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Zonisamide in West syndrome: an open label study

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ABSTRACT – *Aims*. Infantile spasms are usually resistant to conventional antiepileptic drugs. Although adrenocorticotropic hormones or vigabatrin are regarded as standard agents for the treatment of infantile spasms, there are still limitations of their use. We determined the efficacy and tolerability of high-dose zonisamide in patients with recent-onset infantile spasms. *Methods*. Seventeen patients with infantile spasms, who were admitted to our hospital between October 2005 and November 2007, were eligible for enrolment within two months of diagnosis. Zonisamide was administered at a starting dose of 2-8 mg/kg/day, increasing by 2-5 mg/kg/day every three to four days until the seizures disappeared or the dose reached 30 mg/kg/day. Complete response was defined as clinical cessation of infantile spasms over 28 consecutive days and disappearance of hypsarrhythmia by EEG analysis. *Results*. Of the 17 treated patients (nine who received initial monotherapy and eight add-on therapy), five of 12 (42.0%) cryptogenic patients and two of five (40.0%) symptomatic patients showed complete disappearance of spasms. The maximum daily dose was 10–28 mg/kg, and the effective daily dose was 10-22 mg/kg. Mean time period before disappearance of spasms and hypsarrhythmia was eight days. Seizure recurrence was observed in three of the seven patients who showed complete disappearance of spasms. Adverse effects included irritability in four patients and poor oral intake in two patients. *Conclusion*. Although further study of zonisamide is warranted, high-dose zonisamide can be effective and safe in some infants with newly diagnosed West syndrome.

Key words: West syndrome, zonisamide, hypsarrhythmia, high-dose, safety

West syndrome is an age-related epilepsy syndrome occurring in infancy that is characterized by infantile spasms, hypsarrhythmia and developmental regression (West, 1841; Lux and Osborne, 2004). In view of the presence of profound neurodevelopmental sequelae, treatment of infantile spasms is usually initiated quickly and aggressively after diagnosis, with the aim of changing the natural history of the disease. Due to the vague underlying pathophysiology, treatment of infantile spasms has remained empirical, and the mechanisms of action of drugs used to treat this disorder are not fully understood. Because infantile spasms in many patients are resistant to conventional antiepileptic drugs, the treatments of choice have included adrenocorticotropic hormones and steroids, but these agents have been associated with severe adverse effects (Dulac and Tuxhorn, 2005).

Zonisamide (3-sulfamoylmethyl-1,2-benzisoxazole; ZNS) is a new antiepileptic drug with an efficacy profile similar to those of phenytoin and carbamazepine (Peters and Sorkin, 1993). Although the exact mechanism

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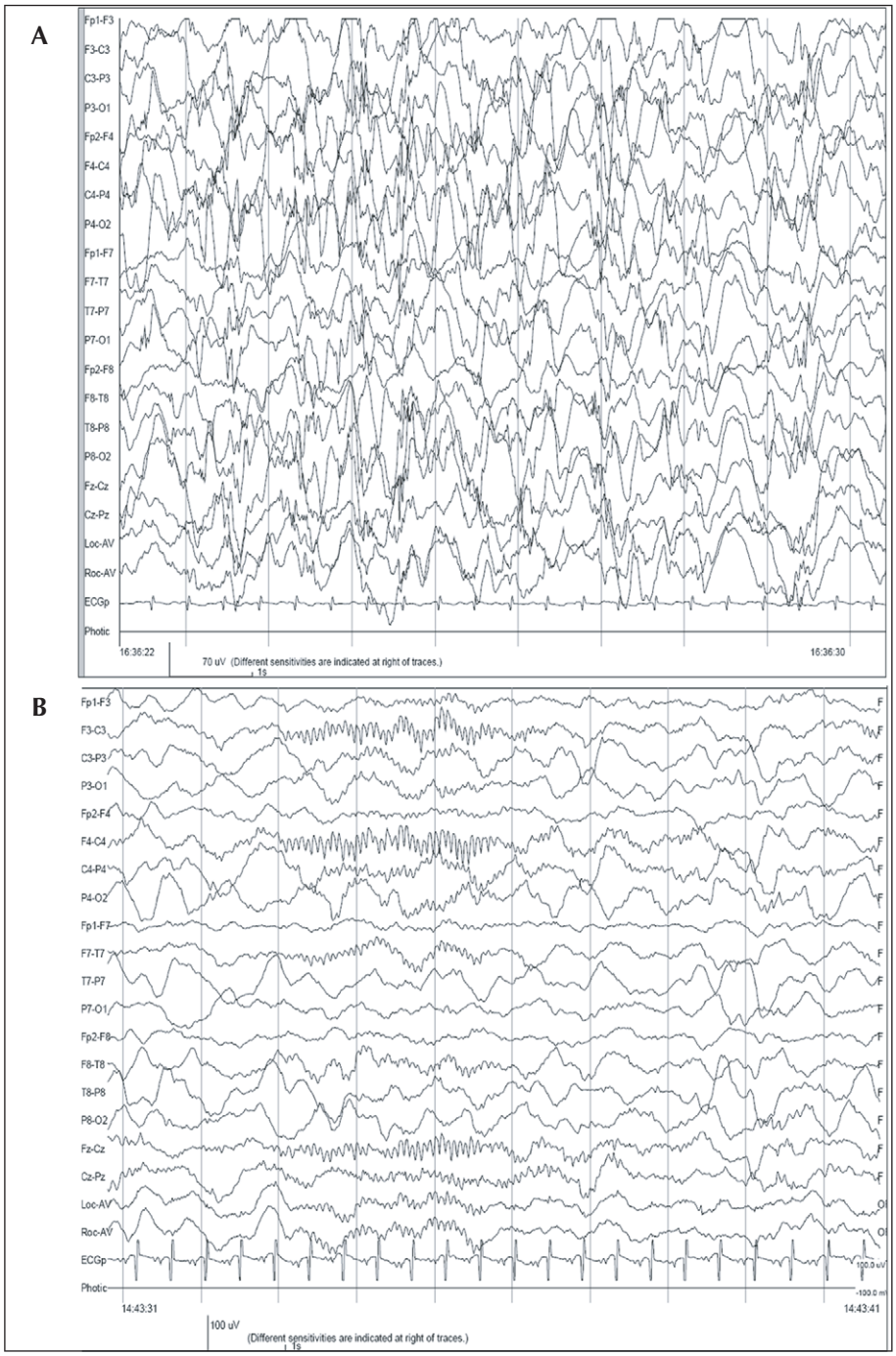

Figure 1. A) Interictal EEG of Patient 4 at six months of age showing hypsarrhythmia while asleep. **B**) EEG of Patient 4 at seven months of age after treatment with zonisamide revealing normal background activity with symmetric sleep spindles.

of action of ZNS is not known, the drug most likely acts by blocking T-type calcium channels (Suzuki *et al.*, 1992), inhibiting slow sodium channels (Schauf, 1987) and/or inhibiting glutamate release (Okada *et al.*, 1998). In addition, ZNS may block the propagation of seizure discharge and suppress the epileptogenic focus (Takano *et al.*, 1995).

Although several recent reports have described the efficacy of ZNS in infantile spasms, these reports were restricted mainly to Japanese populations (Suzuki, 2001; Yanagaki *et al.*, 2005; Yanai *et al.*, 1999). We have assessed the efficacy, safety, and tolerability of high-dose ZNS in the treatment of infantile spasms in patients eligible for treatment within two months of diagnosis.

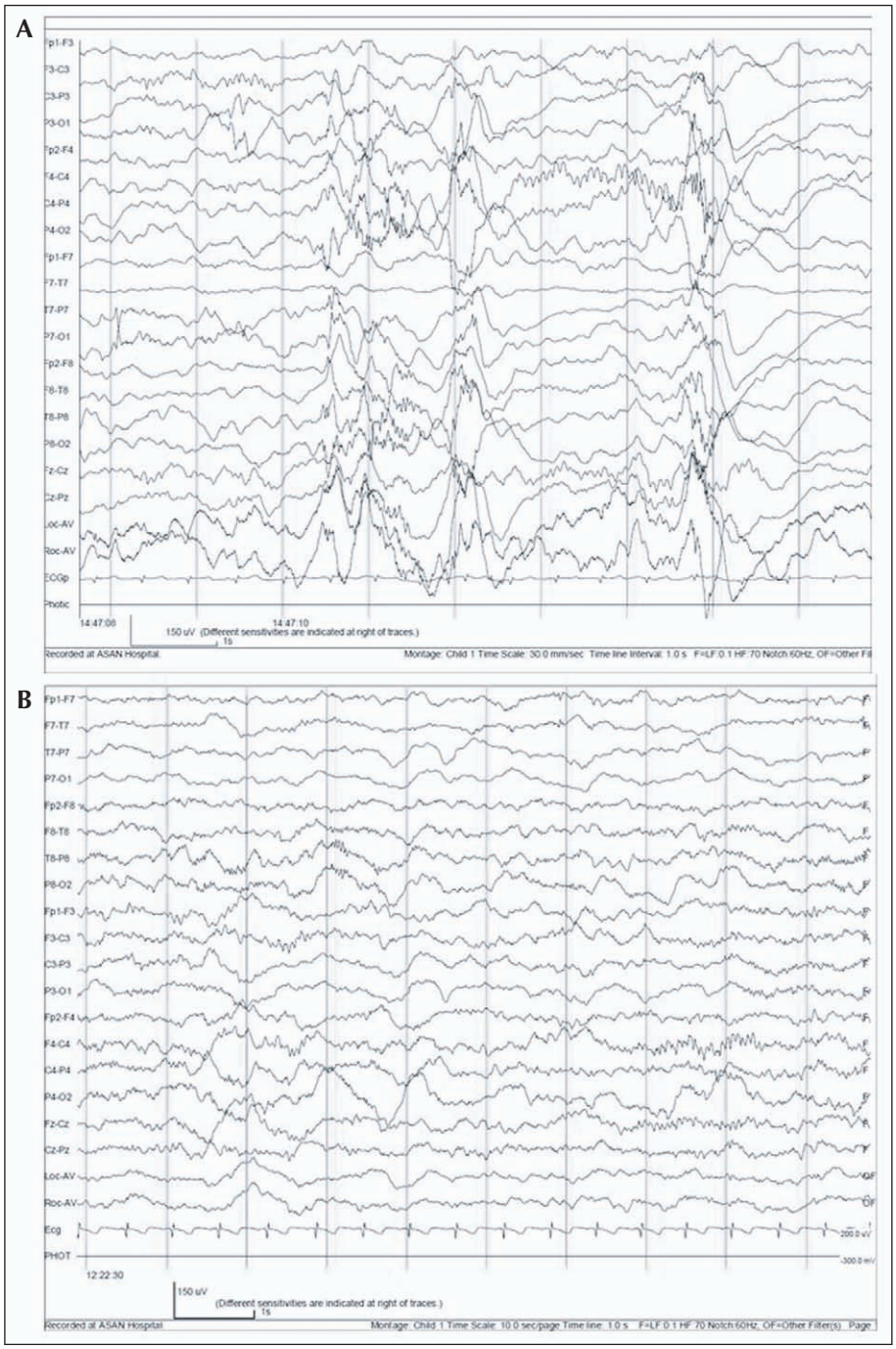

Figure 2. A) Interictal EEG of Patient 7 at seven months of age showing right side dominant asymmetric modified hypsarrhythmia and left posterior focal spike discharges during sleeping. **B**) EEG of Patient 7 at eight months of age after treatment with zonisamide revealing remaining asymmetric background activity and disappearance of modified hypsarrhythmia.

Materials and methods

From October 2005 to November 2007, patients with infantile spasms beginning at ≤ 12 months of age and hypsarrhythmia identified by electroencephalogram (EEG) analysis at the Pediatric Neurology department at the Asan Medical Center were eligible for this study. Prior to study entry, we obtained Ethical Committee and Institutional Review Board approval, and the risks and benefits of ZNS and alternative treatment regimens were discussed with each patient's caregivers.

Patients were treated with ZNS within two months of diagnosis as initial monotherapy or as add-on therapy. Patients older than 12 months at diagnosis were excluded, as were patients in whom spasms were successfully treated with other drugs before the introduction of ZNS.

The initial daily dose of ZNS was 2-8 mg/kg body weight, administered orally in one or two doses. Daily dosage was increased by 2-5 mg/kg every three to four days until the spasms disappeared or to a maximum daily dosage of 30 mg/kg. Routine EEGs were repeated at the time caregivers reported clinical spasm cessation. Outcome measurements included clinical response, EEG evaluation, dosing parameters and tolerability. Complete response was defined as clinical cessation of infantile spasms reported by their caregivers for ≥ 28 consecutive days from the time of the last witnessed spasm, according to the West Delphi consensus (Lux and Osborne, 2004), and disappearance of hypsarrhythmia on EEG between study days 14 and 28 *(figure 1)*. The exit criteria were defined as no cessation of spasms and extant hypsarrhythmia of EEG 21 days from start of ZNS therapy. For those who met the exit criteria, therapy was started without any delay.

Results

During the inclusion period, 17 patients newly diagnosed with infantile spasms were admitted to our hospital and treated with ZNS. The group comprised 13 males and four females, and in all but one patient, developmental milestones at the time of diagnosis were markedly inferior to age-matched normal profiles. The maximum daily ZNS dosage was 9.9-27.8 mg/kg.

Of these 17 patients, seven (41.2%) showed complete resolution of spasms and disappearance of spasms *(figures 1, 2)*, including five of 12 (42.0%) cryptogenic patients and two of five (40.0%) symptomatic patients.

The effective daily dose ranged from 10-22.5 mg/kg and the mean time interval before spasm disappearance was eight days. Spasm recurrence within six months was observed in three of the seven patients *(table 1)*.

ZNS treatment was not effective in 10 patients; these 10 patients received a maximum daily dose of 9.9-27.8 mg/kg (mean 19.8 mg/kg). There was no significant difference in age at clinical spasm onset, lead time from onset of spasms or dose of ZNS between responders and

Table 1. Summary of the patient characteristics (n = 17).

Patient number/ sex	Onset age (mo.)	Etiology	Concomitant drug	Max. ZNS dose (mg/kg)	At spasm control		Spasm recurrence (day)	Add-on therapy after ZNS*
					Time (day)	EEG		
1/M	7	Crypto.	VPA	17.9	20	Normal	48**	CLB
2/M	8	Crypto.	VPA	22.2	15	Normal	-	-
3/M	6	Crypto.	-	22.5	5	Normal	36**	VGB†
4/F	5	Crypto.	-	10.0	8	Both P-O spikes	115§	VGB
5/M	8	Crypto.	VPA, VGB	11.0	3	Normal	-	-
6/M	11	PVL	-	12.4	6	Normal	-	-
7/M	7	Infarct	CBZ, CLB, VGB	16.5	4	Normal	-	-
8/M	4	Crypto.	VGB, TPM	9.9	-	-	-	KD
9/F	12	Crypto.	-	14.3	-	-	-	VGB
10/M	12	Crypto.	-	20.4	-	-	-	VGB†
11/F	6	Crypto.	-	24.1	-	-	-	VGB†
12/M	2	Crypto.	-	27.3	-	-	-	VGB†
13/F	8	Crypto.	-	19.6	-	-	-	VGB
14/M	6	Crypto.	-	22.2	-	-	-	VGB†
15/M	12	TS	VGB	17.4	-	-	-	TPM, KD†
16/M	2	TS	PHB	15.3	-	-	-	VGB†
17/M	12	Ventriculomegaly	VPA	27.8	-	-	-	F/U loss

* For the patients who did not respond to zonisamide or the patients who experienced recurrence, the add-on therapy was started without any delay.

** Spasm recurrence without EEG at the time of recurrence.

§ Spasm recurrence with hypsarrhythmia.

† Patients who showed complete response after add-on therapy.

ZNS: zonisamide; Crypto: cryptogenic; VPA: valproate; Both P-O spikes: both parieto-occipital spikes; VGB: vigabatrin; PVL: periventricular leukomalacia; CBZ: carbamazepine; CLB: clobazam; TPM: topiramate; KD: ketogenic diet; TS: tuberous sclerosis; PHB: phenobarbital; F/U loss: follow-up loss.

Table 2. Summary of studies examining zonisamide efficacy in patients with infantile spasms.

References	N	Response rate* (%) (responder/total numbers of patients)				Dosage (mean), mg/kg/day	S/E
		Overall	Initial monotherapy**	Cryptogenic	Symptomatic		
Yanagihara *et al.*, 1995	9	33.3	-	0	33.3 (3/9)	-	None
Yanai *et al.*, 1999	27	33.3	0	100 (2/2)	28.0 (7/25)	5-12.5 (7.8)	None
Kawawaki *et al.*, 1999	16	25.0	25.0 (4/16)	66.7 (2/3)	15.4 (2/13)	4-8 (5.8)	1/16
Suzuki, 2001; Suzuki *et al.*, 1997	54	20.4	20.4† (11/54).	28.6 (4/14)	17.5 (7/40)	10-13 (-)	None
Lotze and Wilfong, 2004	23	26.1	30.0 (3/10)	0	26.1 (6/26)	8-32 (18)	5/23
Santos and Brotherton, 2005	7	0	0	-	-	3.3-35 (15.9)	-
Lee *et al.*, 2009	26	0	0	-	-	7.2-14 (8.5)	-
Our study	17	41.2	33.3 (3/9)	42.0 (5/12)	40 (2/5)	9.9-27.8 (18.3)	4/17

* Response indicates complete spasm cessations and some patients did not show clearing of the hypsarrhythmia.
** Response rate of the patients who were treatment-naive before zonisamide administration.
† All patients failed to respond to high-dose vitamin B6 therapy and vitamin B6 was discontinued.
-: data are not available.

non-responders. Adverse effects included irritability in four patients (patient 5, 13, 14, and 15) and poor oral intake in two (patient 5 and 14).

Discussion

A review of the current treatment for West syndrome in Japan (Tsuji *et al.*, 2007) noted that ZNS use has significantly increased in recent years and that ZNS is now the second or third choice among the non-hormonal, antiepileptic drugs for treating West syndrome in Japan. Here, we report a relatively high response rate, with complete clinical efficacy in 41.2% of patients with newly diagnosed infantile spasms. We administered ZNS as monotherapy in nine patients and as add-on therapy in eight patients. Three of the nine patients (33.3%) who received ZNS monotherapy and four of the eight patients (50%) who received ZNS add-on therapy achieved a seizure-free outcome. In the natural course of infantile spasms, though, there is a known spontaneous remission rate of approximately 20% during the first year of diagnosis (Hrachovy and Frost, 2003). Considering some of our patients relapsed, the response rate was 2/12 (16.7%) for cryptogenic cases and 4/17 (23.5%) for all patients, which does not seem too different from the potential spontaneous remission rate.

A review of the literature revealed six reports of the clinical response of ZNS in West syndrome *(table 2)*. In summary, for patients with infantile spasms, 3.3-35 mg/kg of ZNS was associated with an overall clinical response rate of 0-33.3%. Including our cases, 40 patients of a total of 163 (24.5%) responded completely to ZNS. When administered as initial monotherapy, 21 of 89 patients (23.6%) completely responded. Except for one study in the United States (Lotze and Wilfong, 2004), all previous studies reported lower response rates to the present study; however, these previous studies used a lower dose, suggesting that the better outcome reported in our study may be due to the higher dose of ZNS (Yanagaki *et al.*, 2005; Yanai *et al.*, 1999; Suzuki *et al.*, 1997). Analysis of response rates in these previous studies according to etiology indicated that the patients with cryptogenic etiology (8/19, 42.1%) showed better responses than those with symptomatic etiology (26/113, 23.0%).

In contrast, our study showed similar outcomes in both groups, suggesting the need for additional, larger studies.

The present observation that there were no serious side effects associated with high dose and rapid titration of ZNS in infants is in agreement with previous reports (Yanagaki *et al.*, 2005; Mandelbaum *et al.*, 2005). Despite the limitations of our study, including the open-label design and the lack of a control group, our results provide evidence that ZNS may be effective and safe in patients newly diagnosed with infantile spasms. □

Disclosure.
None of the authors has any conflict of interest to disclose.

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