Zonisamide: Clinical efficacy and safety in refractory partial epilepsy

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Summary

Epilepsy is a chronic central nervous system disorder, characterized by the recurrence of seizures secondary to excessive and abnormal electrical discharge in the brain tissue. Successful management of epilepsy requires suppression of seizure recurrence by antiepileptic drugs either as single-agent or combination. Zonisamide (ZNS) is 1,2-benzisoxazole-3-methanesulfonamide that has been shown to possess antiseizure activity against partial-onset epilepsy in various animal models. In four randomized, double-blind, placebo-controlled trials, ZNS was shown to be effective in reducing the median frequency of seizures in patients with refractory partial epilepsy while receiving other concurrent antiepileptic drugs (AEDs). A further reduction of 20-50% in seizure frequency was observed at different doses and this was significantly different from placebo. Moreover, the responder rate defined as the proportion of patients achieving more than 50% reduction in median seizure frequency was consistently higher in patients receiving ZNS than placebo. Commonly associated adverse effects of ZNS therapy include somnolence, dizziness, anorexia, and weight loss. The current licensed indication for ZNS in the U.S. is as adjunctive therapy for partial epilepsy in adults over 16 years old. The appropriate starting dose is 100 mg/day and the dose should be titrated in 100-mg increment per day biweekly to the effective maintenance dosage without intolerable adverse effects. The recommended therapeutic serum concentration of ZNS has not been established; however, in most clinical trials the serum concentration of ZNS was usually maintained at 20-30 μg/ml and was shown to be effective.
Keyword: Zonisamide, Epilepsy, Partial epilepsy, Adjunctive therapy, Antiepileptic drugs

Introduction

Epilepsy is a chronic central nervous system disorder, characterized by the recurrence of seizures secondary to excessive and abnormal electrical discharge in the brain tissue. As a result, patients with a seizure attack present with abnormalities of motor function, sensory perception, and emotional responses. Epilepsy may be classified as partial or generalized, based on the type of seizures experienced by the patient. The degree of initial CNS involvement during the episodes determines the seizure types (Brownie & Holmes, 2001; Chang & Lowestein, 2003). Partial or focal seizures occur when a localized area of cerebral hemisphere is involved in neuronal discharge. Partial seizures can secondarily generalize to involve both hemispheres. In contrast, generalized seizures occur when all or large parts of both cerebral hemispheres involve in neuronal discharge at the beginning. Based on the pattern of motor dysfunction, generalized seizures are further classified into absence, tonic-clonic, myoclonic, and atonic seizures. Accurate identification of seizure type is critical in selecting an appropriate medication to prevent seizure occurrence.

The goal of pharmacologic treatment in epilepsy is to achieve complete disappearance of seizure episodes without any intolerable adverse effects. When pharmacotherapy is indicated, monotherapy with the drug of first choice based on the seizure type is recommended (Brown & Holmes, 2001). When the drug of choice fails, an alternative drug should be considered.

If an adequate control is not achieved with monotherapy, a second agent may be added. Several traditional antiepileptic drugs (AEDs), such as phenytoin, carbamazepine, phenobarbital, and valproic acid are effective in controlling epileptic seizures in many patients. However, there remains a large group of patients especially with partial-onset epilepsy for whom seizure episodes cannot be controlled with these agents. Therefore, a number of newer AEDs, including zonisamide (ZNS), have been introduced as adjunctive therapy for treatment of refractory partial epilepsy. This article provides a review of ZNS pharmacology, clinical efficacy and safety as demonstrated in the past and recent clinical trials.

Pharmacodynamics

ZNS is 1,2-benzisoxazole-3-methanesulfonamide (Figure 1), which is chemically classified as a sulfonamide and structurally distinct from other antiepileptic medications (Peters & Sorkin, 1993). Antiseizure effects of ZNS have been demonstrated in animal models, although the exact mechanism of its action is still unknown. In mice, ZNS was effective in preventing maximal seizures (tonic extension) induced by maximal electroshock and pentylenetetrazole, but ineffective against pentylenetetrazole-induced minimal seizures (Masuda et al., 1980). ZNS was shown to suppress both interictal spikes and secondarily generalized seizures (SGS) produced by cortical application of tungstic acid gel in intact and decerebrated rats (Ito et al., 1980). It also suppressed the spikes and SGS induced by cortical freezing in cats. In addition, ZNS was effective in increasing threshold for generalized seizures in the kindled rat model, and shorten the period of cortical focal seizures induced by electrical stimulation of the visual cortex in cats (Ito et al., 1980; Hamada et al., 1990). Taken together, these animal studies suggest that ZNS is effective in suppressing cortical seizure activities, and possibly effective in preventing partial and secondarily generalized tonic-clonic seizures.

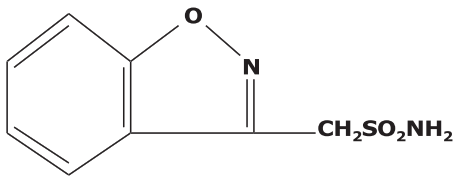

Figure 1 Chemical structure of zonisamide (1,2-benzisoxazole-3-methanesulfonamide)

At the cellular level, ZNS may exert its effects by blocking sodium and calcium channels (Peters & Sorkin, 1993). It was shown *in vivo* to block voltage-sensitive sodium channels and T-type calcium channels, thereby preventing excessive depolarization of neuronal membrane and hypersynchronization (Peters & Sorkin, 1993; Leppik, 2004). ZNS has been shown to bind GABA/benzodiazepine receptor complex without affecting chloride channels, thus not altering synaptic activity induced by GABA or glutamate (Rock et al., 1989; Leppik, 2004). It also possesses a weak carbonic anhydrase inhibiting activity; however, this effect is not believed to play a major role in its antiepileptic activity.

Pharmacokinetics

Following a single oral dose of 200 or 400 mg given to healthy volunteers, ZNS is absorbed rapidly, with a mean peak plasma concentration (C_{max}) of 2-5 μg/ml occuring within 2 to 6 hours after dosing (Ito et al., 1982; Matsumoto et al., 1983). The absorption of ZNS is not significantly altered by food. In 12 healthy volunteers given a 300mg dose of ZNS in a fasting state or with breakfast, C_{max}, time to C_{max} and area under time-concentration curve (AUC) were not different, suggesting that food does not appear to affect the extent or rate of ZNS absorption (Shellenberger et al., 1998). Thus, ZNS can be administered without regard to the timing of meals.

The apparent volume of distribution of ZNS is approximately 1.44 L/kg following a 300mg oral dose in young adults (Wallace et al., 1998). ZNS is about 40% bound to plasma protein, mainly albumin (Kimura et al., 1992; Peters & Sorkin, 1993). Plasma protein binding of ZNS is not affected by phenytoin, carbamazepine, and phenobarbital; however, valproic acid causes a significant displacement of ZNS from albumin. The increase in free fraction of ZNS in the presence of valproic acid is approximately 3% (Kimura et al., 1992). Like other sulfonamides, ZNS has a high affinity for red blood cells (RBCs), leading to its extensive accumulation in RBCs (Ito et al., 1982). The binding to RBCs is saturable, and so the relationship of dosage and whole blood ZNS concentration is nonlinear. Therefore, the plasma concentration of ZNS rather than whole blood concentration should be monitored during therapy (Mimaki, 1998).

In healthy volunteers, the elimination half-life of ZNS ranges from 56 to 68 hours (Ito et al., 1982). Due to its long half-life, it will take approximately two weeks to reach steady state (Kochak et al., 1998). In humans, ZNS undergoes N-acetylation, or reductive cleavage of the 1,2-benzisoxazole ring by cytochrome P450 (CYP450) 3A isoenzymes followed by glucuronide conjugation (Nakasa et al., 1993; Peters & Sorkin, 1993). ZNS is excreted primarily in urine (approximately 62% of given doses) whereas excretion in feces is much less (approximately 3%) (Leppik, 2004). Of the amount excreted in urine, unchanged ZNS, the conjugated metabolite, and N-acetyl-ZNS were recovered by 35%, 50% and 15%, respectively. Since ZNS is metabolized by the liver and renally eliminated, its half-life becomes prolonged in patients with hepatic or renal impairment. Consequently, use of ZNS in patients with severely impaired renal or hepatic function may necessitate plasma concentration monitoring and dosage adjustment accordingly.

Although ZNS is partially metabolized in the liver by CYP450, addition of ZNS has no significant effects on steady state levels of phenytoin, carbamazepine, or valproic acid in epileptic patients (Leppik, 2004; Levy et al., 2004; Ragueneau-Majlessi et al., 2004). However, due to limited data available, serum concentrations of the concomitant AEDs should be monitored when ZNS is added or discontinued. In contrast, drugs that induce or inhibit CYP 3A4 are expected to alter serum concentrations of ZNS. It has been shown that enzyme inducers, such as phenytoin or carbamazepine, induce metabolism and decrease serum concentrations of ZNS (Ojemann et al., 1986). Thus, ZNS doses may need to be increased when an AED with a liver enzyme-inducing property is given concurrently.

Clinical efficacy, safety and tolerability

The MEDLINE database was searched using the key words: zonisamide, partial epilepsy or partial seizure. All of the performed searches were limited to only clinical trials published in English language from 1990 to 2005. Five fully published clinical trials evaluating ZNS in partial epilepsy were found; however, one was excluded due to its open-label and non-randomized approach (Leppik et al., 1993). The cited references from these papers were also searched manually for additional controlled trials, but none met the inclusion criteria. Thus, four randomized, double-blind, placebo-controlled studies were included in this review (Table 1).

Efficacy of ZNS as an adjunctive treatment of refractory partial seizures was evaluated in a European multicenter, randomized, double-blind, placebo-controlled study (Schmidt et al., 1993). In this study, patients were included if they were adults (18-59 years old), who had refractory complex partial seizures, defined as having an average of four or more seizures episodes per month despite therapeutic plasma concentrations of current AEDs. Patients with other seizure types were excluded. Subjects were randomized to receive either ZNS (n=71) or placebo (n=68) as an adjunctive treatment to the present medication(s). The ZNS dose was started initially at 1.5 mg/kg/day, and then titrated up over a 2-week period to 6 mg/kg/day. Subsequently, doses were adjusted by an unblinded investigator to achieve plasma concentrations of 20-30 μg/ml. The result of this study revealed that during the last 8-week of treatment, the median change in the number of seizures was a 26.9% reduction in the ZNS group and a 3.9% increase in the placebo group ($p<0.05$). A decrease in the total number of partial seizures to less than 50% of baseline (defined as responder rate) was observed in 30.3% vs. 10.9% ($p<0.05$) of patients taking ZNS and placebo, respectively. The median daily dose and plasma concentrations of ZNS were not statistically different between responders and nonresponders, suggesting that lack of a therapeutic effect was unrelated to insufficient plasma concentrations from non-compliance. Adverse events were reported more frequently with ZNS (59.2%) than placebo (27.9%). The most frequently reported adverse events included fatigue, dizziness, somnolence, and anorexia. Two patients withdrew from the study because of adverse events. This study demonstrated that ZNS was more effective than placebo as an adjunctive treatment for refractory partial epilepsy, although its use was associated with more adverse effects than placebo.

In a multicenter, randomized, double-blind, placebo-controlled trial, Faught and colleagues assessed the efficacy and safety of ZNS at different dosages for refractory partial epilepsy (Faught et al., 2001). All subjects entered a 4-week run-in period when they received their current AEDs plus a placebo to obtain a baseline seizure frequency. Subjects were required to have at least 4 seizures per month to be further enrolled in the study. Following the run-in period, 203 patients (13-68 years old) were randomly assigned into 3 separate groups to receive either placebo or ZNS together with their concurrent AEDs. The first group (named Group A, n=85) received placebo for 12 weeks. At week 13, they were crossed over to receive ZNS starting at 100 mg/day titrated every week to a maximum of 400 mg/day for the last 5 weeks (weeks 16 through 20). The second group (Group B1, n=60) received 100 mg/day of ZNS for weeks 1 through 5, 200 mg during week 6,

Table 1 Randomized, double-blind, placebo-controlled studies of ZNS in refractory partial epilepsy

Reference	N	ZNS Dosage	Change in seizure frequency from baseline (%)			Responder rate (%)		
			ZNS	Placebo	p value	ZNS	Placebo	p value
Schmidt et al. (1993)	139	6 mg/kg/day adjusted to achieve plasma concentration of 20-30 μg/ml	-27.7	+3.9	< 0.05	30.3	10.9	< 0.05
Faught et al. (2001)	203	100 mg/day	-24.7	-8.3	0.014	25	11.3	0.03
		200 mg/day	-20.4	-4.0	0.003	25	9.8	0.02
		400 mg/day	-40.5	-22.0	0.03	43	22	0.014
Sackellares et al. (2004)	152	400-600 mg/day to achieve plasma concentration of 20-30 μg/ml	-28.9	+4.7	0.0009	26.9	16.2	0.1141
Brodie et al. (2005)	351	100 mg/day	-18.0		NS	28.8		NS
		300 mg/day	-46.4	-19.4	0.0007	42.9	20.2	NS
		500 mg/day	-50.6		<0.0001	50.5		<0.001

Note.

*defined as a proportion of patients who achieves a $\geq$ 50% reduction in partial seizure frequency from baseline during the drug treatment period.

N = Number of patients randomized; NS = Non-significance

300 mg during week 7, and 400 mg for the final 13 weeks (weeks 8 through 20). The third group (Group B2, n=58) received 100 mg/day of ZNS for the first week, 200 mg/day during weeks 2 through 6, 300 mg/day during week 7 and 400 mg/day for weeks 8 through 20. The trial was designed to include staggered timing of dose titration to enable the assessment of ZNS efficacy at 100-mg, 200-mg and 400-mg dosages. All patients received concurrent AEDs with the intention to hold their dosages constant; however, the dosage increase or decrease occurred in 2 and 8 patients, respectively. To the end, 146 of the 203 randomized patients (72%) completed the 20-week trial. By an intention-to-treat analysis, the results revealed that ZNS at 400 mg/day (pooled patients from Group B1 and B2) achieved a significantly higher median reduction in the seizure frequency from baseline during weeks 8 through 12 when compared with placebo (patients in Group A) during the corresponding time period (decreased by 40.5% vs. 9.0%, respectively; p=0.009). The proportion of responder (achieving more than 50% reduction in seizure frequency) was also higher in patients receiving ZNS 400 mg/day than those receiving placebo (43% vs. 22%; p=0.014). In addition, the patients in Group A who received placebo initially and crossed over to ZNS 400 mg/day for the last 5 weeks also showed a significant decrease in median seizure frequency of 40.1% compared to the previous seizure frequency while on placebo. ZNS at 100 and 200 mg/day also achieves a significant higher median reduction in seizure frequency from baseline when compared to the placebo (24.7% vs. 8.3%, p=0.038, for 100 mg/day dose; and 20.4% vs. 4.0%, p=0.003, for 200 mg/day dose). The responder rates for both 100 and 200 mg/day ZNS were also significantly higher compared to placebo. Taken together, these results demonstrated the efficacy of ZNS as add-on therapy to concurrent AEDs in refractory partial epilepsy. In term of safety, patients receiving ZNS reported anorexia and ataxia more frequently than those receiving placebo, but the difference was not significant. Weight loss occurred more frequently in ZNS group than the placebo group (21.6% vs. 10.4%, respectively; p=0.044). The dropout rate due to adverse events was 10% in ZNS group and 8.2% in the placebo group. No symptomatic renal calculi, the previously reported adverse effect of ZNS, occurred during the 20-week period in this study.

Sackellares and colleagues evaluated ZNS as adjunctive treatment for refractory partial epilepsy in randomized, double-blind, placebo-controlled study conducted at four epilepsy centers in the U.S. (Sackellares et al., 2004). During an 8- to 12-week baseline phase, patients received their usual AEDs and were assessed for seizure frequency. Patients were required to have $\geq$15 seizures in 4 weeks or $\geq$30 seizures in 8 weeks to be enrolled further in the treatment phase of the study. Eligible patients (17-65 years old) were randomly assigned to receive placebo (n=74) or ZNS (n=78) with their concurrent AEDs. The ZNS dose was titrated to obtain daily doses of 400-600 mg/day and the plasma concentration of 20-30 μg/ml. By the end, 64 patients (82.1%) in ZNS group and 67 patients (90.5%) in the placebo group completed the trial. Addition of ZNS led to a 28.9% further reduction in the frequency of all partial-onset seizures compared to the baseline phase. In contrast, the frequency increased by 4.7% in placebo-treated patients. The difference between ZNS-treated and placebo-treated patients was significant (p=0.0009). The responder (achieving more than 50% reduction in seizure frequency) rate determined from the

reduction of all partial seizure frequency was higher in ZNS group than placebo group (26.9% vs 16.2%, respectively). However, this was not significantly different (p=0.1141). When only complex partial seizures were determined, the responder rate became significantly different between ZNS and the placebo group (30.8% vs. 13.9%; p=0.0159). In this study, more adverse events occurred in the ZNS group than the placebo group ($p < 0.05$). The adverse events reported were mostly classified as mild or moderate in severity. The most frequently reported adverse events were somnolence, irritability, dizziness, nausea and fatigue. It was also noted that adverse events were reported more frequently in patients taking higher dosages or having faster dosage titration.

In a recently published trial, Brodie and colleagues evaluated safety and efficacy of ZNS as adjunctive therapy in patients with refractory partial epilepsy (Brodie et al., 2005). The study was a randomized, double-blind, placebo-controlled trial conducted at 54 centers mostly in 18 European countries. Patients were included if, while receiving current AEDs, they experienced $\geq$12 partial seizures with no more than a 3-week seizure-free interval during the 12-week baseline period. Eligible patients (12-77 years old) were randomized to receive one of the four treatments: placebo, 100 mg/day of ZNS, 300 mg/day of ZNS, 500 mg/day of ZNS. After randomization, ZNS dose was initiated and increased to the target of 100 mg/day in 1 week, 300 mg/day in 3 weeks and 500 mg/day in 6 weeks. After completion of the 6-week titration phase, all patients entered the 18-week (weeks 19-36) fixed-dose assessment phase when they were assessed for seizure frequency compared with the baseline. Treatments were blinded using a double-dummy technique such that all patients received the same numbers of look-alike capsules in any particular phase throughout the study. It was shown by the primary efficacy-analysis that addition of ZNS at 500 mg/day and 300 mg/day resulted in a significantly greater reduction in frequency of all partial seizures from the baseline phase (50.6% for 500 mg/day; $p < 0.0001$, and 46.4% for 300 mg/day; p=0.0007) when compared with the addition of placebo (19.4%). The difference was not significant when ZNS, 100 mg/day, was compared with the placebo. In addition, the proportion of responders (achieving $\geq$50% reduction in seizure frequency from baseline) was also higher in each ZNS group (500 mg, 50.5%; 300 mg, 42.9%; 100 mg, 28.8%, placebo, 20.2%). However, the treatment difference was significant ($p < 0.001$) for only the 500 mg/day dose, but not the 300 and 100 mg/day doses, compared with placebo. The incidence of withdrawals due to adverse events was higher for the 500- and 300-mg/day groups (27.1% and 18.2%, respectively) than for the 100-mg/day and placebo groups (1.8% and 10.0%, respectively). The majority of adverse events leading to withdrawal in 500-mg/day group were dizziness, difficulty concentrating, nausea, and somnolence during the titration phase. No significant differences were found in clinical and hematologic laboratory results except for a greater decrease in weight observed with the 500 mg/day of ZNS group.

Collectively, the aforementioned trials have demonstrated efficacy of ZNS as adjunctive therapy in patients with refractory partial epilepsy. Addition of ZNS to concurrent AEDs led to a further reduction in frequency of partial seizures compared with baseline. This observed efficacy was significantly different from placebo. In one trial, efficacy of ZNS was demonstrated at dosage

as low as 100 mg/day, whereas other trials supported superior efficacy to placebo at higher doses. The difference in efficacy observed from each study was probably due to variation in the dose and baseline seizure frequency of the patients recruited into each trial. Whether ZNS is effective at lower dose will need further studies for confirmation. ZNS seems to be safe and well-tolerated in most trials. The most common adverse effects include somnolence, dizziness, nausea and weight loss. To minimize adverse effects leading to discontinuation of drug therapy, the lowest effective dose and slower titration schedule was advised.

Indication, dosage and administration

ZNS is thought to be effective against diverse types of epilepsy. However, the published reports of its efficacy in generalized-onset epilepsy have been very limited. Thus, the only approved indication of ZNS in the U.S. is as adjunctive therapy for refractory partial epilepsy with or without secondary generalization in adults over 16 years old. Use of ZNS as monotherapy in the treatment of partial or generalized seizures has not been investigated in large clinical trials, so its use for these indications requires careful consideration.

ZNS can be taken with or without food. The initial recommended dose of ZNS is 100 mg daily. Because of its long half-life, it will take at least 2 weeks to achieve steady state levels. Dosage adjustment may be made in increments of 100 mg/day every two weeks. Dose titration should be individualized, based on patient response and tolerability. Dosages above 100 mg/day should be given in two divided doses to minimize plasma concentration fluctuations (Kochak et al., 1998). The ZNS dose commonly targeted in clinical trials ranges from 100 to 600 mg daily. In most trials, ZNS doses were adjusted to obtain plasma concentration of 20-30 μg/ml and not to exceed 40 μg/ml. Thus, for current practices, it seems reasonable to target ZNS dose to obtain its plasma concentration in this range. Patients with renal or hepatic impairment may require a lower dose of ZNS due to its prolonged half-life. A specific guideline for dosage adjustment in patients with hepatic or renal impairment has not been established. Therefore, a slower titration and more frequent monitoring in these groups of patients are recommended.

In a previous study, ZNS was reported to cause renal calculi in 4% of patients taking the drug (Leppik et al., 1993). In more recent trials, however, no such an adverse effect was reported (Schmidt et al., 1993; Faught et al., 2001). Nevertheless, patients should be encouraged to increase fluid intake and urination while taking ZNS to minimize risk of renal calculi.

Conclusions

ZNS has been approved by the U.S. FDA as an adjunctive therapy for refractory partial epilepsy in adults over 16 years old. The available randomized, double-blind, placebo-controlled trials consistently demonstrated efficacy of ZNS for its approved indication. However, the most effective dosage range of ZNS yet needs to be determined. Currently available data suggest initial dose of 100 mg/day and this should be gradually titrated up to an optimal dose for each patient. Adverse effects including somnolence, dizziness, ataxia, nausea and weight loss may be

encountered during therapy. Using the lowest effective dose and slower titration schedule may minimize those unwanted drug effects.

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