for myoclonic seizures, in 3/5 patients (60%) at months 6 and 12.

With regards to epilepsy syndromes, two of the three patients with CAE (66.6%) were seizure-free after 12 months with ZNS. One of two patients with JAE experienced a reduction of more than 50% in absence seizure frequency. Three of the five patients with JME (60%) that continued with ZNS at month 6 were seizure-free, and for two, no change in seizure frequency was observed. Three of the four patients with JME (75%) that continued at month 12 were seizure-free, and one showed no change in seizure frequency. Both patients with IGE with GTCs only, remained seizure-free at months 6 and 12.

In one patient with CAE a five hour video-EEG monitoring was performed before the introduction of ZNS. Very frequent generalized spike-wave discharges during wakefulness and sleep and numerous typical absence seizures were recorded. A 24 hour video-EEG monitoring performed one month later showed no absence seizures and no epileptiform discharges. Video-EEG Monitoring was also performed in patient 5, eight months before receiving ZNS. Frequent generalized epileptiform activity was observed during wakefulness and sleep. A second video-EEG monitoring was performed five months after initiating ZNS treatment. This second study showed an improvement with generalized epileptiform activity only during sleep and not during the awake state.

Tolerability

Four patients out of 13 (30.7%) experienced adverse events. There were no severe adverse events. The most common adverse events were loss of appetite and weight loss in 3/13 patients. One patient (1/13) experienced headaches, somnolence and irritability. In two patients (15.3%), adverse events led to ZNS withdrawal with remission of the symptoms. These two patients received concomitant AED treatment of either VPA or VPA and CZP.

Discussion

There are few open-label studies and anecdotal case reports in the literature supporting the effectiveness of ZNS for the treatment of the idiopathic generalized epilepsies, however, there is a lack of controlled studies. Data from registration trials in Japan, which included 286 patients with generalized epilepsies (both children and adults), showed responses to ZNS of 66% in this group of patients (≥ 50% reduction in baseline seizure frequency; Ohtahara 2006, Yagi and Seino 1992). In the post-marketing surveillance study in Japan, the responder rates were 78% for patients with IGEs and 58-75% for different types of generalized seizures (similar rates for the subgroup of children; Ohtahara 2006, Yamauchi and Aikawa 2004, Iinuma and Haginoya 2004). Higher response rates have been observed in patients with generalized seizures with ZNS monotherapy (83-93%; Yamauchi and Aikawa 2004, Yagi and Seino 1992). Additional independent studies in children have shown a wide range of responder rates from 18% in small series of children on ZNS polytherapy to 50-90% in children with ZNS monotheraphy (Ohtahara 2006, Glauser and Pellock 2002, Seki *et al.* 2004, Kothare *et al.* 2006). In our study, 66.6-70% of patients treated with ZNS showed a good response (≥ 50% seizure reduction) after 12 months of follow-up, and 58.3-60% were seizure-free at month 12.

The dose of ZNS in this study ranged from 100 to 500 mg/day, similar to the dose published for adults and children (Ohtahara 2006, Kothare *et al.* 2006, Wilfong and Schultz 2005, Kothare *et al.* 2004, Glauser and Pellock 2002).

Most patients in our study presented with JME. In this group of patients, three of five patients (60%) that continued in the study at month 6 were seizure-free and three of four patients (75%) were seizure-free at month 12. Two patients remained seizure-free with ZNS monotherapy at month 12. A study by Kothare *et al.* (2004), in 15 patients with JME receiving ZNS for 2-24 months, showed similar results; 50% or greater reduction in seizure frequency was observed for 50% of the patients with polytherapy and 80% of the patients with monotherapy.

Regarding seizure types, our study showed slightly better responses for absences and GTC seizures. In the post-marketing study in Japan, ZNS showed higher efficacy against absences, followed by clonic and tonic-clonic seizures (Ohtahara 2006, Yamauchi and Aikawa 2004, Iinuma and Haginoya 2004). Kothare *et al.* (2004) found better responses for GTC and myoclonic seizures than for absences in the group of JME patients. However, O'Rourke *et al.* (2007) showed better response rates for myoclonic and absence seizures than for GTC seizures in a small series of JME patients.

In our study, response was observed for typical absences in 3/5 (60%) patients at month 6 and 4/5 (80%) at month 12. These data are consistent with those published in some series with a small number of patients suggesting that ZNS may be efficacious in treating typical absence seizures. For these small series studies (n = 4-8) responder rates were of 50-87.5% (Yamauchi and Aikawa 2004,

Iinuma and Haginoya 2004, Yagi and Seino 1992). Wilfong and Schultz (2005) reported a 100% reduction in absence seizure frequency in 51% of 45 young patients. However, there are no details regarding whether the absences were typical or atypical.

In one patient with CAE, 24 hour video-EEG recording was performed before and one month after introducing ZNS. No absence seizures and epileptiform discharges were found after treatment with ZNS. Szaflarski (2004) also reported a patient with JME that had a significant improvement in the EEG recording after introducing ZNS. Video-EEG monitoring was also performed in patient 5, eight months before starting ZNS treatment. Frequent generalized epileptiform activity was observed during wakefulness and sleep. A second video-EEG monitoring was performed five months after initiating ZNS treatment. This second study showed an improvement with generalized epileptiform activity only during sleep and not during the awake state.

ZNS has been shown to have a well-defined safety profile. In Japan, where an extensive clinical experience has been accumulated (for a review see Arzimanoglou and Rahbani, 2006) ZNS has been shown to be well tolerated. In the post-marketing surveillance study in Japan, 31.5% of patients receiving ZNS for up to three years reported adverse events. This percentage was lower for children (26.2%) than for adults (39.9%; Ohtahara and Yamatogi 2004). Other studies in children on ZNS treatment have reported adverse events in 24-42.2% of patients (Iinuma and Haginoya 2004, Kothare *et al*. 2006, Seki *et al*. 2004, Wilfong and Schultz 2005). The incidence of adverse events is lower among patients on ZNS monotherapy than for those on polytherapy (Ohtahara and Yamatogi 2004, Iinuma and Haginoya 2004). In the study on JME by Kothare *et al*. (2004), adverse events were reported in 20% of the patients. Central nervous system (CNS)-related adverse events (cognitive impairment, somnolence, decreased spontaneity, etc) have been the most commonly reported, followed by gastrointestinal adverse events (mainly anorexia and weight loss; Ohtahara 2006; Kothare *et al*. 2006, Seki *et al*. 2004, Wilfong and Schultz 2005, Kothare *et al*. 2004). In our series, 30.7% of patients experienced adverse effects and these were usually mild leading to withdrawal in only two patients. As previously published, the main adverse effects were gastrointestinal and neurological.

The limitations of this study include a small sample size and a short period of follow-up. Although 6 -12 months is not a long follow-up period for IGEs, the high frequency of seizures prior to the introduction of ZNS (monthly in most patients) allowed us to assess efficacy during this period of time. Other studies reported similar follow-up periods of two to 24 months (Kothare *et al*. 2004, Wilfong and Schultz 2005). Response was evaluated in patients that continued in the study and this could explain the better responses at month 12 than month 6. However, improvement over time has already been described (O'Rourke *et al*. 2007). For four patients, the dose of concomitant AED varied. Except for two patients, it may be that the previous drug worsened the epilepsy (in on patient an attempt to withdraw TPM failed due to seizure worsening and the other one was on a very low dose of carbamazepine). Although four patients were seizure-free when ZNS was introduced, they remained seizure-free even when the dose of the concomitant AED was reduced by more than half (two remained seizure-free on ZNS monotherapy). Most patients in this study were refractory and received polytherapy. As other authors have reported (Yamauchi and Aikawa 2004, Yagi and Seino 1992), lower responses were found in patients receiving polytherapy compared with those receiving ZNS monotherapy, and a better response may be expected in IGE patients receiving ZNS monotherapy.

In conclusion, in this retrospective study, ZNS showed efficacy and was a well-tolerated therapeutic option in patients with IGE. Prospective randomized, double-blind studies are needed to confirm these data. □

Disclosures. All authors have received speaker or consulting fees from one or more of the following compagnies : GSK, Pfizer, Esai, Johnson and Johnson, UCB and Novartis.

References

Arzimanoglou A, Rahbani AZ. Zonisamide for the treatment of epilepsy. *Expert Rev Neurother* 2006; 6: 1283-92.

Benbadis SR. Practical Management Issues for Idiopathic Generalized Epilepsies. *Epilepsia* 2005; 46: 125-32.

Brodie MJ, Duncan R, Vespignani H, *et al*. Dose-dependent safety and efficacy of zonisamide: a randomized, double-blind, placebo-controlled study in patients with refractory partial seizures. *Epilepsia* 2005; 46: 31-41.

Commission on classification and terminology of the International League Against Epilepsy, 1989. Proposal for revised classification of epilepsy and epileptic syndromes. *Epilepsia* 1989; 30: 389-99.

Faught E, Ayala R, Montouris GG, *et al*. Zonisamide 922 Trial Group, 2001. Randomized controlled trial of zonisamide for the treatment of refractory partial-onset seizures. *Neurology* 2001; 57: 1774-9.

French JA, Kanner AM, Bautista J, *et al*. Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2004; 62: 1252-60.

French JA, Kanner AM, Bautista J, *et al*. Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2004; 62: 1261-73.

Futatsugi Y, Riviello Jr. JJ. Mechanisms of generalized absence epilepsy. *Brain Dev* 1998; 20: 75-9.

Glauser TA, Pellock JM. Zonisamide in paediatric epilepsy: review of the Japanese experience. *J Child Neurol* 2002; 17: 87-96.

Iinuma K, Haginoya K. Clinical efficacy of zonisamide in childhood epilepsy after long-term treatment: a postmarketing, multi-institutional survey. *Seizure* 2004; 13: 34-9.

Jallon P, Latour P. Epidemiology of Idiopathic Generalized Epilepsies. *Epilepsia* 2005; 46: 10-4.

Kim D, Song I, Keum S, *et al.* Lack of the burst firing of thalamocortical relay neurons and resistance to absence seizures in mice lacking alpha (1G) T-type Ca(2+) channels. *Neuron* 2001; 31: 35-45.

Kito M, Maehara M, Watanabe K. Mechanisms of T-type calcium channel blockage by zonisamide. *Seizure* 1996; 5: 115-9.

Kothare SV, Valencia I, Khurana DS, *et al.* Efficacy and tolerability of zonisamide in juvenile myoclonic epilepsy. *Epileptic Disord* 2004; 6: 267-70.

Kothare SV, Kaleyias J, Mostofi N, *et al.* Efficacy and safety of zonisamide monotherapy in a cohort of children with epilepsy. *Pediatr Neurol* 2006; 34: 351-4.

Ohtahara S, Yamatogi Y. Safety of zonisamide therapy: prospective follow-up survey. *Seizure* 2004; 13: 50-5.

Ohtahara S. Zonisamide in the management of epilepsy-Japanese experience. *Epilepsy Research* 2006; 68S: S25-33.

O'Rourke D, Flynn C, White M, *et al.* Potential efficacy of zonisamide in refractory juvenile myoclonic epilepsy: retrospective evidence from an Irish compassionate-use case series. *Ir Med J* 2007; 100: 431-3.

Sackellares JC, Ramsay RE, Wilder BJ, *et al.* Randomized, controlled clinical trial of zonisamide as adjunctive treatment for refractory partial seizures. *Epilepsia* 2004; 45: 610-7.

Schmidt D, Jacob R, Loiseau P, *et al.* Zonisamide for add-on treatment of refractory partial epilepsy: a European double-blind trial. *Epilepsy Res* 1993; 15: 67-73.

Seki T, Noboru K, Maezawa M. Effects of zonisamide monotherapy in children with epilepsy. *Seizure* 2004; 13S: S26-32.

Suzuki S, Kawakami K, Nishimura S, *et al.* Zonisamide blocks T-type calcium channels in cultured neurons of rat cerebral cortex. *Epilepsy Res* 1992; 12: 21-7.

Szaflarski JP. Effects of zonisamide on the electroencephalogram of a patient with juvenile myoclonic epilepsy. *Epilepsy Behav* 2004; 5: 1024-6.

Wilfong A, Schultz R. Zonisamide for absence seizures. *Epilepsy Research* 2005; 64: 31-4.

Yagi K, Seino M. Methodological requirements for clinical trials in refractory epilepsies-our experience with zonisamide. *Prog Neuropsychopharmacol Biol Psychiatry* 1992; 16: 79-85.

Yamauchi T, Aikawa H. Efficacy of zonisamide: our experience. *Seizure* 2004; 13: 41-8.