Zonisamide – a review of experience and use in partial seizures

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Abstract: Zonisamide is a modern antiepileptic drug (AED) that is distinguished from other AEDs by its unique structure and broad mechanistic profile. Preclinical studies have reported a range of potential mechanisms of action for zonisamide, such as blocking voltage-gated sodium channels, reduction of T-type calcium channel currents, and enhancement of gamma-aminobutyric acid (GABA)-mediated inhibition, which are indicative of its broad antiseizure effects. Zonisamide has a favorable linear pharmacokinetic profile, a long half-life, and a low incidence of protein-binding interactions with other AEDs. Hepatically metabolized through the cytochrome P450 pathway, zonisamide does not induce its own metabolism or liver enzymes. For more than 2 decades, zonisamide has been extensively used as monotherapy and adjunctive therapy for the treatment of partial and generalized seizures in pediatric and adult patients in Japan. Zonisamide was approved in the USA in 2000 as adjunctive therapy for partial seizures in adults. With over 2 million patient-years of exposure internationally, zonisamide has demonstrated safety and efficacy against a multitude of epilepsy and seizure types, including both partial and generalized seizures. This review focuses on the experience and use of zonisamide in partial seizures, as well as possible new uses for zonisamide.
Keywords: zonisamide, antiepileptic drug, partial seizures, epilepsy, seizure, efficacy

History of zonisamide

Zonisamide (Zonegran®; Eisai Inc, Teaneck, NJ, USA) is a newer, broad-spectrum antiepileptic drug (AED) that has been shown to be effective in the treatment of refractory partial seizures (Schmidt et al 1993; Faught et al 2001; Sackellares et al 2004). Chemically classified as a sulfonamide (Figure 1), zonisamide is characterized by a unique structural, mechanistic, and pharmacokinetic profile that is distinct from that of other AEDs. Zonisamide is a benzisoxazole derivative, originally synthesized in Japan in 1974 during exploratory research on psychiatric drugs, where it was subsequently identified as having anticonvulsant activity during screening (Seino 2004). Preclinical animal studies conducted in Japan revealed the antiseizure effects of zonisamide on maximal electroshock-induced seizures in rats, mice, rabbits, and dogs. In these animal models, zonisamide exhibited a wider therapeutic plasma concentration range compared with phenytoin and carbamazepine (Masuda et al 1979).

In 1979, zonisamide was evaluated in Phase I clinical trials at the National Epilepsy Center in Japan, where it was observed to have a long elimination half-life and good tolerability in a healthy male population. Phase II clinical trials were initiated in 1985 and were followed by Phase III trials. With over 1000 zonisamide-treated patients, the Japanese Phase II and Phase III trials showed that zonisamide was effective against simple and complex partial seizures, partial seizures with secondary generalization, and select generalized seizures (eg, tonic-clonic). In addition, zonisamide as monotherapy was effective in these trials, with 72% of patients

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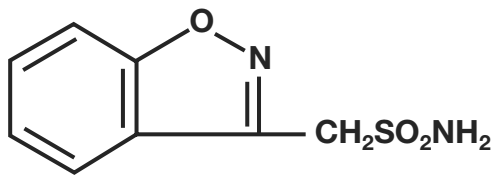

Figure 1 Chemical structure of zonisamide.

experiencing greater than 50% seizure reduction compared with baseline. In these trials, zonisamide was shown to be either superior or equivalent in efficacy and safety to existing AEDs. Adverse events (AEs) observed with zonisamide included drowsiness, ataxia, and loss of appetite (Seino 2004).

With promising results from the animal and clinical studies, zonisamide was approved in Japan in 1989 as both monotherapy and adjunctive therapy for children and adults with generalized or partial seizures. Zonisamide was later marketed for the same indication in South Korea in June 1992 (Seino 2004). Several controlled clinical studies conducted in the USA and Europe further demonstrated zonisamide's efficacy in the treatment of partial seizures in adults. Zonisamide was approved in 2000 in the USA as adjunctive therapy in the treatment of partial seizures in adults with epilepsy (Schmidt et al 1993; Faught et al 2001; Sackellares et al 2004). Currently, clinical experience with zonisamide has yielded a conservative approximation of 2 million patient-years of exposure worldwide (Brodie et al 2005).

Mechanism of action

Although the precise molecular mechanisms behind the antiseizure activity of zonisamide are unknown, zonisamide has demonstrated a broad mechanistic profile in animal models. Zonisamide is thought to act through its blocking of voltage-dependent sodium channels, reduction of voltage-dependent T-type inward calcium currents, binding to the gamma-aminobutyric acid (GABA)–benzodiazepine receptor complex, and facilitation of both dopaminergic and serotonergic neurotransmission, as summarized in Table 1. Although zonisamide exhibits weak carbonic anhydrase inhibition, this is not considered a primary mechanism of action in its antiseizure activity.

Block of selected voltage-gated ion channels

The antiepileptic effects of zonisamide on generalized tonic-clonic and partial seizures are believed to stem from the modulation of voltage-gated sodium channels. In an in vitro study using *Myxicola* giant axons and in another study of cultured mouse spinal cord neurons, zonisamide was shown to reduce high-frequency repetitive firing via a block of voltage-gated sodium channels (Schauf 1987; Rock et al 1989). Other AEDs, including phenytoin, lamotrigine, and carbamazepine, also exhibit this mechanism of action (White 1999; Rogawski and Loscher 2004). In other animal studies, zonisamide was shown to block low-voltage gated T-type calcium channels (Suzuki et al 1992; Kito et al 1996). T-type calcium channels are thought to regulate neuronal firing and play a role in childhood absence epilepsy, and may also account for some of zonisamide's antiseizure effect against catastrophic childhood epilepsy (White 1999; Rogawski and Loscher 2004).

Table 1 Potential mechanisms of action and effects of zonisamide

Potential mechanism of action	Potential effect
Block of voltage-gated sodium channels	Reduction in generalized tonic-clonic and partial seizures
Block of voltage-gated T-type calcium channels	Reduction in absence seizures
Increase in extracellular GABA	Increase in GABA-mediated inhibition of seizures
Reduction in extracellular glutamate	Reduction in seizure activity initiated by extracellular glutamate
Serotonergic interactions	Reduction in seizure activity and/or an increase in positive psychotropic effects
Dopaminergic interactions	Reduction in seizure activity and/or an increase in positive psychotropic effects
Free radical scavenging	Neuroprotective effect

Abbreviations: GABA, gamma-aminobutyric acid.

Enhancement of GABA

Kawai and colleagues (1994) showed that zonisamide enhances the release of GABA from slices of mouse hippocampus tissue. These results suggest that elevations of GABA levels in the brain and increases in GABA-mediated inhibition may be associated with the antiseizure activity of zonisamide (Kawai et al 1994). Ueda et al (2003) showed that zonisamide could also increase extracellular GABA by the up-regulation of a neuronal glutamate transporter (ie, EAAC-1) and a decreased production of the GABA transporter (ie, GAT-1) in the rat hippocampus and frontal cortex. The altered expression of the rat glutamate–GABA transporters and increase in extracellular GABA may enhance GABA's inhibitory effect during seizures (Ueda et al 2003). Hence, it appears that zonisamide can increase

GABA-mediated inhibition through two distinct molecular mechanisms, a primary and secondary mechanism.

Block of glutamate neurotransmission

The effects of zonisamide on neurotransmission and intracellular calcium have been evaluated in several preclinical studies. Results from these studies suggest that zonisamide reduces calcium-dependent, potassium-evoked extracellular glutamate release in the hippocampus (Okada et al 1998; Zhu and Rogawski 1999). Since glutamate is an excitatory neurotransmitter, and excessive release of glutamate may produce seizures, a reduction in glutamate release may reduce seizure activity and may affect epileptogenesis (Carlson et al 1992).

Interaction with other neurotransmitters

Multiple studies have shown that zonisamide affects dopaminergic and serotonergic neurotransmission (Okada et al 1995, 1999; Kiryu et al 1997; Kawata et al 1999). In the rat hippocampus and striatum, zonisamide was noted to have a biphasic, dose-dependent effect on extracellular dopamine levels. At therapeutic zonisamide doses of 20–50 mg/kg, extracellular dopamine levels were increased; however, at higher doses (≥ 100 mg/kg), dopamine levels were decreased. Okada and colleagues (1999) suggested that this effect may account for the antiseizure and mood-stabilizing effects of zonisamide, as well as the adverse effect of sedation (Okada et al 1995). Zonisamide was reported to have a similar biphasic effect on serotonin levels in the rat hippocampus that was also dose-dependent. Again, it was thought that these effects may be involved with the antiseizure effects of zonisamide, as well as with positive psychotropic effects, such as improvements in bipolar and schizophrenic manic states (Okada et al 1999).

Free radical scavenging and neuroprotective effects

Current research has associated free radical damage with epilepsy (Komatsu et al 1995; Sudha et al 2001), and the use of antioxidants early in the treatment of seizure-precipitating injuries is an attractive prevention target (Schwartzkroin 2004). Several studies have shown that the mechanism of antiepileptic effects of zonisamide may involve protection of neurons from free-radical damage by scavenging hydroxyl and nitric oxide radicals in a dose-dependent manner (Mori et al 1998, 2004; Noda et al 1999). Zonisamide has also been reported to have free-radical scavenging activity and an inhibitory effect on lipid peroxide formation in rats with iron-induced epileptogenic foci (Komatsu et al 1995). In addition, the inhibition of excessive glutamate release following ischemic insult has been shown to protect against glutamate-induced neuronal damage in gerbils (Owen et al 1997). Another neuroprotective effect of zonisamide, unrelated to its anticonvulsant activity, was noted by Hayakawa et al (1994). In that study, a reduction in hypoxic-ischemic brain damage in neonatal rats was observed with zonisamide treatment; however, the exact mechanism by which the drug exerted this effect is unknown.

Pharmacokinetics (PK)

Population PK parameters were used for determining dose regimens in epileptic patients (Peters and Sorkin 1993; Hashimoto et al 1994; Kochak et al 1998). A favorable linear PK profile has been reported for zonisamide, and the zonisamide parameters are summarized in Table 2.

PK profile

The PK profile of zonisamide has been well characterized. Zonisamide is rapidly and completely absorbed after oral administration. The time to maximal concentration (T_{max}) following oral administration of 200–400 mg zonisamide is 2–6 hours and is slightly delayed with food intake at 4–6 hours. The PK parameters of zonisamide are dose proportional with 200- to 400-mg dosing, but at 800-mg dosing and above, the area under the curve (AUC) and maximum plasma concentration (C_{max}) increase disproportionately. It has been suggested that this disproportion occurs due to the saturation of red blood cells with zonisamide. With a stable maintenance dosage, steady state is usually achieved within 14 days (Peters and Sorkin 1993; Eisai Inc 2004; Leppik 2004).

Table 2 Pharmacokinetic profile of zonisamide

Parameter	Value
T_{max}	2–6 h
Bioavailability	> 95%
Protein binding	40%
Elimination	Renal
Elimination half-life	63 h
Elimination half-life after concurrent administration of other AED(s)	
Phenytoin	27 h
Phenobarbital, carbamazepine	38 h
Valproate	46 h

Abbreviations: AED, antiepileptic drug; h, hour; T_{max}, time to maximal concentration.

Long half-life

Zonisamide is concentrated in red blood cells through carbonic anhydrase and protein binding. It is only 40% protein bound, which suggests a relatively low risk of protein-binding interactions with concomitant AEDs. The elimination half-life of zonisamide in plasma is between 63 and 69 hours in healthy volunteers, and the elimination half-life in red blood cells is approximately 105 hours. The long half-life of zonisamide is a key advantage that enables a once-daily dose regimen and assures attainment of steady therapeutic drug levels. Even when zonisamide is given with isoenzyme-inducing AEDs, its half-life remains above 24 hours (Kochak et al 1998; Leppik 1999; Eisai Inc 2004; Leppik 2004).

Metabolism

Hepatically metabolized through the cytochrome P450 pathway by isoenzyme 3A4, zonisamide does not induce its own metabolism, nor does it induce liver enzymes. Concomitant AEDs may affect the PK of zonisamide by inducing liver isoenzymes at the cytochrome P450 pathway, and may require dosage adjustments of zonisamide; however, zonisamide does not affect the PK of other AEDs (Eisai Inc 2004).

Zonisamide is metabolized via two major pathways. It undergoes acetylation to form N-acetyl zonisamide and reduction to form the open-ring metabolite 2-sulfamoylacetyl phenol (SMAP). The cytochrome P450 isoenzyme 3A4 (CYP3A4) mediates reduction to SMAP. Unlike some AEDs, zonisamide does not produce any active metabolites. Unchanged zonisamide constitutes about 35% of the excreted dose, which is excreted primarily in the urine (Stiff et al 1992; Nakasa et al 1993; Eisai Inc 2004).

Drug-drug interactions

Concomitant drugs that either induce or inhibit CYP3A4 may alter serum concentrations of zonisamide. Concurrent administration of phenytoin and carbamazepine with zonisamide has been shown to increase zonisamide plasma clearance from 0.30 to 0.35 mL/min/kg to 0.35 to 0.5 mL/min/kg (Ragueneau-Majlessi et al 2004). The 63-hour elimination half-life of zonisamide has been reported to be decreased to 27 hours by phenytoin, to 38 hours by phenobarbital and carbamazepine, and to 46 hours by valproate. Hence, when these AEDs are coadministered with zonisamide, therapeutic monitoring is necessary and dosage adjustments of zonisamide may be required. However, recent studies have reported that valproate does not affect the PK of zonisamide, and no dosage adjustment of either drug should be required when used together (Ragueneau-Majlessi et al 2005). Studies have also shown that concurrent administration of lamotrigine

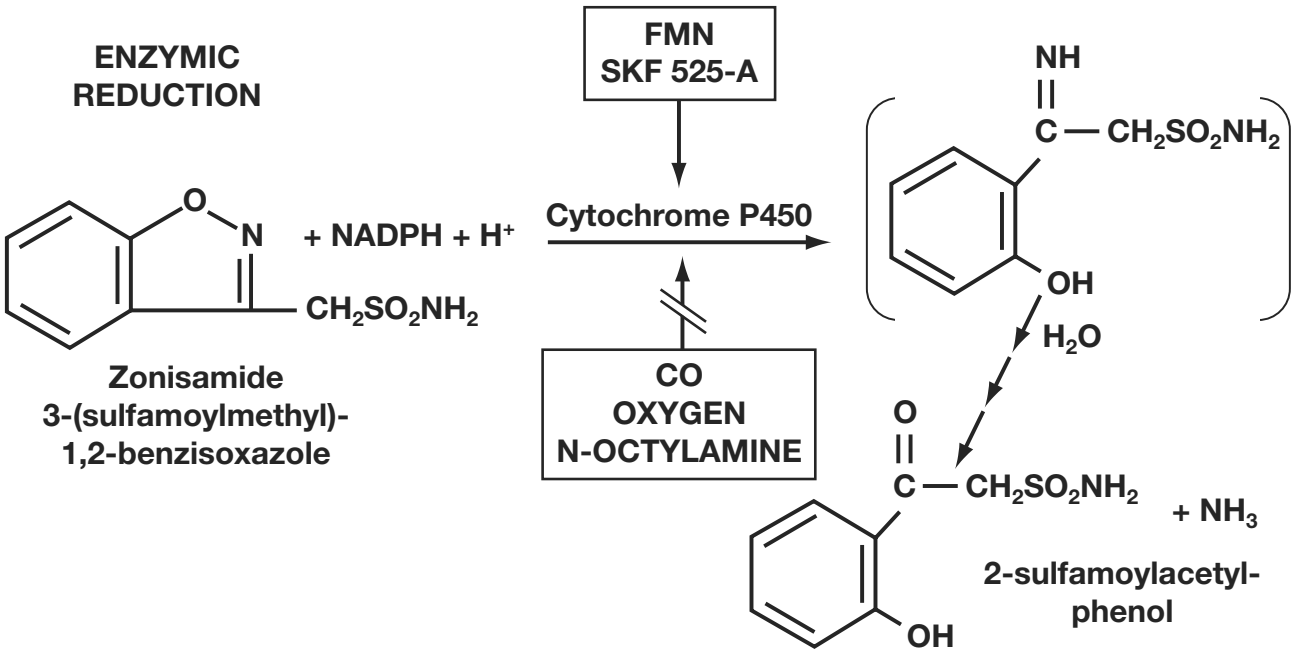

Figure 2 Cytochrome P450 reduction and nonenzymic hydrolysis. Zonisamide is metabolized through two major pathways: (1) by reductive cleavage of the benzisoxazole ring of the parent drug by cytochrome P450 isoenzyme 3A4 (CYP3A4) to form 2-sulfamoylacetyl phenol (SMAP) and (2) by acetylation to form N-acetyl zonisamide. Reprinted from: Leppik IE. 2004. Zonisamide: chemistry, mechanism of action, and pharmacokinetics. *Seizure*, 13(Suppl 1):S5–9. Copyright © 2004, with permission from BEA Trading Ltd.
Abbreviations: FMN, flavin mononucleotide; SKF 525-A, inhibitor and inducer of cytochrome P450.

and zonisamide does not alter the steady-state PK of either drug, also demonstrating that no dosage adjustment is required (Levy et al 2005). Zonisamide does not alter the PK parameters of concomitant AEDs due to its low protein binding (Cloyd and Remmel 2000; Eisai Inc 2004).

Effects on oral contraceptives (OCs)

Unlike other AEDs, steady-state zonisamide dosing has been shown to have no significant effect on the PK of a combination OC, specifically ethinyl estradiol (EE, 0.035 mg) and norethindrone (NOR, 1 mg), in healthy, premenopausal women aged 18–51 years (mean age 26.1 years). Additionally, zonisamide did not increase concentrations of luteinizing hormone, follicle-stimulating hormone, or progesterone, which are indicators of contraceptive efficacy. Hence, no pharmacodynamic evidence of zonisamide reducing the effectiveness of OCs containing EE or NOR has been documented (Griffith and Dai 2004).

Safety

Zonisamide is generally safe and well tolerated for use in patients with epilepsy. The most commonly reported AEs associated with zonisamide use in controlled clinical trials were somnolence, anorexia, dizziness, headache, nausea, and agitation–irritation (Eisai Inc 2004).

Postmarketing studies conducted in Japan revealed that pediatric patients appear to be at an increased risk for oligohidrosis and hyperthermia in association with zonisamide use. Patients should be monitored closely for signs of decreased sweating and increased body temperature, especially in warm or hot weather (Eisai Inc 2004).

In some patients taking zonisamide, weight loss has been observed, in contrast to the weight gain that is often observed in clinical studies of other AEDs. In a pivotal clinical study of zonisamide in 203 patients with refractory partial-onset seizures, weight loss of greater than 5 pounds was reported in 21.6% of zonisamide-treated patients, while it was reported in only 10.4% of placebo-treated patients ($p = 0.044$) (Faught et al 2001).

Management of partial seizures

Since up to 30% of patients with epilepsy, specifically those with partial seizures, become refractory to treatment with standard AEDs, effective treatment for this group is of interest (Chadwick and Marson 2000). Extensive clinical data worldwide have shown that zonisamide is effective and well tolerated for the treatment of refractory partial seizures. In the USA and Europe, 22 Phase II/III studies of zonisamide have been conducted, including two controlled studies each in the USA and Europe. Three of these (two in the USA and one in Europe) were pivotal for US approval in evaluating the safety and effectiveness of adjunctive zonisamide in a total of 493 adult patients with refractory partial seizures who were receiving one or two other AEDs (Schmidt et al 1993; Faught et al 2001; Sackellares et al 2004). These were all double-blind, randomized, parallel-group, placebo-controlled, multicenter studies. Efficacy results for these studies, including the median percentage reduction in partial seizures and percentage of responders (ie, patients having ≥50% seizure reduction), are presented in Table 3 (Eisai Inc 2004). A more recent investigation into the effectiveness and tolerability of adjunctive zonisamide, as well as their dose-response relationship, was conducted in a large cohort of patients with epilepsy (Brodie 2005). These four studies are described in detail below.

Schmidt et al 1993

Schmidt et al (1993) conducted a European placebo-controlled, double-blind study in 139 patients with partial epilepsy. All enrolled patients were previously receiving one

Table 3 Median percentage reduction in all partial seizures and percentage responders in primary efficacy analyses: intent-to-treat analysis

	Median % reduction in partial seizures		% Responders[a]	
Study	**Zonisamide**	**Placebo**	**Zonisamide**	**Placebo**
Faught et al 2001	n = 98	n = 72	n = 98	n = 72
Weeks 8–12	40.5[b]	9.0	41.8[b]	22.2
Sackellares et al 2004	n = 69	n = 72	n = 69	n = 72
Weeks 5–12	29.6[b]	−3.2	29.0	15.0
Schmidt et al 1993	n = 67	n = 66	n = 67	n = 66
Weeks 5–12	27.2[b]	−1.1	28.0[b]	12.0

[a] Responders are patients with ≥ 50% reduction in partial seizure frequency.
[b] $p < 0.05$ compared with placebo.

to three AEDs, such as carbamazepine, phenobarbital, phenytoin, and primidone. The median frequency reduction for all partial seizures (eg, complex and simple) was significantly higher for patients taking zonisamide (26.9%) than for the placebo group ($p < 0.05$), who experienced a 3.9% median increase. For simple partial seizures, zonisamide-treated patients experienced a higher median seizure frequency reduction (72.6%) than did placebo-treated patients (48.1%). For all partial seizures, 30.3% of zonisamide-treated patients experienced a greater than 50% reduction, while 10.9% of placebo-treated patients reported the same effect ($p < 0.05$). For generalized and partial seizures, 29.9% and 9.4% of patients on zonisamide and placebo, respectively, were considered responders ($p < 0.05$). Fifty-nine percent and 27.9% of zonisamide- and placebo-treated patients experienced AEs, respectively. The most common AEs included fatigue, somnolence, and dizziness (Schmidt et al 1993).

Faught et al 2001

Faught and colleagues (2001) conducted a dose-response study of adjunctive zonisamide in 203 patients with refractory partial seizures, 146 (72%) of whom completed the 5-month study. The study included patients who were receiving one or two standard AEDs consisting of carbamazepine, phenobarbital, phenytoin, primidone, or valproic acid. After the baseline phase, zonisamide was titrated to a daily dose of 400 mg at three staggered titration rates. Efficacy and safety were evaluated at zonisamide dosages of 100, 200, and 400 mg/day. Efficacy (change in seizure frequency from weeks 8 to 12 compared with baseline) was reported to be comparable between zonisamide daily dosages of 100 and 200 mg, with a median reduction in seizure frequency of 24.7% for the zonisamide group compared with 8.3% for the placebo group (100-mg/day dose) and 20.4% for zonisamide versus 4.0% for placebo (200-mg/day dose). The median seizure frequency reduction was 40.5% for patients receiving zonisamide 400 mg/day, and 9.0% for placebo-treated patients ($p = 0.009$). The difference in efficacy observed between low and high dosages of zonisamide suggested a dose-response effect (Table 4). For all zonisamide dosages, the number of zonisamide-treated patients who were responders (ie, had ≥50% seizure frequency reduction) was significantly greater than that reported for placebo-treated patients ($p < 0.05$, Table 4). Adverse events of somnolence, anorexia, and rhinitis were reported most frequently, and occurred at a slightly higher incidence with zonisamide than placebo. Weight loss was the only AE with a significantly higher incidence rate in zonisamide-treated patients (21.6%) compared with patients on placebo (10.4%, $p = 0.044$). The percentage of patients who discontinued treatment due to AEs while on zonisamide therapy (10%) was comparable to those on placebo (8.2%, p = NS). Overall, most AEs were mild to moderate and declined with time (Faught et al 2001).

Sackellares et al 2004

In the study reported by Sackellares and colleagues (2004), 152 patients (age range 18–68 years, mean 36 years) who were receiving one to two AEDs, such as carbamazepine, phenobarbital, phenytoin, and primidone were randomized to either a maximum zonisamide dosage of 400–500 mg/day (given twice daily) or placebo. Of these, 131 patients completed treatment at week 12, including 64 patients (82.1%) in the zonisamide group and 67 patients (90.5%) in the placebo group. A 28.9% reduction in partial seizure

Table 4 Median percentage reduction in all partial seizures and percentage responders for dose analysis in Faught et al 2001: intent-to-treat analysis

	Median % reduction in partial seizures		% Responders[a]	
Dose group	**Zonisamide**	**Placebo**	**Zonisamide**	**Placebo**
100–400 mg/day	n = 112	n = 83	n = 112	n = 83
Weeks 1–12	32.3[b]	5.6	32.1[b]	9.6
100 mg/day	n = 56	n = 80	n = 56	n = 80
Weeks 1–5	24.7[b]	8.3	25.0	11.3
200 mg/day	n = 55	n = 82	n = 55	n = 82
Weeks 2–6	20.4[b]	4.0	25.5[b]	9.8
400 mg/day	n = 98	n = 72	n = 98	n = 72
Weeks 8–12	40.5[b]	9.0	41.8[b]	22.2

[a] Responders are patients with ≥50% reduction in partial seizure frequency.
[b] $p < 0.05$ compared with placebo.

frequency was reported for the zonisamide group, while a 4.7% increase in partial seizure activity was reported for the placebo group ($p = 0.0009$). The zonisamide group had a greater percentage of responders: 26.9% compared with 16.2% for the placebo group ($p = 0.1141$). On the basis of patient and physician global assessments, more patients on zonisamide were rated as improved compared with placebo. The most common AEs were somnolence, irritability, and dizziness. During this study, the authors determined that a slower titration of zonisamide (100 mg/day Week 1, 200 mg/day Week 2, 400 mg/day Week 3 versus starting at 400 mg/day) was associated with fewer AEs (Sackellares et al 2004).

Brodie et al 2005

In a double-blind, placebo-controlled, dose-response study, 351 patients with refractory partial seizures on a stable regimen of one to three AEDs were randomized to placebo or zonisamide 100, 300, or 500 mg/day. Patients (efficacy-analysis population) given zonisamide 300 and 500 mg/day experienced a significantly greater median reduction in frequency of all partial seizures (complex and simple) than did placebo-treated patients (zonisamide 300 mg/day, 46.4% [$p = 0.0007$ vs placebo]; zonisamide 500 mg/day, 50.6% [$p < 0.0001$ vs placebo]; placebo, 19.4%; efficacy-analysis population). The median reduction in frequency of all partial seizures in zonisamide-treated patients at 100 mg/day was similar to placebo. In addition, the percentage of responders for all partial seizures was higher for all zonisamide groups (500 mg, 50.5%; 300 mg, 42.9%; 100 mg, 28.8%) compared with placebo (20.2%), with a statistically significant treatment difference between the 500-mg/day group and placebo ($p < 0.001$). In this study, and in the 2001 US study (Faught et al 2001), a significant dose-response relationship was observed with all seizure types ($p < 0.0001$). The most frequent AEs were somnolence, headache, and dizziness (Brodie et al 2005). The results presented in this study were pivotal for approval of zonisamide use in Europe.

Clinical applications of zonisamide

Pediatric patients

Many AEDs do not have indications for pediatric use, yet these agents are commonly used in pediatric epilepsy. In the US, while zonisamide is not approved for use in pediatric patients, data are accumulating from its clinical use in children. One open-label chart review completed in the US evaluated 50 charts of pediatric patients with epilepsy (mean age, 9.1 years; age range, 9 months to 20 years) who were on zonisamide therapy (Santos and Brotherton 2005). Three patients were taking zonisamide as monotherapy, the remainder of the patients as adjunctive therapy; lamotrigine and valproate were the most common concomitant AEDs. Prior to treatment, the children averaged three to four seizures per week. The mean daily dose of zonisamide was 15.8 mg/kg or 412 mg. At the end of treatment, 8 patients (16.0%) were seizure free, and 11 (22.0%) were responders to treatment with greater than 50% reduction; of these patients, 11 (22.0%) were previously unsuccessfully treated while on 6 or more AEDs. Antiseizure activity for seizure-free patients and responders was reported to occur within the first 2 weeks of treatment. Eleven patients (22.0%) had less than 50% seizure reduction. Thirty-one patients (62.0%) experienced at least one AE; 14 discontinued treatment due to an AE. The most frequently reported AEs were reduction in appetite (28.0%), weight loss (10.0%), and increased phenytoin levels in patients concurrently taking phenytoin (10.0%).

Juvenile myoclonic epilepsy (JME)

Juvenile myoclonic epilepsy is found in 5%–11% of all patients with epilepsy, and it possesses multiple seizure types, including myoclonic, generalized tonic-clonic, and absence. Valproate is currently recommended as the drug of choice in treating JME. With the knowledge of zonisamide's broad spectrum of antiepileptic effects, several retrospective studies have been conducted to assess the efficacy and safety of zonisamide as a treatment for JME. In a study by Kothare and colleagues (2004), 15 patients aged 11–20 years who were diagnosed with JME and treated with zonisamide were identified. Patients received zonisamide 200–500 mg/day for a mean follow-up period of 12 months (range, 2–24 months); 2 patients were given zonisamide adjunctively, with the remainder of the patients on zonisamide monotherapy. Eighty percent of patients on zonisamide monotherapy experienced 50% or greater seizure frequency reduction. Seizure freedom was achieved with 69%, 62%, and 38% of patients for generalized tonic-clonic, myoclonic, and absence seizures, respectively. One patient on adjunctive therapy experienced a greater than 75% seizure reduction, while another patient showed no effect. Three patients (20.0%) experienced AEs, including weight loss, headache, and dizziness, which resolved with maintenance (Wallace 1998; Kothare et al 2004). A retrospective study conducted by Welty and colleagues (2004) also showed that zonisamide may be effective for

JME. In this chart review, the efficacy and safety of zonisamide were examined in 36 patients on various AEDs (eg, lamotrigine, topiramate, levetiracetam, and zonisamide). The authors concluded that zonisamide was associated with a decrease in frequency of myoclonic, generalized tonic-clonic, and absence seizures, which are all characteristic of JME. They also noted that the use of zonisamide allowed for the discontinuation of concomitant valproate (Welty 2004).

Absence seizures

Wilfong and Schultz (2005) conducted a chart review of 45 patients (mean age, 11.4 years; range, 2.8–17.9 years) with absence seizures to assess the effectiveness and safety of zonisamide in absence epilepsy. Patients received a mean daily dose of zonisamide 343 mg or 9.0 mg/kg (range, 100–600 mg or 2–24 mg/kg). Twenty-three of 45 patients (51.1%) obtained seizure freedom, while 16 of 45 patients (35.6%) experienced 50% or greater seizure reduction. Five patients (11.1%) had less than 50% seizure reduction, while one patient (2.2%) had an increase in seizure frequency. Nineteen patients (42.2%) reported one or more AEs, with decreased appetite (15.5%) and sleepiness (11.1%) being the most common. Two patients discontinued zonisamide therapy due to an increase in seizure frequency for one, and apparent inefficacy and sleepiness in the other.

The Japanese experience

Zonisamide is approved for use with pediatric patients in Japan and has consequently been used extensively in children by physicians and in controlled clinical studies. Japanese clinical and postmarketing data have demonstrated that zonisamide adjunctive and monotherapy is efficacious and well tolerated in children with various epileptic syndromes, as well as in adults.

In a Japanese PK and efficacy study, zonisamide monotherapy as once-daily dosing was investigated in 72 pediatric patients aged 3 months to 15 years (mean, 8 years and 3 months). These patients were diagnosed with cryptogenic localization-related epilepsy with partial seizures and had not received prior treatment for epilepsy. Zonisamide was started at a daily dosage of 2 mg/kg and was doubled each week to obtain a maintenance dosage (mean, 7.97 mg/kg). Seizure control was achieved in 57 of the 72 patients (79.2%). The therapeutic range for zonisamide plasma levels for these pediatric patients was found to be 15–40 μg/mL. Peak-to-trough ratios were small (mean, 1.28; SD 0.15), similar to those observed in healthy adult volunteers (Kochack et al 1998). There was no clear relationship between zonisamide plasma levels and seizure control. For patients with less than 50% seizure reduction, the addition of carbamazepine to the drug regimen helped seizure control with limited success. Overall, this study demonstrated that zonisamide can provide effective control as monotherapy in pediatric patients. The authors recommended that age and weight be taken into consideration for the initial maintenance dose, because ratios of plasma zonisamide levels to dose increase with age (Miura 2004).

In 2002, 20 Japanese pediatric clinical trials were summarized and analyzed in a review of the Japanese postmarketing experience. Fourteen of these trials were predominately open-label assessments of the efficacy and safety of zonisamide for the treatment of partial- and generalized-onset seizures. The remainder of the trials evaluated zonisamide use in children with Lennox-Gastaut syndrome (LGS) or infantile spasms (IS) (Glauser and Pellock 2002).

In the five open-label trials of zonisamide as adjunctive therapy in pediatric patients with partial- and generalized-onset seizures, 34% and 15% of children with partial and generalized seizures, respectively, were considered responders to zonisamide at a daily dosage of 0.7–18.6 mg/kg, or where not reported as mg/kg, at 50–600 mg. In five trials that examined zonisamide monotherapy, data from 209 pediatric patients with partial seizures and 49 patients with generalized-onset seizures were analyzed. Results indicated that 78% of patients (164/209) with partial seizures and 71% of patients (35/49) with generalized-onset seizures were responders to zonisamide monotherapy at daily dosages of 1–12 mg/kg (Glauser and Pellock 2002).

Five small, open-label studies assessed the efficacy of zonisamide adjunctive therapy in a total of 64 children with IS. In these studies, the number of patients reported as responders ranged from 22% (2/9) to 36% (8/22). A few studies of zonisamide have been performed in children with LGS as well, with reports of 26% (10/39) to 50% (10/20) of patients being responders to zonisamide (Glauser and Pellock 2002).

In these Japanese pediatric postmarketing studies, the most commonly reported AE was somnolence. The AEs were generally mild to moderate in severity, were similar to those seen in adults, and were typical of other AEDs. The incidence of AEs was greater with increasing zonisamide dosage and concomitant AEDs in use. Resolution of most AEs was reported to occur with adjustments of dosage or drug regimen. Zonisamide was best tolerated in children

when the daily dosage was increased in small increments of 0.5–1.0 mg/kg every 2 weeks (Glauser and Pellock 2002). Overall, clinical experience in Japan has demonstrated that zonisamide is safe and well tolerated in children with various seizure disorders and epileptic syndromes.

Zonisamide as monotherapy

Published literature has reported that monotherapy, if effective, is a more attractive option for patients with epilepsy than adjunctive therapy, although this goal is often not realized. Monotherapy prevents drug-drug interactions with other AEDs, reduces the incidence of AEs, and improves patient compliance. Short- and long-term efficacy of zonisamide as monotherapy for epilepsy has been investigated in the USA and Japan. In one Japanese study, zonisamide as monotherapy was assessed for up to 5 years in 77 pediatric patients aged 8 months to 15 years. Nine patients were withdrawn due to AEs and were not included in the efficacy analysis, but were included in the assessment of AEs. Patients were administered zonisamide at a daily dosage of 2–12 mg/kg. In general, both patients with partial seizures and patients with generalized seizures were responders to zonisamide therapy. Patients who were seizure-free or responders (≥ 50% seizure reduction) to zonisamide therapy tended to have a longer duration exposure to zonisamide (mean, 1.75 years) compared with nonresponders (< 50% seizure reduction; mean, 4 months). Thirty patients (39.0%) reported AEs, including somnolence (11.7%), reduction in spontaneity (7.8%), anorexia (6.5%), and rash (6.5%) (Seki et al 2004).

In 2004, a Japanese prospective postmarketing study investigated the long-term effectiveness of zonisamide in over 1600 pediatric and adult patients with partial and generalized epilepsy. Results of this study indicated that zonisamide was significantly effective in treating idiopathic generalized epilepsy and treating partial epilepsy, with 78% and 58% of patients reporting seizure improvement (ie, ≥ 50% reduction in seizure frequency), respectively. In addition, more than 50% of patients with myoclonic and atypical absence seizures and 28% of patients with West syndrome or LGS showed improvements with zonisamide therapy. The authors of the postmarketing study found that patients on zonisamide monotherapy had greater improvement than patients on polytherapy (Yamauchi and Aikawa 2004). Overall, the efficacy of long-term use of zonisamide was maintained and was significantly effective against partial and generalized seizures, while showing promise for the treatment of other epilepsies.

The long-term effects of zonisamide as monotherapy were also assessed by Fukushima and Seino (2004) in a Japanese database survey. More than 790 patients with epilepsy were treated with zonisamide as adjunctive or monotherapy; 51 adults and children (24 males, 27 females) were selected for analysis. In this study, partial seizures, generalized seizures, drop attacks (ie, atonic seizures), atypical absence seizures, myoclonic seizures, and LGS were shown to be effectively controlled with zonisamide. Thirty-eight patients continued zonisamide monotherapy, but 13 patients discontinued zonisamide due to lack of efficacy (n = 10), restlessness and insomnia (n = 2), and failure to take zonisamide (n = 1) (Fukushima and Seino 2004).

In a recent US chart review study of pediatric and young adult patients with a range of seizure types, 131 patients aged 1–22 years using zonisamide as monotherapy were evaluated via seizure diaries and patient subjective assessments of efficacy. Patients were given a median maintenance dosage of zonisamide 260 mg/day (range, 100–800 mg/day). Of the 131 patients, 101 (77.1%) achieved a 50% or greater reduction in seizure frequency, and 39 (29.8%) were seizure free. The percentage of patients in each age group who achieved seizure freedom is shown in Figure 3. Forty-three patients (32.8%) experienced at least one AE, with decreased appetite (9.2%), weight loss (6.9%), sleeplessness (5.3%), and sedation (3.8%) as the most common AEs. Only three patients (2.3%) discontinued due to an AE, specifically for sleeplessness and increased seizure frequency, failure to gain weight, and behavioral changes (Wilfong 2005).

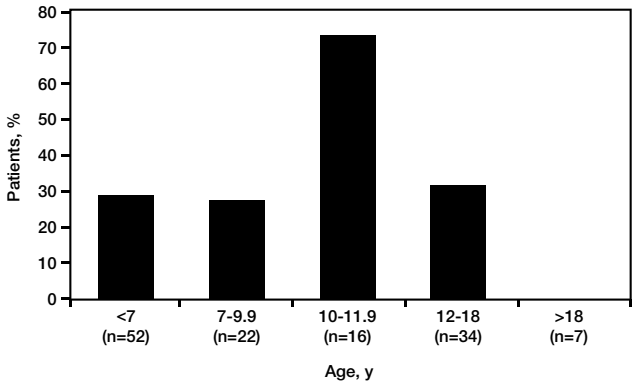

Figure 3 Proportion of seizure-free patients on zonisamide monotherapy stratified by patient age. Reprinted from: Wilfong AA. 2005. Zonisamide monotherapy for epilepsy in children and young adults. *Pediatr Neurol*, 32:77–80. Copyright © 2005, with permission from Elsevier.

Catastrophic epilepsies of childhood

Catastrophic epilepsies, such as progressive myoclonic epilepsy (PME) and IS pose a significant treatment challenge. Many patients with catastrophic epilepsies are refractory to standard AED treatment. Further, the occurrence of multiple seizure types in patients with these epilepsies complicates treatment, as one AED may decrease the occurrence of one seizure type while exacerbating another type (Conry 2004). Zonisamide has shown promise as an effective treatment for these childhood epilepsies, as described in the following studies.

Progressive myoclonic epilepsy (PME)

Etiologically categorized into multiple subtypes, PME is characterized by progressive neurodegeneration and myoclonic seizures. Myoclonic seizures are difficult to classify since they may be focal or regional, rhythmic or arrhythmic, small or massive contractions, and they can occur unilaterally or bilaterally. In addition, patients with PME often present with other seizure types, including generalized tonic-clonic, absence, and partial seizures (Leppik 2003). Treatment of seizures in patients with PME is complicated and determining efficacy is confounded by a multitude of factors, such as the progression of the PME (Conry 2004). As PME progresses, myoclonic seizures may debilitate the patients, as normal daily activities, such as eating and drinking, become more challenging (Leppik 2003).

Progressive myoclonic epilepsy can be divided into severe myoclonic epilepsy syndromes of infancy and childhood, or the less severe progressive PMEs of juvenile or adult onset. There are many different forms of PMEs but the most common type of PME is Unverricht-Lundborg disease (ULD), an autosomal recessive inherited disorder. The onset of ULD generally occurs between 8 and 13 years of age, with a late peak occurrence. The progression of this disease usually stabilizes at the age of 40. Lafora's disease is another type of PME distinguished from ULD by dementia, fast progression, and intracellular inclusion bodies. Onset of Lafora's disease occurs between the ages of 14 and 16 years, and patient survival usually does not exceed 12 years post-onset (Leppik 2003).

Currently, valproate is the gold standard for treatment of PME; however, a potential for hepatic and pancreatic dysfunction requires constant monitoring of patients receiving such medication (Conry 2004). Recent studies have suggested the use of zonisamide for the treatment of PME (Henry et al 1988; Kyllerman and Ben-Menachem 1998; Vossler and the Zonisamide PME Study Group 2002; Leppik 2003; Conry 2004). Henry and colleagues (1988) reported that two patients with PME had a marked reduction in seizure frequency and significant improvements after treatment with zonisamide, including normal speech and improved short-term memory and ataxia. In a case study by Kyllerman and Ben-Menachem (1998), five patients with ULD and one patient with Lafora's disease (ages 19–42 years) were evaluated for a follow-up period of 2–3 years after receiving a daily dose of zonisamide of 100–600 mg with concomitant AEDs, such as valproate and benzodiazepine. A dramatic reduction in myoclonic and generalized seizures was obtained with zonisamide in all patients; however, in 3 patients, the antiseizure effect on myclonic seizures was absent after 2–4 years of treatment (Kyllerman and Ben-Menachem 1998).

One open-label study of zonisamide was performed with 30 patients with PME (mean age, 18.4 years; range, 4–41 years). Ten patients (33.3%) discontinued treatment due to AEs (n = 5), noncompliance–selection criteria (n = 3), inefficacy of treatment (n = 1), and no test confirming PME (n = 1). Fifteen patients counted myoclonic seizures either in 10-minute periods in the morning, afternoon, and evening, while 8 patients counted myoclonic seizures over 24-hour periods. Forty percent of patients with the 10-minute counts and 50% of patients with the 24-hour counts experienced greater than 50% reduction in seizure frequency. Global assessments from investigators revealed patient improvement as well. The most common AEs were anorexia (26.7%), somnolence (23.3%), and asthenia (23.3%) (Vossler and the Zonisamide PME Study Group 2002).

Infantile spasms (IS)

IS are present in childhood and are characterized by a distinct electroencephalographic (EEG) pattern of hypsarrhythmia. IS etiologically are categorized into two broad yet distinct subtypes, cryptogenic and symptomatic, defined by the absence or presence of an underlying cause or neurologic abnormality. Cryptogenic spasms have no identifiable cause, no evidence of brain-imaging abnormalities, and normal development before the onset of seizures. Approximately 10%–15% of patients with IS have a cryptogenic etiology. Symptomatic patients have definable abnormalities and often have poor outcomes, with less than 5% displaying normal neurodevelopment. Currently, corticosteroids and vigabatrin are used for treating IS; however, they are often associated with serious adverse effects, such as cushingoid facies, immunosuppresion, and retinopathy (Conry 2004).

Recently, zonisamide has been suggested as a treatment option for IS. In one study, 23 patients with symptomatic IS were treated with zonisamide for a mean duration of 6.5 months. Patients received a mean maximum zonisamide daily dosage of 18 mg/kg (range, 8–32 mg/kg). Of the 23 patients, 6 (26.1%) were spasm free and showed clearing of EEG abnormalities, specifically hypsarrhythmia, which occurred at a mean of 19 days after the introduction of zonisamide. No patients discontinued treatment due to AEs (Lotze and Wilfong 2004). A chart review study completed by Wilfong (2005) evaluating zonisamide monotherapy for epilepsy in children and adults included 9 subjects diagnosed with IS. Five of these patients (55.6%) became seizure free and three subjects (33.3%) reported 75% or greater decrease in seizure frequency while on zonisamide monotherapy. These results were similar to those of a Japanese study that assessed the efficacy of zonisamide in 11 patients with IS (Suzuki et al 1997).

Discussion

Spanning a period of 31 years, preclinical and clinical experience with zonisamide has established the drug as a broad-spectrum antiepileptic agent. Zonisamide has provided immense benefits for those afflicted with various seizure disorders. Its multiple mechanisms of action are consistent with antiseizure activity reported in the clinical studies of zonisamide. Zonisamide was well tolerated and effective even in patients with absence epilepsy and catastrophic epileptic disorders, such as myoclonic epilepsy and IS, which warrant a universal treatment.

Zonisamide has a PK profile that is ideal with its long half-life, which allows for once-daily dosing. It has shown efficacy as monotherapy, thus possibly improving patient compliance. Additionally, zonisamide does not affect the PK of concomitant drugs, including AEDs and OCs, which is advantageous for adjunctive therapy.

Japanese experience with zonisamide therapy for the treatment of pediatric patients with refractory epilepsy illustrates that zonisamide is effective and well tolerated for long periods of time in children. In addition, extensive clinical and postmarketing data from Japan demonstrates that zonisamide as monotherapy is effective and safe in both pediatric and adult patients with epilepsy. However, additional controlled pediatric studies of zonisamide as monotherapy are warranted in the USA. Overall, positive experience with zonisamide as monotherapy in Japanese pediatric patients has further demonstrated the need for an adequate treatment for US children with refractory seizures.

In summary, zonisamide, as adjunctive therapy, and potentially as monotherapy, is successful in treating patients with refractory partial seizures because of its favorable PK profile, unique structural and mechanistic profile, safety, tolerability, and wide spectrum of antiseizure activity.

Disclosures

AW is a consultant to Eisai Inc, and a member of their speaker's bureau. LW has no conflicts of interest to disclose.

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