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Comparative trial of low- and high-dose zonisamide as monotherapy for childhood epilepsy

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ABSTRACT

Purpose: To evaluate the effectiveness of zonisamide (ZNS) as monotherapy in children with newly diagnosed epilepsy.
Methods: This randomized, multicenter trial included a 2–4-week titration and a 24-week maintenance phase after randomization to low-(3–4 mg/kg/day) or high-(6–8 mg/kg/day) dose groups as target maintenance dosages. The primary outcome measure was the seizure-free rate over 6 months, while a secondary measure was the change in cognition and behavior from screening to the end of the maintenance phase.
Results: Out of 125 patients enrolled, 90 (49 low-dose and 41 high-dose) completed the study. Forty-one patients (63.1%) in the low-dose group and 34(57.6%) in the high-dose group achieved 6 months' freedom from seizures ($p = 0.66$). After treatment, the picture arrangement subtest improved in the low-dose group ($p = 0.047$) while the vocabulary subtest worsened in the high-dose group ($p = 0.020$). Comparing between the two groups, the vocabulary subtest in the high-dose group was significantly worse than that in the low-dose group ($p = 0.002$). Social competence, somatic complaints, depression/anxiety and delinquent and aggressive behavior in the low-dose group were significantly improved ($p < 0.05$). Moreover, total social competence, somatic complaints, delinquent behavior, externalizing, and total behavior problems were significantly more improved in the low-dose group than the high-dose group ($p < 0.05$).
Conclusions: ZNS is an effective monotherapy for newly diagnosed childhood epilepsy. Lower doses of ZNS have a similar efficacy and more beneficial neurocognitive effects compared to higher doses. When prescribing higher doses of ZNS, one must be aware of the possible manifestation of problems associated with language development, such as those affecting vocabulary acquisition.

1. Introduction

Zonisamide (ZNS) is an antiepileptic drug (AED) with a broad-spectrum action that has demonstrated good efficacy in controlling seizures as an add-on therapy in adult and pediatric epilepsy.[1–6] However, few studies have evaluated ZNS as a primary monotherapy in children with newly diagnosed epilepsy. Cognitive and behavioral effects are key considerations in the selection of AEDs because of their influence on the acquisition of new skills and on the ability to develop social strategies at crucial stages of

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development. Generally, AEDs exert a dose-dependent effect on cognitive functioning. Here, we have used a dose-controlled study design to evaluate the efficacy of ZNS as monotherapy for seizure control and tolerability, including an analysis of neuropsychological effects, in children less than 16 years of age with newly diagnosed epilepsy.

2. Methods

2.1. Subjects

Children less than 16 years of age were eligible for the study if they had been diagnosed with epilepsy and had experienced two or more seizures in the previous 6 months. All subjects had normal intelligence at baseline (intelligence quotient [IQ] > 70), and the decision had been made to start medication. Exclusion criteria included evidence of a progressive cerebral lesion or a neurodegenerative metabolic disorder, pre-existing cognitive impairment at baseline that could interfere with future cognitive testing procedures, and a history of psychiatric disorder. Patients previously treated with AEDs were also excluded.

The study was conducted in 10 referral hospitals for pediatric epilepsy care. The protocol was approved by the institutional review boards of all of the centers involved. Informed consent was obtained from all participants and their guardians before any trial-related procedures were performed.

2.2. Study design

The study was a multicenter, randomized, open-label, parallel-group clinical trial of dose-comparison design with a low or high ZNS dose given as monotherapy. Each study center received a separate and independent randomization procedure by random code assignment. The study included a retrospective baseline phase of 6 months and a screening phase of 1 week during which eligibility was determined and all screening procedures were carried out. The 28-week treatment period included the initial 2–4 weeks of titration and 24 weeks of maintenance. Following the screening phase, the titration was started, during which either a low- or a high-dose was introduced.

In the low-dose group, ZNS was introduced at 1 mg/kg twice daily and increased by 1–2 mg/kg/day after 1–2 weeks. The maintenance dose for the low-dose group was 3–4 mg/kg/day. However, if a patient with partial seizures experienced one or more convulsive seizures or other types of seizures more than twice in 4 weeks, or if the seizure frequency or intensity increased in comparison with the baseline of other seizure patients, the dose was increased gradually. In the high-dose group, ZNS was

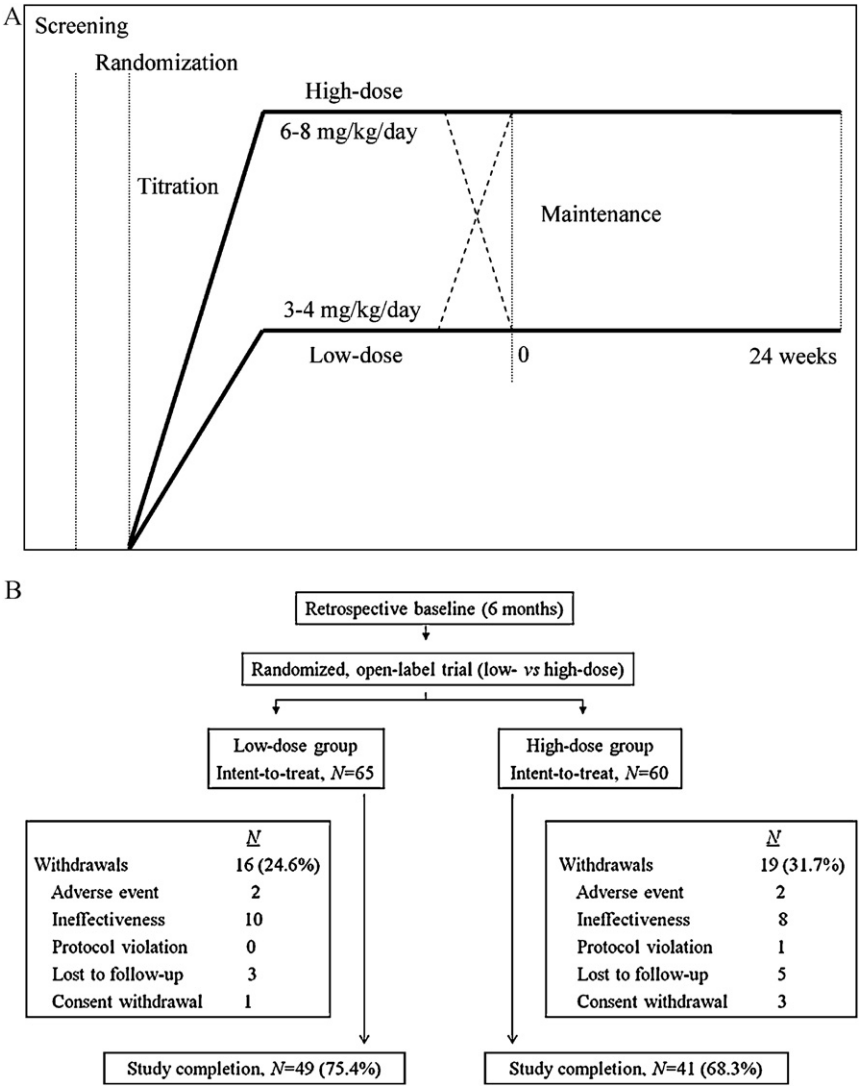

Fig. 1. Design (A) and progression (B) of the trial.

introduced at 1 mg/kg twice daily and increased by 1–2 mg/kg/day every 1–2 weeks. The maintenance dose for the high-dose group was 6–8 mg/kg/day. However, if maintenance of the high-dose was rendered difficult because of adverse effects during titration or within 8 weeks of reaching the maintenance high-dose, the dose was gradually decreased (Fig. 1A).

2.3. Outcome measures

Throughout the trial, patients (or their parent or legal guardian) maintained diaries to record the type and frequency of seizures as well as adverse effects. At each hospital visit, the investigator reviewed the patient's seizure diary. Patient visits were scheduled for days 1 (randomization), 29, 57, 85, 141 and 197.

The primary efficacy analysis was the seizure-free rate during the maintenance period. Secondary efficacy analyses included changes in cognition and behavior in a combined analysis of standardized measures from screening to the end of the maintenance phase. Comprehensive neuropsychological tests were carried out during the screening period (up to 7 days before the start of the titration) and at the end of the study (28 weeks). The Korean Wechsler Intelligence Scale for Children – Third edition (K-WISC-III) was used for cognitive assessment. The K-WISC-III comprises a full scale IQ, verbal IQ, and performance IQ with 13 subtests: information, similarities, arithmetic, vocabulary, comprehension, digit span, picture completion, picture arrangement, block design, object assembly, coding, mazes and symbol search. Verbal IQ is based on information, similarities, arithmetic, vocabulary and comprehension. The performance IQ is based on picture completion, coding, picture arrangement, block design and object assembly. The integrated cognitive function index was obtained with the K-WISC-III as follows: (1) verbal comprehension index: information, similarities, vocabulary and comprehension; (2) perceptual organization index: picture completion, picture arrangement, block design and object assembly; (3) freedom from distractibility index: arithmetic and digit span; (4) processing speed index: coding and symbol search. The Korean child behavior checklist (K-CBCL) was used to measure behavioral problems. K-CBCL is divided into social competence and behavioral problems, with the former providing assessment of total social competence, school and social problems, and the latter providing one score representing total behavioral problems, two second-order factor scores (internalizing problems and externalizing problems) and eight syndrome scales (aggressive behavior, anxious/depressed, delinquent behavior, attention problems, social problems, thought problems, withdrawn and somatic complaints). The *T* scores of the 14 subscales of the K-CBCL were used in the analysis. The Korean quality of life survey for childhood epilepsy (K-QOLCE) consists of a 42-item scale that assesses well-being, social activity, physical activity, cognitive functioning, behavioral functioning, general health and overall quality of life within the previous 4 weeks. The overall quality-of-life scoring scale ranges from 0 to 100, with the highest score reflecting excellent quality of life.

The tolerability and safety of ZNS were monitored throughout the dose-controlled trial by neurological and physical examinations that took into account weight, vital signs and evaluation for treatment-related adverse effects (one visit during the baseline period and five subsequent visits during the 28-week trial). Clinical laboratory evaluations were performed at baseline, after 4 weeks of treatment, and at the end of the study. The incidence of treatment-related adverse effects was compared between the two dosage groups.

2.4. Statistical methods

The efficacy parameter of interest was the seizure-free rate during the treatment period. The intention-to-treat (ITT) population for efficacy analyses included all randomized patients who received at least one dose of ZNS and provided at least one post-randomization, on-treatment efficacy evaluation. To compare the seizure outcomes between the two groups, the chi-square test and Fisher's exact test ($n \leq 5$) were used. The data from neuropsychological analyses are presented as mean with standard deviation (SD) or number (percentage). Neuropsychological analyses for low- versus high-dose were performed with an analysis of covariance (ANCOVA) model and paired *t* tests across the neuropsychological variables to compare changes over time for the treatment groups. All statistical tests on neuropsychological test data were two-sided and conducted at the 95% confidence intervals based on the *t* distribution and pooled estimate of variance. A $p < 0.05$ was taken as the level of significance. Statistical analyses were performed using Statistical Product and Services Solutions (version 13.0, SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Subject characteristics and distribution

The ITT population included 125 subjects (65 in the low-dose group and 60 in the high-dose group). Sixty-five were boys and 60 were girls, and their mean age was 8.1 ± 3.1 (range, 2–16) years. Low- and high-dose groups were similar with regard to demographic characteristics (Table 1). For patients with localization-related epilepsy, there were 62 patients in the idiopathic type and 38 patients in the cryptogenic/symptomatic type; the idiopathic type was composed of 54 patients with benign rolandic epilepsy and eight patients with benign occipital epilepsy. For patients with generalized epilepsy, there were seven patients with juvenile absence epilepsy, five patients with childhood absence epilepsy, four patients with generalized tonic clonic seizure on awakening, three patients with juvenile myoclonic epilepsy, and two patients with other types of idiopathic generalized epilepsy. Epilepsy classification and etiology did not differ between the two groups. Fig. 1B shows the distribution of the 125 subjects following randomization. Among the 125 ITT patients, dosage changes were realized in 13 patients. Eleven patients in the low-dose group had their dosage increased to a higher maintenance dosage due to inadequate seizure control, while two patients in the high-dose group had their dosage decreased to a lower maintenance dosage due to adverse effects. Out of the 125 patients

Table 1
Baseline characteristics of study patients included in the intent-to-treat analysis.

	Zonisamide dosage		*p*-Value[a]
	Low (n = 65)	High (n = 59)	
Age (years), mean ± SD	8.3 ± 3.0	7.8 ± 3.0	0.96
Male:female ratio	31:34	34:26	0.55
Mean age at fist seizure, year (SD)	7.5 ± 3.2	6.9 ± 3.4	0.51
Time since diagnosis, months, mean ± SD	8.5 ± 18.8	8.7 ± 11.9	0.59
Epilepsy classification and etiology, % (n)			
Localization-related	53	47	0.31
Idiopathic	34	28	0.44
Symptomatic	2	2	0.72
Cryptogenic	17	17	0.41
Generalized	11	10	0.83
Idiopathic	11	10	
Symptomatic	0	0	
Cryptogenic	0	0	
Undetermined	1	2	0.56
Enroll failure due to protocol violation	0	1	

[a] Student's *t*-test and Fisher's exact test ($n \leq 5$).

Table 2
Seizure-free state for 24 weeks classified according to epilepsy type.

Epilepsy classification	Low-dose	High-dose	*p*-Value[a]
Localization-related	35/53 (60.3%)	31/47 (66.0%)	0.99
Idiopathic	21/34 (61.8%)	18/28 (64.3%)	0.68
Cryptogenic	8/17 (47.1%)	9/17 (52.9%)	1.0
Symptomatic	0/2 (0%)	1/2 (50.0%)	0.5
Generalized, idiopathic	5/11 (45.5%)	3/10 (30.0%)	0.47
Undetermined	1/1 (100.0%)	0/2 (0%)	0.67
Total	41/65 (63.1%)	34/59 (57.6%)	0.66

[a] Chi-square test and Fisher's exact test ($n \leq 5$).

enrolled, 90 completed the study, including 49 (75.4%) of 65 in the low-dose group and 41 (68.3%) of 60 in the high-dose group. Thirty-five patients (28.0%) did not complete the study due to drug ineffectiveness (18 patients, 14.4%), follow-up loss (9, 7.2%), adverse effects (4, 3.2%), consent withdrawal (3, 2.4%), and protocol violation (1, 0.8%). Among the 18 patients that were discontinued due to drug ineffectiveness, five patients had typical absence seizures. Among the nine patients that were lost in follow-up, four patients had benign rolandic epilepsy. Seizure frequency was not related to drop-out.

3.2. Efficacy analysis—seizure-free rate during 6 months of maintenance

Forty-one (63.1%) patients in the low-dose group and 34 (57.6%) in the high-dose group achieved 6 months of freedom from seizures ($p = 0.66$). Table 2 shows the seizure-free rate for different epilepsy types for the 24 weeks of the maintenance period. Overall, ZNS was more effective in localization-related epilepsy (66.0% seizure-free rate, 66 of 100) than in idiopathic generalized epilepsy (38.1%, 8 of 21) ($p = 0.017$). In localization-related epilepsy, ZNS was more effective in the idiopathic type (64.5% seizure-free rate, 40 of 62) than the cryptogenic type (47.4%, 18 of 38). Among the patients with idiopathic generalized epilepsy, 4 of 12 patients (33.3%) with absence epilepsy were seizure-free. However, seizure-free rates for each epilepsy type did not differ between the low- and high-dose groups.

In spite of the dose being increased to a higher maintenance dosage due to inadequate efficacy in 11 patients of the low-dose group, only one (9.1%) became seizure-free. Moreover, two patients in the high-dose group whose dosage was decreased to a lower maintenance dosage due to adverse effects, maintained a seizure-free state with elimination of the adverse effects after decreasing the dose. Moreover, two patients in the high-dose group achieved a seizure-free state with elimination of adverse effects after their maintenance dosage was decreased.

3.3. Neuropsychological assessments

3.3.1. Cognition

The results of statistical analyses of baseline-to-endpoint changes are summarized in Tables 3 and 4. Neuropsychological data for cognitive variables were available for 51 patients (23 on a low-dose and 28 on a high-dose regime). After treatment, the picture arrangement subtest improved in the low-dose group ($p = 0.047$) and the vocabulary subtest worsened in the high-dose group ($p = 0.020$). A comparison of the low- and high-dose groups showed that the vocabulary subtest in the high-dose group was significantly worse than that in the low-dose group ($p = 0.002$) (Table 3).

3.3.2. Behavior

Neuropsychological data for behavioral variables were available for 63 patients (27 on a low-dose and 36 on a high-dose regime). In the low-dose group, social competence, somatic complaints, depression/anxiety and delinquent and aggressive behavior were improved after treatment ($p < 0.05$), but no significant change was seen in the high-dose group. Comparison of the low- and high-dose groups showed that total social competence, somatic complaints, delinquent behavior, externalizing, and total behavior problems exhibited greater improvement in the low-dose group than in the high-dose group ($p < 0.05$) (Table 4).

3.3.3. Quality of life

Neuropsychological data concerning quality of life were available for 51 patients (23 on a low-dose and 28 on a high-dose regime). No significant change was seen in the low-dose group after treatment. In the high-dose group however, energy/fatigue and mood/anxiety were improved after treatment ($p < 0.05$), but there was no significant difference between the two groups (Table 5).

Table 3
Cognition changes in low- and high-dose groups after ZNS treatment.

K-WISC-III	Low-dose ($n = 23$)			High-dose ($n = 28$)			Low *vs* high *p*-value[a]
	Pre	Post	*p*-Value	Pre	Post	*p*-Value	
FSIQ	101.74	100.35	0.473	90.57	90.68	0.958	0.821
VIQ	104.22	103.43	0.668	93.96	92.11	0.359	0.366
PIQ	97.57	96.70	0.710	88.46	90.68	0.292	0.635
Verbal comprehension	103.74	102.96	0.629	94.86	93.43	0.505	0.198
Perceptual organization	95.87	98.61	0.272	87.61	91.18	0.074	0.545
Attention and concentration	98.22	102.52	0.084	91.89	92.11	0.911	0.491
Processing speed	88.84	88.79	0.984	88.11	87.48	0.727	0.670
Information	10.22	10.09	0.756	8.79	9.25	0.267	0.526
Similarities	11.78	11.04	0.163	9.93	10.07	0.811	0.947
Arithmetic	9.96	10.35	0.401	8.86	8.29	0.206	0.093
Vocabulary	10.61	11.09	0.134	9.96	8.85	0.020*	0.002*
Comprehension	9.83	9.78	0.945	8.11	8.07	0.948	0.282
Digit span	10.62	11.00	0.390	8.85	8.77	0.908	0.202
Picture completion	9.87	9.48	0.501	8.18	8.61	0.217	0.622
Picture arrangement	9.00	10.43	0.047*	7.74	8.56	0.068	0.184
Block design	9.52	10.26	0.081	9.07	9.11	0.946	0.209
Picture assembly	9.96	9.57	0.549	8.11	8.79	0.076	0.324
Coding	8.43	9.00	0.262	9.19	8.89	0.597	0.432

ZNS, zonisamide; K-WISC-III, Korean Wechsler Intelligence Scale for Children – Third Edition; Pre, pre-medication; Post, post-medication; FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal Intelligence Quotient; PIQ, Performance Intelligence Quotient.

[a] ANCOVA.

* *t* distribution, 95% confidence interval (95% CI); $p < 0.05$.

Table 4
Behavioral changes in low- and high-dose groups after ZNS treatment.

K-CBCL (*T*-score)	Low-dose ($n=27$)			High-dose ($n=36$)			Low *vs* high *p*-value[a]
	Pre	Post	*p*-Value	Pre	Post	*p*-Value	
Social competence	48.67	51.85	0.091	53.83	50.75	0.100	0.631
Academic competence	43.30	49.78	0.053	42.39	43.14	0.768	0.158
Total social competence	42.11	49.52	0.002*	45.89	44.56	0.473	0.003*
Withdrawn	58.22	53.81	0.136	53.89	53.33	0.770	0.247
Somatic complaints	51.04	46.89	0.010*	52.39	51.86	0.626	0.048*
Depression/anxiety	52.11	48.96	0.021*	51.08	50.39	0.462	0.117
Social problems	51.93	50.04	0.166	52.06	50.97	0.310	0.539
Thought problems	52.93	50.85	0.281	50.61	50.42	0.865	0.372
Attention problems	51.30	49.48	0.269	50.67	49.61	0.217	0.655
Delinquent behavior	52.11	48.85	0.003*	48.03	48.53	0.642	0.016*
Aggressive behavior	51.78	47.11	0.001*	51.06	49.28	0.095	0.073
Internalizing problems	52.81	48.85	0.014*	51.33	50.81	0.587	0.050
Externalizing problems	51.85	47.19	<0.001*	50.50	49.08	0.138	0.032*
Total behavior problems	52.96	47.70	0.001*	51.08	49.47	0.106	0.031*

A high *T* score is good for competence scores, but bad for other subscales.
ZNS, zonisamide; K-CBCL, Korean-Child Behavior Checklist; Pre, pre-medication; Post, post-medication.
[a] ANCOVA.
* *t* distribution, 95% confidence interval (95% CI); $p<0.05$.

Table 5
Changes to quality of life in low- and high-dose groups after ZNS treatment.

K-QOLCE		Low-dose ($n=23$)			High-dose ($n=28$)			Low *vs* high *p*-value[a]
		Pre	Post	*p*-Value	Pre	Post	*p*-Value	
Physical function	Physical restriction	18.39	19.43	0.401	21.69	21.46	0.625	0.109
	Energy/Fatigue	7.67	7.89	0.587	8.03	7.34	0.014*	0.088
Well-being (Mood)	Depression	7.89	8.41	0.219	8.46	8.29	0.493	0.465
	Anxiety	11.75	12.14	0.501	11.91	13.29	0.028*	0.118
	Control/helplessness	8.74	8.37	0.265	8.46	8.80	0.368	0.215
	Self-esteem	11,24	11.16	0.876	12.17	11.66	0.383	0.623
Cognition	Concentration	8.22	8.48	0.416	8.40	8.57	0.661	0.977
	Memory	8.18	8.07	0.785	7.91	8.29	0.290	0.493
	Language	13.32	12.79	0.394	13.53	13.06	0.264	0.534
	Other Cognition	8.41	8.03	0.407	8.17	8.23	0.864	0.555
Social function	Social activities	11.04	12.04	0.066	12.29	12.66	0.498	0.410
	Social interactions	8.96	9.00	0.941	9.56	9.44	0.739	0.574
General	Behaviors	30.48	32.17	0.227	28.57	30.26	0.283	0.522
	General Health	3.85	3.80	0.871	4.00	3.87	0.650	0.871
	Quality of Life	3.67	3.56	0.607	4.00	4.04	0.770	0.172
Total	156.41	161.21	0.167	165.86	167.09	0.776	0.980	

ZNS, zonisamide; K-QOLCE, Korean-Quality of life survey for childhood epilepsy; Pre, pre-medication; Post, post-medication.
[a] ANCOVA.
* *t* distribution, 95% confidence interval (95% CI); $p<0.05$.

Table 6
Adverse effects.

	Low-dose ($n=65$)	High-dose ($n=59$)
Somnolence	2 (3.1%)	3 (5.1%)
Dizziness	1 (1.6%)	3 (5.1%)[a]
Appetite decrease	3 (5.1%)[a]	1 (1.6%)
Fatigue	2 (3.1%)	1 (1.6%)
Voiding problem	0	3 (5.1%)
Headache	1 (1.6%)	1 (1.6%)
Weight loss	2 (3.1%)[a]	0
Memory loss	1 (1.6%)	1 (1.6%)
Paresthesia	1 (1.6%)	0
Nausea	0	1 (1.6%)
Epigastric pain	0	1 (1.6%)[a]
Diarrhea	0	1 (1.6%)
Anxiety	0	1 (1.6%)
Hypodiaphoresis	0	1 (1.6%)
Rash	1 (1.6%)[a]	0

[a]One of the patients withdrew because of adverse effects of the medication.

3.4. Adverse effects

Mild rash (1 patient) and decreased appetite (1 patient) in the low-dose group, and dizziness (1 patient) and abdominal pain (1 patient) in the high-dose group led to withdrawal from the study during the titration and maintenance period. There were no serious adverse effects reported in this study period. Other drug-related adverse effects are summarized in Table 6.

4. Discussion

The purpose of this study was to evaluate the efficacy for seizure control and the tolerability of ZNS monotherapy in children. The results showed that ZNS as monotherapy produced a 60.5% seizure-free rate in childhood epilepsy and that the efficacy of the lower dose (3–4 mg/kg/day) for seizure control was not different from that of the higher dose (6–8 mg/kg/day). Moreover,

the lower dose of ZNS had more cognitive and behavioral benefits than the higher dose.

Previous studies on ZNS have mostly addressed its adequacy as an add-on therapy in intractable epilepsy patients.[1–6] Some reports have studied the effects of ZNS monotherapy in children and young adults in retrospective analyses through chart review.[7] In contrast, this study was conducted on newly diagnosed, untreated pediatric patients (less than 16 years of age) to evaluate the seizure-controlling effects of ZNS as a first-line therapy and to address its safety and adverse effects, including its effects on cognitive functions and behavior. The results show that ZNS can be used effectively as the first-line therapy in pediatric patients with epilepsy without causing serious systemic adverse effects. However, we found that, in relation to cognition, the vocabulary is impaired when higher doses of ZNS are used. This is a troublesome finding, particularly given that the use of this drug may interfere with language development in children.

In a previous study that retrospectively observed the effects of ZNS monotherapy, it was stated that long-term ZNS monotherapy is effective at treating a broad spectrum of seizure disorders, but a specific adverse effect, such as cognitive impairment, is common and long-lasting.[8] However, in our study, which observed the effects prospectively according to the drug dose, we found that a relatively lower dose of ZNS is effective in controlling seizures without causing cognitive impairment; in fact, some cognitive functions are even improved after treatment. Compared with the earlier study by Seki et al., in which a much higher dose (12 mg/kg/day) of ZNS was used while the seizure-controlling effects of the drug were observed,[9] our study showed a lower frequency of adverse effects, particularly in the lower dose group.

ZNS is considered to be effective at controlling various seizure types because of its multiple pharmacodynamic actions,[10,11] with many clinical studies supporting this view. However, a review that combined study results from Japan, where the majority of ZNS studies have been conducted, showed a tendency towards better seizure-controlling effects in localization-related epilepsy compared with generalized epilepsy.[11] Our study also showed better seizure-free effects in localization-related epilepsy than in idiopathic generalized epilepsy. This may be because this study was conducted in pediatric patients with normal cognitive function, which means that, unlike other studies, all patients with generalized epilepsy were of the idiopathic type, and the number of patients with childhood or juvenile absence epilepsy was greater than that with juvenile myoclonic epilepsy. The fact that ZNS is more effective in the treatment of myoclonic seizures than in typical absence seizures is known from previous studies.[4,10–12]

Generally, the adverse effects of an AED increase in parallel with the seizure controlling effects as the drug dose is increased.[13,14] In this study, several adverse effects increased and a significant worsening of vocabulary variables was observed when ZNS was used at the higher rather than the lower dose. In contrast, compared with the pre-treatment period, several cognition and behavior variables were significantly improved with the lower dose of ZNS treatment. The authors have observed similar results with benign rolandic epilepsy patients treated with topiramate, which has several characteristics similar to ZNS.[15] Moreover, similar results have been observed in older patients with partial seizures.[16] Although the number of target patients in this study was small, the results from patients whose dose was changed due to either inadequate efficacy or to adverse effects after randomization, show that patients whose seizures could not be controlled with lower dose ZNS could only with difficulty attain complete seizure control after increasing to a higher dose. Furthermore, patients who were seizure-free but who suffered from adverse effects with the higher dose could eliminate these adverse effects yet maintain their seizure-free state after decreasing to a lower maintenance dose. Based on these results, we propose that the ideal first-line therapy of ZNS for pediatric epilepsy may be to start with a lower dose and then gradually increase the dose while observing the response. In addition, once-daily ZNS treatment may be more effective in pediatric epilepsy, considering the results of a prior study in which effective seizure control was achieved with ZNS administered on once-daily basis.[17]

In conclusion, ZNS is an effective monotherapy for newly diagnosed childhood epilepsy. Lower doses of ZNS have similar efficacy to higher doses and have more beneficial neurocognitive effects than the higher doses. If using higher doses of ZNS, the treating doctor must pay careful attention to monitor the appearance of problems associated with language development, particularly that involving vocabulary acquisition.

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