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Zonisamide: chemistry, mechanism of action, and pharmacokinetics

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KEYWORDS
Zonisamide;
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Summary Zonisamide is a synthetic 1,2-benzisoxazole-3-methanesulfonamide with anticonvulsant properties. The sulfamoyl group on zonisamide was expected to suppress seizures in a manner similar to another sulfonamide analogue, acetazolamide, through inhibition of carbonic anhydrase. However, this does not appear to be the primary mechanism of action since zonisamide requires much higher doses than acetazolamide to achieve equivalent titration in vivo.

Studies with cultured neurons indicate that zonisamide blocks repetitive firing of voltage-sensitive sodium channels and reduces voltage-sensitive T-type calcium currents without affecting L-type calcium currents. Its dual mechanism of action may explain its efficacy in patients resistant to other antiepileptic drugs (AEDs).

Zonisamide has a pharmacokinetic profile favorable for clinical use. It is rapidly and completely absorbed and has a long half-life (63—69 h in healthy volunteers) which allows twice-daily, or even once-daily, dosing. Zonisamide is not highly bound to plasma proteins. Consequently, it does not affect protein binding of other highly protein-bound AEDs. Furthermore, zonisamide does not induce its own metabolism and does not induce liver enzymes. However, since zonisamide is metabolized by cytochrome P450, liver enzyme-inducing AEDs will increase zonisamide clearance, and dosage adjustments may be necessary when it is used in combination with certain AEDs.

Introduction

Zonisamide is a novel antiepileptic drug (AED) that was developed in search of a less toxic, more effective anticonvulsant. The drug has been used in Japan since 1989, and is effective for simple and complex partial seizures, generalized tonic-clonic seizures, myoclonic epilepsies, Lennox—Gastaut syndrome, and infantile spasms.[1,2] In Japan, zonisamide is currently indicated for monotherapy and adjunctive therapy for partial onset and generalized onset seizures in adults and children. In the United States, zonisamide was approved by the Food and Drug Administration (FDA) in 2000 as an adjunctive treatment for partial seizures.

The drug's broad spectrum of activity and favorable pharmacokinetic profile offer certain advantages in the epilepsy treatment armamentarium. Chemically distinct from other AEDs, zonisamide has been shown to be effective in patients whose seizures are resistant to other AEDs. Zonisamide's long plasma elimination half-life has allowed it to be used in a once-daily or twice-daily treatment regimen in Japan.[2]

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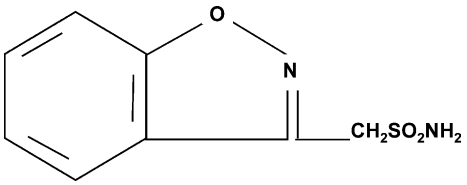

Figure 1 Molecular structure of zonisamide.

Chemistry

The molecular formula of zonisamide is $C_8H_8N_2O_3S$ (Fig. 1). Zonisamide is classified as a member of the methanesulfonamide group even though it has a sulfamoyl group in common with acetazolamide, an arylsulfonamide analog that also has anticonvulsant properties.[2,3]

Mechanism of action

The anticonvulsant activity of zonisamide, which shares pharmacological properties with phenytoin, carbamazepine, and sodium valproate, has been demonstrated in many animal and cultured neuron models, as well as in clinical studies.

Like phenytoin and carbamazepine, zonisamide blocks the spread or propagation of seizure discharges. Zonisamide has been shown to prevent the tonic extensor components of maximal electroshock seizures in mice, rats, rabbits, and dogs;[3] restrict the spread of focal seizures evoked by electrical stimulation of the visual cortex in cats;[4] and prevent the propagation of seizures from the cortex to subcortical structures, which are evoked by cortical freezing in cats,[4] and by electrical stimulation in visual cortex-kindled cats.[5]

It is believed that zonisamide's effect on the propagation of seizure discharges involves blocking the repetitive firing of voltage-sensitive sodium channels, and reducing voltage-sensitive T-type calcium currents without affecting L-type calcium currents. These mechanisms stabilize neuronal membranes and suppress neuronal hypersynchronization, leading to the suppression of partial seizures and generalized tonic—clonic seizures in humans.[2,6]

Zonisamide possesses mechanisms of action that are similar to those of sodium valproate, e.g., suppression of epileptogenic activity and depression of neuronal responses. These mechanisms are thought to contribute to the suppression of absence and myoclonic seizures.[2]

Since zonisamide has a sulfamoyl group on its side chain, it was anticipated that the drug might exert its anticonvulsant effects in a manner similar

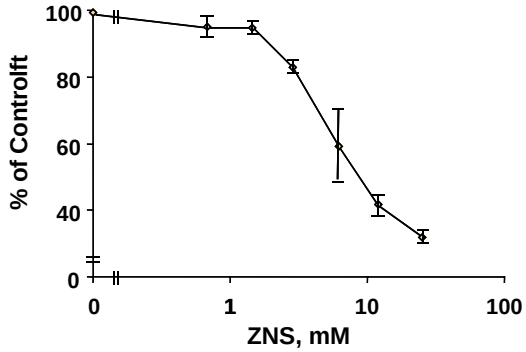

Figure 2 Hydroxyl radical scavenging activity of zonisamide.

to the related compound acetazolamide, which inhibits seizure activity, i.e. via inhibition of carbonic anhydrase. However, when zonisamide was compared with acetazolamide in vivo, zonisamide had only weak carbonic anhydrase inhibiting activity, requiring 100—1000 times higher doses than acetazolamide to achieve equivalent inhibition.[3] Thus, carbonic anhydrase inhibition was ruled out as the primary mechanism of action of zonisamide.[2] The presence of a methylene group on zonisamide's side chain may explain the differences in carbonic anhydrase inhibition.

Unlike some other AEDs, zonisamide does not appear to affect the synaptic activity induced by γ-aminobutyric acid (GABA) or glutamate,[2] as do other AEDs.

One study has suggested that the anticonvulsant effect of zonisamide may also involve protecting neurons from free radical damage. In this in vitro study, as zonisamide dosage increased, activity of hydroxyl and nitric oxide radicals decreased (Figs. 2 and 3). Hydroxyl radicals are thought to be the most harmful radical for neuromembranes. Nitric oxide, a messenger molecule in the central nervous system, may also cause pathological nervous tissue damage under some conditions.[7]

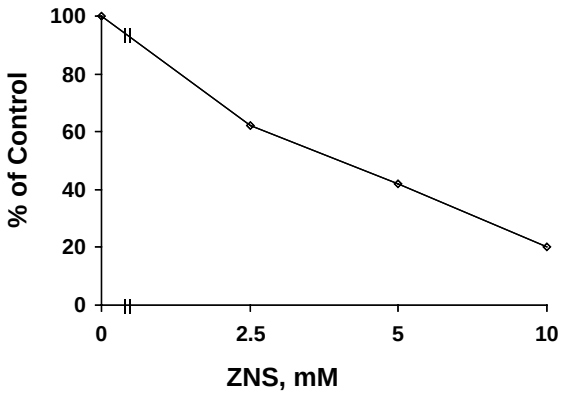

Figure 3 Nitric oxide scavenging activity of zonisamide.

In summary, zonisamide is believed to exert anticonvulsant effects by blocking sustained, repetitive neuronal firing via a blockade of voltage-sensitive sodium and by reducing voltage-sensitive T-type calcium channels. Zonisamide has no effect on neuronal responses to GABA or glutamate, and its activity is not due to carbonic anhydrase inhibition.

Pharmacokinetics

Zonisamide is rapidly and completely absorbed, with peak plasma concentrations occurring 2—4 h following 100- to 400 mg oral doses in healthy volunteers.[6] The mean plasma elimination half-life is long-about 60 h in noninduced subjects after single and multiple doses,[6] with ranges from 52 to 69 h reported.[8]

Steady state plasma concentrations of zonisamide in placebo-controlled studies ranged from 1.9 to 55.3 μg/mL (median, 18 μg/mL) after 10—12 days of dosing.[6] The plasma or serum levels of zonisamide have been shown to be linearly dose-related in adult and pediatric patients.[2]

At zonisamide concentrations of 1.0—7.0 μg/mL, the drug is only about 40% bound to human plasma proteins.[6] However, zonisamide has a high binding affinity for red blood cells (RBCs), and a marked concentration of zonisamide is observed in human red blood cells.[2] The affinity of zonisamide for RBCs is 8 times higher than that for plasma proteins,[6] and is dependent on the extracellular concentration of zonisamide.[2] For plasma concentrations >5 μg/mL, the zonisamide plasma versus erythrocyte concentration relationship appears to be relatively linear due to a dominant passive-diffusion distribution process.

Zonisamide undergoes acetylation to form *N*-acetyl zonisamide, and reduction to form the open ring metabolite, 2-sulfamoylacetyl phenol (SMAP) (Fig. 4).[9]

Reduction of zonisamide to SMAP is mediated by the cytochrome P450 isozyme 3A4.[10] Zonisamide does not induce its own metabolism and does not induce liver enzymes.[8]

Urine is the major route of zonisamide excretion in humans; excretion in feces is a minor elimination route.[2] Following multiple dosing, 62% of the radiolabelled dose was recovered in the urine, with 3% in the feces. Of the excreted dose, 35% was recovered as zonisamide, 15% as *N*-acetyl zonisamide, and 50% as the glucuronide of SMAP.[6]

Drug interactions

Since zonisamide is not highly bound to plasma proteins, it does not affect protein binding of other highly protein-bound AEDs. Protein binding of zonisamide is unaffected in the presence of therapeutic concentrations of phenytoin, phenobarbital, or carbamazepine.[6]

Since zonisamide is metabolized by the cytochrome P450 3A4, other drugs that induce or inhibit this enzyme may induce or inhibit zonisamide metabolism. Concomitant administration of phenytoin and carbamazepine increases zonisamide clearance from 0.32 to 0.51 mL/(min kg). The plasma elimination half-life of zonisamide is decreased to 27 h by phenytoin, to 38 h by phenobarbital and carbamazepine, and to 46 h by sodium valproate.[6] The differential effects of phenytoin and carbamazepine were also documented in a study where zonisamide was administered to patients receiving phenytoin or carbamazepine as monotherapy. The area under the curve (AUC) of zonisamide was 20% higher in the carbamazepine group compared to the phenytoin group (Table 1).[11]

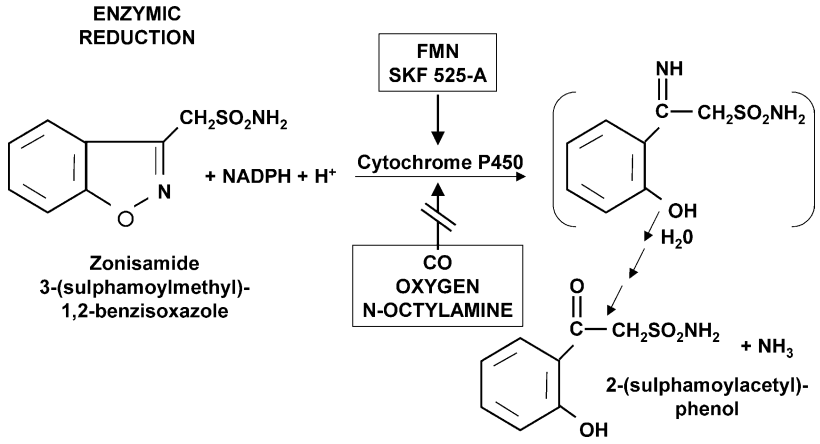

Figure 4 Enzymic cytochrome P450 reduction and nonenzymic hydrolysis.

Table 1 Median pharmacokinetic parameters for zonisamide in plasma (ranges).[10]

Concurrent medication	C_{max} (μg/mL)	T_{max} (h)	AUC[a] (μg/mL)	Cl/F (mL/h/kg)	$t_{1/2}$ (h)
Phenytoin	4.8 (3.8—5.9)	2.5 (1.9—4.9)	171 (130—245)	33.9 (19.3—37.4)	27.1 (20.7—34.9)
Carbamazepine	5.2 (3.1—6.6)	2.5 (2—4)	242 (215—386)	20.6 (14.8—26.8)	36.4 (31.8—54.6)

C_{max}, maximum concentration; T_{max}, time to reach C_{max}; AUC, area under the curve; Cl/F, oral clearance; $t_{1/2}$, half-life.
[a] Phenytoin median = Carbamazepine median, Mann—Whitney *U*-test, $P < 0.05$.

Table 2 Effect of concomitant administration of AEDs on zonisamide steady state.[11]

Medications	*n*	C/D[a] ratio of zonisamide
Zonisamide alone	28	4.71 ± 0.21
Zonisamide + phenobarbital	11	3.33 ± 0.22
Zonisamide + phenytoin	14	2.88 ± 0.39
Zonisamide + sodium valproate	24	3.79 ± 0.16
Zonisamide + clonazepam	8	4.31 ± 0.49
Carbamazepine alone	34	
Zonisamide + carbamazepine	17	2.89 ± 0.22

Values are expressed as means ± S.E.
[a] C/D, concentration-to-dose.

Concomitant administration of zonisamide with phenobarbital, phenytoin, or carbamazepine significantly decreased the concentration-to-dose (C/D) ratio (ratio of the steady-state plasma concentration to the administered dose) of zonisamide, whereas clonazepam and sodium valproate did not change the C/D ratio (Table 2). In one clinical trial, the ratio of plasma concentration of carbamazepine-10,11-epoxide, the major active metabolite of carbamazepine, to the plasma concentration of carbamazepine, was decreased by concomitant administration of zonisamide, but the significance of this is not clear.[12] A number of studies have evaluated the effect of zonisamide on the pharmacokinetics of other drugs, including AEDs, and have concluded that concomitant administration of zonisamide does not affect serum concentrations of carbamazepine, phenytoin, or sodium valproate to any clinically significant extent.

Conclusions

The pharmacokinetic profile of zonisamide is favorable for clinical treatment of seizures. Zonisamide is rapidly and completely absorbed. Its long plasma elimination half-life allows for twice-daily, or even once-daily, dosing. Its dual mechanism of action may account for its efficacy in patients resistant to other AEDs.

Zonisamide does not affect protein binding of other highly protein-bound AEDs, such as phenytoin or carbamazepine. However, liver enzyme-inducing AEDs (such as phenytoin, carbamazepine, sodium valproate, or phenobarbital) will increase the plasma clearance of zonisamide, shorten its half-life, and lower its concentration/dose ratio. Therefore, dosage adjustments may be necessary to maintain therapeutic levels of the drug when it is used in combination with certain AEDs.

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