Profile of once-daily zonisamide as monotherapy for treatment of partial seizures in adults

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Abstract: Epilepsy is one of the most common neurologic disorders, affecting about 50 million people around the world. It is recognized that around 50% of patients with newly diagnosed epilepsy become seizure-free with the first drug treatment, so the choice of first antiepileptic drug is crucial. This paper provides a comprehensive overview of zonisamide as monotherapy for partial seizures, with special attention to the possibility of a once-daily regimen. The available data suggest that zonisamide is an effective and well tolerated option as monotherapy. Once-daily dosing is indicated, considering the long plasma half-life and linear pharmacokinetics of the drug. Zonisamide 300 mg was shown to be noninferior to carbamazepine 600 mg in terms of efficacy and safety, but even lower doses may be effective. Finally, the broad spectrum of efficacy in different seizure types, the low drug interaction potential, and the possibility of weight loss make zonisamide a preferred option in many epilepsy practices. Further data on monotherapy, especially in special populations, such as women of childbearing potential, are needed.

Keywords: epilepsy, zonisamide, monotherapy

Introduction

Epilepsy is one of the most common neurologic disorders, affecting about 50 million people worldwide.[1] The World Health Organization reports that the overall health burden due to epilepsy accounts for 0.5% of the global burden of the disease, with total annual costs of approximately 15.5 billion Euros in Europe,[2] and 9.5 billion dollars in the US.[3] Over 40 types of epilepsies are known, and they fall into two main categories, ie, partial onset (also known as focal or localization-related)[4] epilepsies and generalized onset epilepsies, the former accounting for about 60% of all adult epilepsy.[5]

In general terms, about 50% of patients with newly diagnosed epilepsy are expected to become seizure-free with the first treatment.[6] Another 20% can reach long-lasting and complete seizure control with a second drug or on dual therapy.[7] Therefore, it is evident that choice of the first antiepileptic drug is critical. Moreover, monotherapy has a number of advantages in terms of good patient compliance, a low risk of drug interactions, and potential cost savings.[8]

A number of treatment guidelines have been published giving priority to certain compounds in specific seizure patterns and epilepsy syndromes.[9,10] However, well designed and properly conducted randomized controlled trials are lacking, and some of the existing ones have significant methodologic problems. Therefore, selection of a specific antiepileptic drug is often influenced by a number of considerations, including mechanism of action, pharmacokinetics, patient gender and age, presence of comorbidities, and the familiarity of the treating physician with a specific antiepileptic drug.

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Zonisamide is a benzisoxazole derivative with a sulfonamide side chain (1,2-benzisoxazole-3-methanesulfonamide) and is structurally unrelated to other antiepileptic drugs (Figure 1). It has been available in Japan since 1989, in South Korea since 1992, in the US since 2000, and in the European Union since 2005. In the US, zonisamide is currently approved for the adjunctive treatment of partial seizures (with or without secondary generalization) in adults, while in Japan and Korea it is approved for both partial and generalized epilepsy in adults and children. In 2012, the European Medicine Agency issued marketing authorization approval to extend the use of zonisamide from adjunctive therapy to include monotherapy for partial seizures (with or without secondary generalization) in adults with newly diagnosed epilepsy. This review provides a comprehensive overview of zonisamide as monotherapy for partial seizures, with special attention to the possibility of a once-daily regimen. References were identified by searches of Medline and PubMed using the key words "zonisamide", "epilepsy", "partial seizures", and "monotherapy". The list of relevant articles was hand-searched for additional publications (eg, book chapters or review papers) if relevant to the discussion.

Mechanism of action

Zonisamide demonstrates a wide range of mechanisms of action. Primarily, it modulates voltage-gated ion channels. Zonisamide prolongs the inactive state of sodium channels,[11] similar to carbamazepine, phenytoin, and lamotrigine,[12] thus reducing sustained high-frequency repetitive firing of sodium-dependent action potentials.[13] At the same time, zonisamide inhibits low-threshold, T-type calcium currents,[14] similarly to ethosuximide and valproate,[12] thereby preventing the spread of seizure discharge between cells.[15] Zonisamide also modulates gamma aminobutyric acid and glutamatergic neurotransmission, potentiating the former and inhibiting the latter. This may be indirectly related to activity at voltage-gated channels, but seems also to
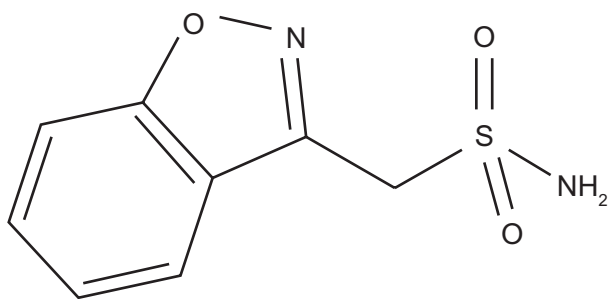
be related to modulation of specific transporters, such as gamma aminobutyric acid transporter 1 and glutamate transporter 1.[16]

Finally, zonisamide appears to increase extracellular concentrations of dopamine and serotonin as well as increasing acetylcholine metabolism.[17] It is currently unclear to what extent these mechanisms contribute to the antiseizure activity of zonisamide. The same applies to the weak carbonic anhydrase inhibitor properties.[18]

Pharmacokinetic profile

Zonisamide has a bioavailability of almost 100%.[19] Single-dose studies show that the time taken to reach peak plasma concentrations is 2–5 hours under fasting conditions and 4–6 hours with food.[20] Zonisamide is about 40% protein-bound, with a volume of distribution of 1.27 L/kg.[19] Zonisamide preferentially accumulates in red blood cells,[21] with a red blood cell to plasma ratio of 8. This phenomenon, observed in general with the sulfonamide agents,[22] seems to be irrelevant in terms of the final plasma half-life of zonisamide.[21] For doses of 200–400 mg, zonisamide shows a linear relationship between dose and area under the curve (AUC).[23] Above 800 mg, the pharmacokinetics become nonlinear, possibly due to saturation of red blood cells.[12] Zonisamide has a long plasma half-life (63–69 hours), with steady state achieved in about 14 days.[23]

Zonisamide is metabolized primarily in the liver, with subsequent elimination via the renal route. Approximately 50% of zonisamide is metabolized by the cytochrome P450 (CYP)3A4 isoenzyme, although CYP2C19 and CYP3A5 may also contribute.[24] Polymorphisms in CYP2C19, but not in CYP3A4 or CYP3A5, can alter zonisamide clearance, although probably not to a degree requiring adjustment of dosing.[25] Acetylation accounts for a further 20% of zonisamide metabolism.[21] None of the metabolites of zonisamide appear to have anticonvulsant activity.[26] Finally, the remaining 30% of unaltered zonisamide is excreted in the urine. The oral clearance of zonisamide is about 700 mL per hour, and renal clearance is relatively low at about 3.5 mL per minute.[21] In subjects with renal impairment, renal clearance of single doses is positively correlated with creatinine clearance, and plasma AUC is increased by 35% in those with creatinine clearance < 20 mL per minute.[19]

In special populations, such as the elderly (>65 years), zonisamide shows no clinically significant pharmacokinetic differences.[26] Moreover, there is no significant interaction between zonisamide and oral contraceptives, in particular ethinylestradiol and norethindrone.[27]

Figure 1 Chemical structure of zonisamide.

A major advantage of the pharmacokinetics of zonisamide is its long half-life, which allows once-daily dosing. However, concomitant use of enzyme-inducing medications alters the clearance rate of zonisamide, reducing the plasma half-life to 27–38 hours.[21]

Efficacy in monotherapy studies

The efficacy of zonisamide as addon treatment in patients with partial seizures has been investigated in four pivotal, randomized, double-blind, placebo-controlled Phase III trials.[28–31] At the moment, data on monotherapy are limited to two studies, comprising a randomized double-blind study[32] and a Phase III noninferiority trial.[33]

A 40-week, randomized, double-blind, monotherapy study comparing zonisamide 25, 100, and 300 mg/day[32] enrolled 169 patients with newly diagnosed epilepsy and complex partial seizures. Although no significant differences were observed between the dosing groups, a general trend towards a greater effect was observed in the 300 mg group, with more patients remaining seizure-free for ≥6 months (50.8%) as compared with those receiving 25 mg/day or 100 mg/day (33.9% and 30.8%, respectively). The lack of difference in response rates over such a wide dose range of zonisamide is of interest in light of earlier data on drug-refractory patients. In fact, all previous studies unanimously showed significant effects on median seizure rates and the number of patients showing a 50% seizure reduction compared with placebo in dose ranges of 300–600 mg/day, and a Cochrane review confirmed these findings.[34] In general terms, patients in the early stages of epilepsy show high responsiveness to medical treatment compared with highly refractory patients undergoing addon treatment. Therefore, it is possible that doses of zonisamide as low as 50 mg and 100 mg daily may be effective in monotherapy.

A multicenter, randomized, double-blind, Phase III noninferiority trial involving 583 patients aged 18–75 years compared zonisamide once daily (n = 282) with flexible dosing of controlled-release carbamazepine (n = 301).[33] After initiation of treatment (zonisamide 100 mg/day versus carbamazepine 200 mg/day) and uptitration (zonisamide to 300 mg/day versus carbamazepine to 600 mg/day), the patients entered a 26–78-week flexible dosing period (zonisamide 200–500 mg versus carbamazepine 400–1200 mg daily, according to response and tolerability). Once seizure-free for at least 26 weeks, the patients entered a 26-week maintenance phase. The primary endpoint was the proportion of patients in the per protocol population achieving seizure freedom for at least 26 weeks. Overall, 79.4% of the zonisamide-treated

patients and 83.7% of the carbamazepine-treated patients remained seizure-free for at least 26 weeks (Figure 2). This trial is one of the few done according to International League Against Epilepsy guidance,[10] which recommends that active-controlled trials have a duration of at least 48 weeks, no forced exit criteria, and information on the proportion of patients who remain seizure-free for at least 24 weeks as part of the efficacy assessment. A relative 20% margin is considered in the International League Against Epilepsy guidelines for noninferiority trials. In this study, zonisamide was noninferior to controlled-release carbamazepine, showing an adjusted absolute treatment difference of 4.5% (95% confidence interval [CI] 12.2–3.1), and a relative treatment difference of 5.4% (95% CI 14.7–3.7).

Safety in monotherapy studies

A pooled analysis of data from the four pivotal trials for zonisamide as addon therapy in patients with partial seizures shows treatment-emergent adverse events in about 77.9% of patients taking zonisamide versus 67.7% of those on placebo, with discontinuation rates of 19.3% and 8.6% respectively.[35] Such adverse events were usually mild to moderate and generally related to the central nervous system (ie, somnolence, dizziness, depression, anorexia). Cognitive and psychiatric adverse events during treatment with zonisamide have been considered to be of concern.[36,37] However, they seem to develop in predisposed subjects[36] and careful patient selection reduces this problem.[38] Serious adverse events show a similar incidence in patients taking zonisamide (4.8%) or placebo (4.6%).[35]

Zonisamide and carbamazepine had a very similar safety profile in the noninferiority monotherapy trial, except for the effect on body weight.[33] In fact, the overall incidence of treatment-emergent adverse events was similar for
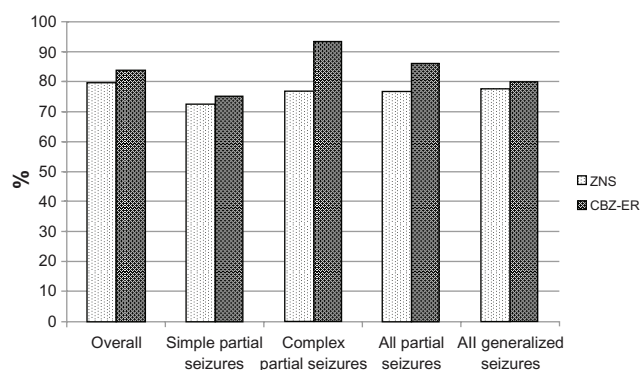

Figure 2 Seizure freedom rates by seizure type in a noninferiority trial comparing zonisamide with extended-release carbamazepine.[33]
Abbreviations: ZNS, zonisamide; CBZ-ER, carbamazepine extended-release.

zonisamide (60%) and carbamazepine (62%), as was the incidence of treatment-related adverse events (36% and 38%, respectively). In the majority of cases, adverse events were mild to moderate, with serious adverse events being rare in both groups (1% for zonisamide versus 2% for carbamazepine). The discontinuation rate due to adverse events was similar in both groups (11% for zonisamide versus 12% for carbamazepine) and, interestingly, the spectrum of adverse events was also similar, apart from decreased appetite (8% for zonisamide versus 2% for carbamazepine), dizziness (4% for zonisamide versus 8% for carbamazepine), and weight loss (7% for zonisamide versus 0% for carbamazepine, see Figure 3).

Discussion

In general terms, all the data presented suggest that zonisamide is an effective and well tolerated treatment option for adult patients with focal epilepsy. Results of retention rate studies are currently available only for zonisamide as addon treatment, showing a two-year retention rate of about 60%.[39,40] However, zonisamide is one of the few antiepileptic drugs with a noninferiority trial performed according to International League Against Epilepsy guidance.[10] The only other two studies done according to these criteria involve levetiracetam versus controlled-release carbamazepine[41] and pregabalin versus lamotrigine.[42] The scarcity of such trials is indicative of the numerous methodologic problems associated with data regarding antiepileptic monotherapy. However, it is important to bear in mind that such trials, although providing clinically useful information, also have methodologic considerations that, if ignored, may affect their interpretation. Methodologic considerations include ensuring that the limits of noninferiority are properly defined, that additional evidence is provided to show that the active comparator is effective in the population studied, and that the

assay system has adequate sensitivity to detect any difference between treatments. In the study by Baulac et al,[33] as pointed out by the authors themselves, almost twice as many patients in the zonisamide group discontinued because of withdrawal of consent in the per protocol population.

The broad efficacy spectrum of zonisamide, due to its multiple mechanisms of action, represents an advantage, especially for patients without clearly classified seizures. In fact, zonisamide seems to be effective against both partial and primarily generalized seizures,[43] making exacerbation of some generalized seizure types less likely than that found with carbamazepine.

The pharmacokinetic profile of zonisamide also has a number of advantages. First, the long half-life allows once-daily dosing, improves patient compliance, and suggests a low impact of missed doses on seizure control. Second, the lack of inducing properties means a low potential for drug interactions and a low potential on hormones and probably on bone density, although data on the latter are still lacking. However, it has to be acknowledged that the long half-life may represent a limitation when a rapid onset of action is required.

Data on the adverse events of zonisamide in monotherapy are urgently needed. Data from addon studies are clearly not in favor of zonisamide, especially regarding adverse effects on cognition and behavior.[36,44] However, preliminary data seem to suggest good tolerability.[33] Such a discrepancy is frequently observed when the drug is used in monotherapy and individualized prescribing habits are adopted. Regarding adverse events, it has to be noted that zonisamide seems to be less problematic than other compounds (ie, carbamazepine and lamotrigine) in terms of idiosyncratic rash.

Finally, a peculiarity of zonisamide is weight loss, that seems to occur in about one third of treated patients, particularly in those who were overweight before treatment.[45] This effect seems to be more evident with zonisamide than with topiramate,[46] another sulfamated antiepileptic drug, and may be particularly advantageous in some patients.

Conclusion

Zonisamide represents an effective and well tolerated option as monotherapy for adult patients with newly diagnosed focal epilepsy. Once-daily dosing is indicated in view of the long half-life and linear pharmacokinetics of this drug. The broad spectrum of efficacy in the treatment of different seizure types may be advantageous in seizure patterns that are not clearly classified. The low potential for drug interactions and the possibility of weight loss make zonisamide a preferred option
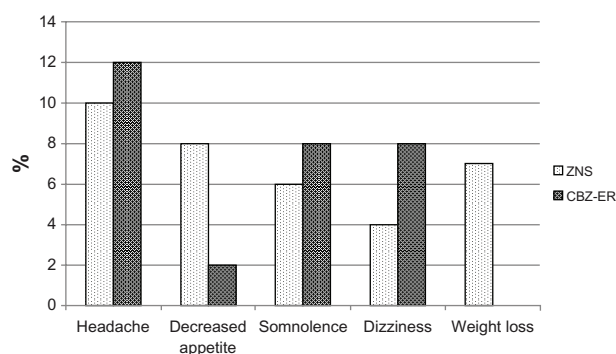

Figure 3 Treatment-emergent adverse events reported by ≥5% of patients in the noninferiority trial comparing zonisamide with extended-release carbamazepine.[33]
Abbreviations: ZNS, zonisamide; CBZ-ER, carbamazepine extended-release.

in many epilepsy practices. Further data on monotherapy in special populations, such as women of childbearing potential, are needed.

Disclosure

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