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REVIEW

ZONISAMIDE: A NEW ANTIEPILEPTIC DRUG

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Although the significant progress in pharmacotherapy of epilepsy during last decade was achieved, about one third of patients are resistant to the current treatment. When the monotherapy is not efficient, the polytherapy should be applied. Zonisamide (ZNS) is a new antiepileptic drug (AED) efficient in treating refractory epilepsy. Its efficacy in different types of seizures was confirmed in various animal studies as well as in clinical conditions. ZNS inhibits voltage-dependent Na^+ channels and Ca^{2+} channels of T-type. The drug influences also monoamine neurotransmission and exhibits free radical scavenging properties. ZNS has a linear and favorable pharmacokinetics with excellent oral bioavailability. Furthermore, ZNS treatment, compared to other anticonvulsants, is relatively safe and well tolerated. Since ZNS is often used in polytherapy, its interactions with other AEDs seem to be of particular importance. However, the experimental data are rather inconsistent and further studies are necessary to elucidate exact effects of coadministration of ZNS with other AEDs. Recently, the clinical and experimental studies have suggested some new indications for ZNS administration, as mania, neuropathic pain, Parkinson's disease or migraine prophylaxis. Nowadays, it is also well established that ZNS exerts neuroprotective properties.

Key words: *zonisamide, epilepsy, experimental seizures, clinical trials*

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Abbreviations: AEDs – *antiepileptic drugs,* CBZ – *carbamazepine,* CNS – *central nervous system,* CYP 450 – *cytochrome P-450,* DA – *dopamine,* FE – *flurothyl,* 5-HT – *serotonin,* LTG – *lamotrigine,* MAO-A – *monoamine oxidase type A,* MAO-B – *monoamine oxidase type B,* MES – *maximal electroshock,* NO – *nitric oxide,* PB – *phenobarbital,* PHT – *phenytoin,* PTZ – *pentetrazole,* SMAP – *2-sulfamoylacetylphenol,* VPA – *valproate,* ZNS – *zonisamide*

Introduction

Epilepsy, a chronic neurological disorder that manifests itself as seizures resulting from sudden patologic and synchronic depolarization of neurons, affects about 1–2% of the population [5]. Although the last decade brought the introduction of several new antiepileptic drugs (AEDs) and essential progress in the pharmacotherapy of epilepsy was noted, about 30% of patients still have seizures that continue despite taking AEDs [19]. When the monotherapy occurs not efficient, polytherapy treatment is usually required. Therefore, possibility of interactions between AEDs can be a considerable problem in such situations.

Furthermore, current AEDs do not seem to influence the epilepsy progression and no drug preventing the development of this neuropathology (e.g. after head trauma) is available [19, 46]. In the light of the presented data, extensive experimental and clinical research dealing with new AEDs should be performed.

Zonisamide (ZNS, 1,2-benzisoxazole-3-methanesulfonamide; Zonegran; Excegran) is one of the new AEDs. It is a sulfonamide derivative exhibiting a broad spectrum of antiepileptic activity and effective in the treatment of refractory seizures. ZNS is available in Japan for over a decade and marketed in the USA from 2000 [3].

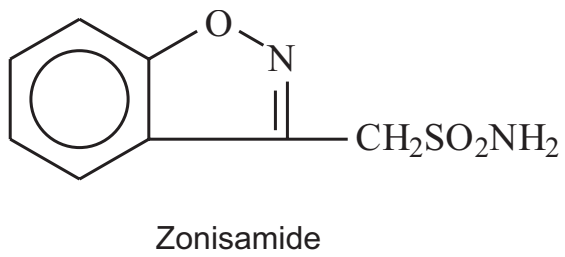

Fig. 1. Chemical structure of zonisamide. *From:* Willmore: Neurology, 2000, 55, Suppl. 3, S17–S24

Anticonvulsant activity

ZNS showed anticonvulsant activity in various animal models of epilepsy as well as in clinical conditions. It appears to inhibit the spread of seizure discharges and suppress epileptogenic focus. Clinical experience documented its efficacy in treatment of medically refractory simplex and complex partial seizures, generalized convulsions including tonic-clonic, absence, myoclonic seizures, as well as secondary generalized or combined seizures [12, 42]. Significant effectiveness was also demonstrated in both Lennox-Gastault and West syndrome [44]. In infantile spasms, the disappearance of hypsarrhythmia and cessation of seizures after ZNS treatment was observed [48]. ZNS has demonstrated both efficacy and safety, equivalent to that of carbamazepine (CBZ) in patients with partial seizures, and to that of valproate (VPA) in a study of children with generalized seizures [44].

The drug occurred also effective in a variety of animal models of epilepsy. Anticonvulsant ZNS activities were demonstrated by protecting animals against maximal electroshock (MES)-induced seizures in rodents, by Uno et al. [51] and Masuda et al. [21]. ZNS exerts antiepileptic activity in MES-induced seizures without causing general depression of the central nervous system (CNS) [9]. It limits development of maximal seizure activity and reduces the spread of the seizure process from an activity focus [9].

Moreover, the drug exerted antiepileptic effect in seizure susceptible EL mouse mutant strain, an animal model of complex partial seizures or temporal lobe epilepsy [31]. ZNS showed also anticonvulsant effect against chemically induced seizures in flurothyl (FE) [9] and pentetrazole (PTZ) models. However, data from PTZ test seem to be quite inconsistent [18]. In amygdala and hippocampal kindling seizure models, ZNS was reported to exhibit either modest therapeutic and prophylactic effects [7] or no depressant action on amygdala-kindled seizures [14]. Wada et al. [52] reported that zonisamide possessed potent anticonvulsant action against focal seizure and inhibits a second generalization from the visual cortex.

Some authors [9] postulate that ZNS may inhibit the development of the seizure phenotype and possesses significant aniepileptogenic properties. During chronic experiment with FE-induced seizures, the characteristic change in seizure pheno-

type from clonic to tonic was blocked by ZNS [9]. These results suggest that ZNS can suppress the development of seizure showing antiepileptogenic effect.

Mechanism of action

ZNS prevents repetitive neuronal firing by blocking voltage-dependent Na^+ channels. It inhibits also T-type Ca^{2+} channels, which was demonstrated in the rat cerebral cortex [41, 47]. Another postulated mechanism is associated with the blockade of K^+-evoked glutamate-mediated synaptic excitation [3].

Moreover, ZNS biphasically facilitates dopaminergic (DA) and serotoninergic (5-HT) transmission. At effective concentrations, the drug enhances, whereas at supraeffective concentrations it reduces DA and 5-HT neurotransmission [35, 36]. Okada et al. [36] demonstrated that ZNS inhibited type-B monoamine oxidase (MAO-B), without affecting activity of type-A (MAO-A) of this enzyme.

Although some authors [25] hypothesized that central benzodiazepine receptors were specific for ZNS binding, it was evidenced that ZNS did not potentiate $GABA_A$ receptor-related events [1, 41].

Other considered potential mechanisms of ZNS action comprise its inhibitory effect on the excessive nitric oxide (NO) production and free radical generation including hydroxyl and NO radicals [3, 28]. By scavenging excess NO the drug can modulate cGMP formation which is known to be related to initiation and propagation of seizures [28]. ZNS was also shown to inhibit lipid peroxidation in iron-induced epileptic foci of rats [28]. These effects can result in protection of neurons from free radical-induced damage and in stabilization of neuronal membranes. ZNS was also described as an inhibitor of carbonic anhydrase. However, the exact mechanism of action of this novel AED and its affinity for various receptors remain still unclear, requiring further investigations.

Pharmacokinetics

ZNS is rapidly absorbed with a T_{max} ranging between 2.0 and 6.0 h and shows excellent oral bioavailability greater than 95% [2]. The drug is primarily bound to erythrocytes and in approximately 40–60% to plasma proteins, mostly albumins. Erythrocyte-borne drugs are known as available for distribution to the tissues and equilibrate the concentration across the blood-brain barrier. ZNS penetrates the blood-brain barrier in the course of a single transcapillary transit but not by carrier-mediated mechanism [33].

Cornford [6] reported that brain/serum concentration ratio of ZNS exceeded 1, at least after oral administration of the drug applied at doses of 5, 20, 80 mg/kg. In some experiments, markedly higher concentration of ZNS in brain than in serum was observed during 1–6 h after *ip* injection [31]. Effective serum level of ZNS in both experimental animals and in humans ranges from 10 to 30 μg/ml, while neurotoxic plasma concentrations evaluated in animal studies were higher than 70 μg/ml [22, 39]. Nevertheless, some adverse effects were observed at concentrations higher than 30 μg/ml [40], suggesting real usefulness of therapeutic drug monitoring.

ZNS has a linear pharmacokinetics, at least within its usual therapeutic dose range of 200–400 mg per day in humans. Serum levels were noted to be uniform across the 12-h dose interval, with only 14% fluctuation in twice-daily dosing, 27% fluctuation in once-daily dosing, and are proportional to the dose across the whole therapeutic range [2].

ZNS half-life varies between 52–66 h, however, much lower values (27–36 h) can be evaluated in patients taking enzyme-inducing co-medications [1]. ZNS is partly eliminated by the renal route and partly metabolized by cytochrome P-450 (CYP3A4)-mediated reduction. The main result of this reductive biotransformation is an open ring metabolite, 2-sulfamoylacetylphenol (SMAP). ZNS can also undergo N-acetylation, so finally, unchanged form of ZNS, SMAP, and N-acetyl-ZNS are usually detected in urine [1].

It should also be mentioned that ZNS does not influence CYP3A4 activity, so it does not induce its own metabolism. On the other hand, liver enzyme inducing AEDs, such as phenytoin (PHT), barbiturates, CBZ, accelerate ZNS metabolism and significantly reduce its half-life [2].

Clinical efficacy and new indications

ZNS proved to be efficient in treatment of refractory partial seizures during three double-blind placebo-controlled add-on trials in the USA and Europe [3]. In all studies, ZNS produced significant reduction (20–40%) in the frequency of partial

seizures with responder rates ranging from 25 to 42% [1]. Monotherapy studies performed in Japan found responder rates as 80–93% in various types of epilepsy (simple partial, complex partial, secondarily generalized tonic-clonic, tonic, absence and myoclonic seizures), while comparative monotherapy studies in complex partial seizures showed advantage of ZNS over VPA and CBZ treatment [2].

Recently, new experimental and clinical studies suggested usage of ZNS in non-epileptic disorders. Kanba et al. [15] reported that ZNS exerted mood stabilizing properties and could have some potential value in the treatment of acute mania and recurrence prevention in patients with bipolar disorder. In animal experiments, ZNS dose-dependently antagonized both mechanical hyperalgesia [49] and formalin-induced flinching in rats without depressing spontaneous activity, behavior or reflexes [23]. These results may suggest possibility of ZNS usage in the treatment of neuropathic pain. The inhibition of MAO-B activity and facilitatory action on DA transmission caused by ZNS incited interest in this AED as a new adjuvant in the Parkinson's disease treatment. The pilot clinical study revealed significant alleviation of clinical symptoms in patients with this neuropathology [29]. Another new indication for ZNS administration can be migraine prophylaxis and a clinical trial is just under way [3].

Neuroprotection

Several animal models and clinical studies revealed that the epileptic brain undergoes continuous modifications caused by underlying factors and recurrent seizures, leading to neuronal cell loss and irreversible brain damage. This neurodegeneration can result not only in the CNS dysfunction but also in the decreased efficacy of some AEDs [50]. Since considerable progress and intensification of seizures as well as cognitive decline were usually observed, it became obvious that antiepileptic treatment should be supported by neuroprotective action. ZNS is an anticonvulsive compound that probably fulfills these two criteria. Minato et al. [27] reported that ZNS reduced infarct volume in ischemia-induced neuronal damage. These results are in agreement with another finding [11], showing the neuroprotective efficacy of ZNS pretreatment in hypoxic-ischemic damage in neonatal rats. Similarly, Owen et al. [38] demonstrated the reduction of neuronal damage caused by ZNS pretreatment in global forebrain ischemia model in gerbils. It should be underlined that ZNS post-treatment did not exhibit such histological or behavioral effects, as when the drug was administered before the ischemic stimulus. ZNS significantly reduced ischemia-induced memory impairment, probably by minimizing ischemic injury to the CA1 hippocampal area responsible for spatial memory [38]. The mechanism of ZNS neuroprotective activity in the described model was probably due to the reduction of ischemia-induced glutamate release and subsequent excitotoxic neuronal damage. ZNS-induced blockade of sodium and calcium channels may contribute to antiglutamatergic action of the drug. However, other not clarified mechanisms cannot be excluded [38].

Both neuroprotective and antiepileptic efficacy of ZNS may also be connected with its antioxidant properties. ZNS scavenges hydroxyl and NO radicals in a dose-dependent manner [28], which results in protection of neurons from free radical-induced damage and in stabilization of neuronal membranes. Moreover, elimination of NO molecules and modulation of cGMP formation may also lead to better control of seizure initiation and propagation [28].

Undesired effects and drug tolerability

Experience from almost 750 thousands patients indicates that ZNS is relatively safe AED [1]. Most commonly reported adverse effects concern the influence of ZNS on CNS and include somnolence (17%), dizziness (13%), ataxia, headache (10%), nausea (9%), agitation (9%), irritability (9%), and fatigue. ZNS treatment can also evoke loss of appetite or anorexia (13%) [3]. There were few reports of ZNS-induced behavioral and cognitive effect [21].

In animal toxicological studies, the drug did not appear to affect the spontaneous alteration behavior, active avoidance performance, and relative power of cortical EEG. ZNS did not influence brain pH parameters or regional cerebral blood flow. The antiepileptic showed a tendency to depress the flexor reflex without affecting the neuromuscular transmission in anesthetized cats. Generally, ZNS even at dose of 100 mg/kg *po* did not influence behavior in mice, except pelvic lowerings, change in tail and body position and ptosis [13]. The function

of the autonomic nervous system was only slightly affected during the high-dose therapy.

Other ZNS-evoked adverse effects include rash, gastrointestinal disorders and developing of kidney stones [3], although the incidence of renal calculosis seems to be low (4%), insignificantly different from the placebo-treated group [1]. Thirteen cases of oligohydrosis were reported in pediatric patients taking ZNS in Japan, although this effect was not observed in clinical trial [3]. First reports on the teratogenic effects of ZNS do not indicate greater risk than that associated with other AEDs, however, the data must be completed [17].

Influence of ZNS on various functions was investigated in animal studies. In detail, ZNS administered *iv* transiently lowered blood pressure in anesthetized dogs. What is interesting, this effect was not observed after the oral administration, even at high doses. Depression of the gastric juice volume, pyloric pH and gastric emptying in rats was observed, although the intestinal transit in mice was not inhibited [32]. The renal blood flow and glomerular filtration were only little changed by ZNS at high doses [32].

Undesired effects occurred mostly in early phase of the treatment, and, sometimes, slow introduction of ZNS could improve the tolerability [2]. Only 12% of patients discontinued treatment with ZNS because of adverse effects in clinical trial [3].

Most often undesired effects as drowsiness, loss of appetite, somnolence or fatigue appeared at high doses of ZNS, when its blood concentration exceeded 30 mg/l [37]. It should be underlined that not only the narrow range of therapeutic blood concentration, but also factors increasing brain level of ZNS may be problematic from the clinical point of view [10].

Drug interactions

The older generation of AEDs affects hepatic metabolism of other drugs. Thus, pharmacokinetic interactions during polytherapy are relatively frequent. Furthermore, conventional AEDs may disturb the turnover rate of several endogenous substances, like hormones and vitamins [4]. ZNS does not induce its own metabolism and does not inhibit cytochrome P-450 [2].

When the monotherapy of epilepsy is not effective, drug combinations can achieve proper seizure control. However, polytherapy may also lead to pharmacodynamic interactions. Since ZNS is often administered as an adjuvant drug, interactions between this drug and other anticonvulsants are of the great importance. Unfortunately, available data on this subject are neither complete nor consistent. ZNS was reported not to exert any effect on steady-state concentrations of PHT, CBZ and VPA [1]. During clinical add-on study, a significant decrease in the clearance rate of lamotrigine (LTG) and CBz-10,11-epoxide were observed, however, no significant changes in the pharmacokinetic profiles of VPA, LTG, PHT, and CBZ were noted [45].

Influence of some AEDs, modulating the activity of hepatic enzymes, on ZNS pharmacokinetics was examined in several clinical studies [34, 44]. The half-life ($t_{1/2}$) of ZNS was reduced during its co-administration with CBZ and PHT [34], which may result from the acceleration of ZNS metabolism. VPA only moderately decreased the steady-state plasma levels of ZNS [44]. On the other hand, the level of ZNS binding to plasma proteins was unaffected in the presence of therapeutic concentrations of CBZ, PHT and phenobarbital (PB) [20]. Kimura et al. [16] evidenced that PB and CBZ but not PHT decreased the $t_{1/2}$ value for ZNS. In animal studies, co-administration of ZNS with PHT or VPA suppressed seizures more effectively than ZNS alone [30]. Both serum and brain concentrations of ZNS tended to increase proportionally to the applied dose of VPA and PHT [30]. The anticonvulsant effect of the combination of ZNS and PB was greater than that of ZNS alone. However, the increased brain but not serum concentrations of ZNS were observed during concomitant PB treatment [31].

It was also found that barbiturates increased the number and density of the specific binding sites for ZNS in the CNS [25]. In clinical conditions, the increased serum concentration of ZNS was observed with LTG co-administration, suggesting that LTG can inhibit ZNS elimination [24]. The presented data imply that interactions between ZNS and other AEDs may play an important role in add-on therapy, and some modification of ZNS dosage should be considered in such situations [3]. Synergistic interactions between ZNS and other AEDs are, certainly, the most favorable from the clinical point of view.

It should also be mentioned that chronic intake of caffeine lowered the brain concentration of ZNS and attenuated its anticonvulsant effect [8].

Conclusions

ZNS is a new AED with a broad spectrum of anticonvulsant activity, efficient in many types of seizures. The drug is relatively safe and well tolerated. ZNS is usually used in treatment of refractory epilepsy, very often as an add-on therapy. During polytherapy, interactions between ZNS and other AEDs seem to be of a great importance. However, the data on this subject are still inconsistent and need further investigations.

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