ZONISAMIDE: EFFECTIVENESS AND SAFETY IN CHILDREN WITH EPILEPSY: A POSTMARKETING STUDY IN INTELLECTUALLY NORMAL AND DISABLED CHILDREN

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Abstract

An analysis was done to determine zonisamide's long-term efficacy and safety in the treatment of childhood epilepsy, comparing its outcomes for intellectually normal and intellectually disabled children. Among the 349 subjects, all were younger than 15 years of age; they were divided into two groups based on their intellectual abilities: the intellectually normal group (n=184) and the intellectually disabled group (n=165). It was found that 62 percent of subjects improved on seizure control over the previous month, with 78 percent of subjects responding better than 45 percent of subjects with intellectual disabilities. There is some evidence that zonisamide is not only effective in partial and generalized seizures, but it is also superior in this case when applied to people who are intellectually normal. There were 24 percent of patients who reported having adverse effects that were more severe when monotherapy was used compared to combination therapy. It is clear that zonisamide may be useful in treating partial and generalized seizures in children, but adverse events should be monitored, especially when used in combination with other medications.

Keywords: Zonisamide, Pediatric epilepsy, Seizure control, Intellectually disabled children and Adverse effects.

Introduction

There is a new antiepileptic medicine, zonisamide, that has a broad antiepileptic spectrum for both generalized and partial seizures (1). A commercial license has been granted for the drug in Japan since 1989. There were randomized, controlled trials of zonisamide for adults, children, and adolescent patients, and their average length of study time was 1216 weeks for adults and 8 weeks for children. Almost all of the studies examined zonisamide's effect on generalized seizures (2). 25 institutions have conducted a five-year clinical trial on zonisamide in the treatment of childhood epilepsy. Zonisamide was studied in this post-marketing trial in comparison with intellectually disabled children to determine whether it provided long-term epilepsy relief to children with intellectual normalcy.

Methods

An overview of the patients and study design

Three hundred and forty-nine patients participated in the study. Their ages ranged from 15 to 14 years old. Among the patients, 10 were younger than 1 year of age (3%); 98 were between 1-5 years of age (28%); 129 were between 6-10 years of age (37%); 102 were between 11-15 years of age (32%). Subjects found to be intellectually normal and intellectually disabled in the study were 184 and 165, respectively. These subjects were evaluated based on their intelligent quotient (IQ) or developmental quotient (DQ). We used Tanaka-Binet (a Japanese version of Stanford-Binet's Intelligence Scale) and, in rare cases, Wechsler Intelligence Scale of Children redesigned to assess IQ. Tsumori-Inage and Enjoji methods were used to assess DQ (both evaluations are conducted through interviews with parents, such as the Denver Developmental Screening Test). During the study's observation period, 5 to 6 months were observed. On the basis of the general increase in seizures control, people with intellectual disabilities and those with intellectual disabilities were

evaluated. The study shows that 15 percent of intellectuals with normal type epilepsy have temporal lobe epilepsy and 55 percent have non-temporal lobe epilepsy. A total of less than 20 percent of this group suffered from generalized epilepsy. While intellectually disabled patients had approximately 7 percent and 35 percent of temporal lobe epilepsy, respectively, as compared to the general population. Generalized epilepsy was prevalent among over half of the subjects in this study. Three hundred and forty-four patients were assessed at the end from a first group of three hundred and forty-nine patients. Five patients were removed from the study following loss to follow-up due to adverse events, address changes, and insufficient number of seizures (3). Among the patients with intellectually normal capabilities, 182 were able to complete the study, while 162 were able to accomplish the same in the intellectually disabled group.

Evaluating safety and effectiveness.

An observation period of at least five months was required following zonisamide treatment to determine its efficacy. We did not analyze the effectiveness of patients who had been followed for less than five months. We analyzed the data using chi-square. The dosage of zonisamide ranged from 2 mg/kg to over 10 mg/kg by patients, with approximately 70% receiving dosages of 2-8 mg/kg each day. Zonisamide has also been found to be effective when seizures are reduced by at least 50% over baseline when the rate of seizures falls below that level. As a measure of improvement, this study measured the percentage of patients who reached the standard of effectiveness. Neither patients nor staff reported any adverse effects (4,5).

Zonisamide monotherapy was administered to 61% of the normal group. Two-hundred eighty-six percent of the patients received zonisamide and another antiepileptic drug (6). The percentage of patients with intellectual disabilities using zonisamide monotherapy was only 14%. In this group of patients, zonisamide and two other antiepileptic medications were administered to three out of ten patients. There was a greater prevalence of AED usage in the intellectually normal population (1.61 vs. 2.94).

Results

Efficiency

Based on Table 1, seizures have been rated as improving overall. Both groups experienced different types of seizures. In general, improved performance was highly significant in cases with normal intelligence (80%, P=0.001), in cases of tonic seizures (89%, P=0.001), in cases of generalized tonic-clonic seizures (87%, P=0.05) and in cases of other types of seizures (80%, P=0.01). A much higher percentage of improvement was rated for all types of partial seizures in the intellectually normal group (81) when compared with the intellectually disabled (64) (P0.001).

Table 1. Improvement in the rating of generalized seizures

Intensity of the seizure	The number of seizures has been reduced by 50% (The number of seizures has been reduced by 50%)	
	Normal intellectual ability	Disabled Persons
Incapacity	3/4 (75%)	None
Absences that are unusual	4/8 (50%)	6/19 (32%)
Seizures of myoclonus	3/6 (50%)	23/43 (53%)
Seizures of tonic amplitude	16/18 (89%)***	28/77 (36%)
GTC (generalized tonic-clonic)	26/30 (87%)**	21/37 (57%)
Various	19/23 (83%)*	14/28 (50%)

In the intellectually normal, the intellectually disabled, and the GTC populations, respectively, the P is .05, .01, and 0.001, respectively. GTC = generalized tonic clonic.

Table 2. A general improvement in the rating: partial seizures

Description of seizure	Improved (Reduction ≥50% of Seizure Frequency)	
	Intellectually Normal	Intellectually Disabled
Partial SPSs (Simple Partial Seizures)	73/89 (82%)***	27/39 (69%)
Complex Partial Seizures (CPS)	146/170 (86%)***	74/123 (60%)
SGS (Secondary Generalized Seizures)	131/150 (87%)***	70/103 (68%)
Various	11/13 (85%)***	3/5 (60%)

The terms SPS and CPS refer to simple partial seizures, respectively; SGS refers to secondarily generalized seizures. There was no significant difference between the intellectually normal and intellectually disabled groups with P=0.001.

Keeping safe

Patients with intellectual disabilities were affected 21% while patients with typical intellectual functioning were affected 28% (see Table 3). However, there was no significant difference between the groups with and without intellectual impairments when it came to negative events. Twenty-four patients were found to have experienced adverse effects after participating in this research study, which involved 349 patients.

Table 3. A list of medications that could negatively affect zonisamide

Group	Patients Experiencing Adverse Effects (%)	Patients Experiencing No Adverse Effects (%)	Total
Intellectually Normal	18 (21%)	66 (79%)	86 (100%)
Intellectually Disabled	27 (28%)	69 (72%)	96 (100%)

According to Table 4, zonisamide monotherapy (16%) was associated with fewer adverse events than combined therapy (28%); monotherapy had a statistically significant preference (P0.001). There was no significant age difference in adverse effects, except for the combined therapy group, where adverse effects increased 50%.

Table 4. A review of zonisamide adverse effects when taken in monotherapy and combination with other drugs

Age of Onset (years)	Zonisamide Monotherapy	Zonisamide Combination Therapy	Total
<1	2/14 (14%)	3/6 (50%)	5/20 (25%)
1–5	13/71 (18%)	34/142 (24%)	47/213 (22%)
6–10	15/112 (13%)	48/170 (28%)	63/282 (22%)
11–15	14/70 (20%)	53/174 (30%)	67/244 (27%)

****P*<0.001 (monotherapy vs. combination therapy).

Discussion and Conclusions

The placebo-controlled trial of zonisamide and valproate in Japan before commercial licensing showed zonisamide and valproate to reduce seizure frequency by 50 percent or more. An eight-week study was conducted in this study (8). Over the long-term, the general improvement rate was 62, which isn't substantially different from placebo-controlled studies. Patients with more than four seizures per month during the pre-launch study accounted for a significant portion of the sample. In addition to being administered to patients with infrequent seizures, zonisamide was also licensed for commercial use (9). Zonisamide's current efficacy differs from that of its previous effective period since background seizures are more common among patients today. According to the study, 78 percent of children with intellectually normal abilities enhanced their abilities, and 82 percent of children with generalized epilepsy did as well.

Partial epilepsy is more responsive to zonisamide than generalized epilepsy, according to strong consensus (10). It has been reported that patients who had an abnormality of the temporal lobe assessed by electroencephalographic recording, computed tomography, or positron emission tomography benefited from zonisamide. The same study also found that zonamide was ineffective for treating partial and generalized epilepsy with lesions in the temporal lobe. There was success in treating partial epilepsy and generalized epilepsy using zoneisamide, but not with generalized epilepsy. Several patients who responded well to zonisamide could have temporal lobe abnormalities that caused their generalized epilepsy.

A study comparing zonisamide's effects on intellectually normal patients and those with intellectual disabilities found that it had a greater effect on the intellectually normal patients. There is usually a disturbance of the central nervous system in children with intellectual disabilities. As a result of severe seizures, patients with intellectual disabilities may experience these disturbances. Even people with intellectual disabilities were able to control their seizures with zonisamide. In cases of intellectual disability and epilepsy, zonisamide can be used to treat both partial and generalized seizures.

Treatment-related adverse effects were often experienced by individuals with normal intelligence as well as those with intellectual disabilities. There were fewer adverse effects for zonisamide monotherapy than for zonisamide combined therapy, according to a study comparing monotherapy with combination therapy. Antiepilepsy drugs, including zonisamide, are more likely to have adverse effects when combined together [8-10].

In epileptic children treated with Zonisamide, anhidrosis and high temperatures have been reported. Shimizu et al. reported on a 2-year-old boy with intellectual disabilities who exhibited symptoms of heatstroke-like conditions while receiving zonisamide treatment. The patient suffered from hypopyrexia and oligohidrosis. As far as the present study was concerned, doctors did not report cases of anhidrosis. Those with intellectual disabilities, however, are less likely to notice anhidrosis and oligohidrosis. If you have hyperpyrexia or oligohidrosis, it is important that you use zonisamide.

Conclusion

When it came to treating partial and generalized seizures in children, zonisamide was more effective when administered to those with intellectual disabilities rather than those with normal intellectual abilities. It was found that generalized tonic-clonic seizures changed significantly, with 62 percent of patients improving overall. Drugs were effective, however, they showed less effectiveness in intellectually disabled children, perhaps due to these children's common problems with the central nervous system. There were some adverse reactions observed in 24% of patients, and the rate was higher in children with intellectual disabilities. A smaller number of adverse effects are associated with zonisamide monotherapy than with combination therapy. It is important to closely monitor side effects in young children with anhidrosis and high body temperatures. In order to achieve the best

possible outcomes for each child with epilepsy, safety should be observed when administering zonisamide, both for partial seizures and generalized seizures.

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