

Zonisamide in the management of epilepsy in the elderly

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Abstract: Zonisamide (ZNS), a second-generation antiepileptic drug, indicated as add-on treatment of focal epilepsy, has been recently approved as monotherapy for the treatment of partial seizures in adults affected by newly diagnosed epilepsy in Europe. Evidence on the efficacy and tolerability of antiepileptic drugs in the elderly is still lacking as these patients are frequently excluded from clinical trials. Here, a comprehensive overview of available data regarding the use of ZNS in the treatment of epilepsy in elderly people is provided. In a pooled analysis conducted in patients aged ≥ 65 years, no new/unexpected safety findings have emerged. Few data from uncontrolled investigations suggest that ZNS may be effective and well tolerated when administered as monotherapy or adjunctive antiepileptic treatment in the elderly. However, evidence from these observational studies is less than satisfactory, and randomized controlled trials focused on these patients are still needed.

Keywords: zonisamide, elderly, epilepsy, safety, efficacy

Introduction

Epilepsy is one of the most serious disorders of the brain with about 50 million people affected worldwide.¹ The incidence of epilepsy is highest at the younger and older age, and around 30% of new epilepsies arise in older patients. The prevalence rate of epilepsy in subjects aged over 70 years is quite twice that in children,² and the incidence rates increase significantly with age for every decade after 60 years of age.^{1,3} With life expectancy becoming progressively longer, especially in high-income countries, the prevalence of epilepsy in the elderly should increase and to understand its epidemiology is a matter of significant public health importance. Evidence on the optimal treatment of epilepsy in old age is limited, mainly because older patients are often excluded from randomized clinical trials.⁴ Because of the unfavorable pharmacokinetic and safety profile^{5,6} of first-generation antiepileptic drugs (AEDs) in the elderly, there has been an increasing attention on newer pharmacological alternatives for this population. However, comparative randomized double-blind studies about the use of second-generation AEDs in older subjects with newly diagnosed epilepsy are few,⁷⁻⁹ and only observational studies have been carried out for some medications.¹⁰⁻¹²

Zonisamide (ZNS), a second-generation AED, has been recently approved in Europe as monotherapy for the treatment of partial seizures in adults with newly diagnosed epilepsy. This agent is also approved in Europe and USA as adjunctive therapy of focal seizures with or without secondary generalization with a proven safety and tolerability profile.^{13,14} A recent pooled analysis of clinical studies, where patients with epilepsy aged ≥ 65 years treated with ZNS were enrolled, showed a favorable safety/tolerability profile.⁴ This, in combination with the negligible expected drug interactions, and the advantage of once-daily dosing,¹⁵ has led to an increasing

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interest in the potential use of this AED for epilepsy therapy in the elderly.

This review provides a comprehensive overview of available data on ZNS in the management of elderly people with epilepsy.

Literature search strategy

Studies discussed in this paper were searched by using the EMBASE and the PubMed databases from inception to November 28, 2014. The following keywords were used: “zonisamide”, “epilepsy”, and “elderly.”

Further data were also searched from abstracts of International Conference Proceedings (Annual Meetings of the American Epilepsy Society and the Congresses of the International League Against Epilepsy). However, abstracts often do not show all relevant details and are not as rigorously peer reviewed as journal articles. Finally, the references of the selected papers were reviewed for additional articles.

Pharmacology: mechanism of action

ZNS has been documented to exhibit multiple mechanisms of action. ZNS has been shown to block both sodium and T-type Ca^{2+} channels.¹⁵ These mechanisms of action contribute to the stabilization of neuronal membranes and to the suppression of hypersynchronization.

In addition, ZNS has been reported to affect the glutamatergic and γ -aminobutyric acid-ergic neurotransmitter systems,^{16–20} to increase striatal and hippocampal concentration of dopamine and serotonin (total and extracellular) and to alter acetylcholine metabolism. Furthermore, ZNS has been demonstrated to weakly inhibit carbonic anhydrase activity.^{16,17} The clinical relevance of these mechanisms to antiseizure activity is still unclear.²⁰

Pharmacokinetic profile

After oral administration, ZNS is rapidly absorbed and its oral bioavailability is virtually complete. The peak plasma concentration (C_{max}) ranges between 2.3 mg/mL and 12.5 mg/mL (from 200 mg to 800 mg), depending on the dosage, and is reached in 2.4–3.6 hours (T_{max}). The presence of food does not modify the extent of the drug absorption, but delays T_{max} to 4–6 hours.¹⁷

ZNS has an apparent volume of distribution of about 1.1–1.8 L/kg. Plasma ZNS levels increase proportionally for doses of 200–400 mg.^{21,22}

ZNS is partially bound to the human serum albumin (about 50%) and preferentially accumulated in erythrocytes.²³ The elimination half-life of ZNS in plasma depends

on the presence of cytochrome P450 (CYP)3A4 microsomal enzyme inducers (ie, phenobarbital, carbamazepine, and phenytoin) and ranges from about 50–70 hours in patients non-treated with enzyme inducers to 25–35 hours in the treated ones.²⁴ This long half-life allows the once-daily dosing.¹⁷ The apparent oral clearance is 15–20 mL/h/kg in patients non-treated concomitantly with enzyme inducers and 20–30 mL/h/kg in patients treated with enzyme inducers.²⁴

The favorable pharmacokinetic profile supports the increasing use of ZNS. No major influences of ZNS on the pharmacokinetics of other concomitant medications have been reported. In particular, in patients on monotherapy with carbamazepine,²⁵ valproic acid,²⁶ phenytoin,²⁷ or lamotrigine,²⁸ the introduction of ZNS (up to 400 mg/day) as add-on treatment did not affect the steady-state serum levels. In patients co-medicated with phenobarbital, carbamazepine, and phenytoin, the exposure to ZNS is decreased and the steady-state plasma levels are reached within a week.¹⁷

Metabolism and excretion

ZNS, before predominant excretion by renal route, undergoes hepatic biotransformation.²⁹

In particular, ZNS is mainly metabolized in the open-ring metabolite, 2-sulfamoylacetyl phenol, by the CYP3A4 isoenzyme, in the *N*-acetyl derivative by the *N*-acetyltransferase, and, to a lesser extent, directly conjugated to the glucuronic acid. These metabolites are pharmacologically inactive. Of the excreted dose, 15%–30% was recovered as unchanged drug, 20% as ZNS glucuronide and *N*-acetyl ZNS, and 50% as the 2-sulfamoylacetyl phenol glucuronide.^{29,30}

Pharmacokinetic profile in special groups

The influence of aging on the pharmacokinetic profile of ZNS was assessed in a study^{16,31} conducted in healthy volunteers, 11 elderly (65–71 years) compared to 11 young (21–40 years), after oral administration of a single dose (300 mg). Wallace et al³¹ found that the elimination half-life of ZNS was 51.9 hours in the older subjects and 65.7 hours in the younger subjects, probably as a result of the smaller volume of distribution in the older population (1.19 L/kg) compared with the non-elderly segment (1.44 L/kg). No significant differences in renal clearance, mean plasma area under the serum concentration-time curve (AUC), and mean plasma clearance were found, and dose adjustments were not necessary. A single-dose study in subjects with renal impairment demonstrated that ZNS clearance was decreased

significantly, and a 35% AUC increase was observed in subjects with creatinine clearance values <20 mL/min.^{16,23}

Efficacy

There are limited data available on the efficacy of ZNS in the elderly population with focal epilepsy. Only one Phase IV randomized controlled trial and few uncontrolled studies reported data regarding the efficacy of ZNS in elderly patients with epilepsy.

Randomized controlled study

Results from a 16-week Phase IV randomized placebo-controlled study investigating the safety and tolerability profile of ZNS as add-on therapy in elderly patients with refractory focal epilepsy concomitantly treated with one or two AEDs³² (NCT01546688 clinicaltrials.gov/show/NCT01546688) show exploratory efficacy data on ZNS. This research has not yet been published but only a few data have been made available by the sponsor. Evidence from the results section of clinicaltrials.gov/show/NCT01546688 (last updated June 30, 2014) indicates that 33 patients (mean age 72.5 years) were enrolled in the treatment arm (five not completed study, none for lack of efficacy) and 18 (mean age 71.1 years) in the placebo arm (three not completed study, one for lack of efficacy). Although statistical analysis of efficacy data is not provided, the treatment group showed 75% of responders compared to 62% of responders in the placebo group during the last 28 days of the maintenance period. In addition, the median percent change in seizure frequency from baseline during the last 28 days of the maintenance period was similar in both the groups.

Uncontrolled studies

Data presented at the 25th International Epilepsy Congress Proceedings reported in a retrospective open-label study³³ efficacy and safety of ZNS as monotherapy/add-on treatment in patients affected by focal and primary generalized epilepsy stratified by age. A large part of the elderly group (>60 years) received concomitant antiepileptic treatment, and the mean dosage of ZNS was 475 mg/day. Seizure freedom was achieved in 27% of elderly patients, while a 75%–99.9% reduction in seizure frequency was reached in 27%. The authors did not state the exact number of older patients treated.

A further retrospective 8-week open-label study³⁴ investigated 20 elderly patients (range 49–89 years, mean 64.1 years) with complex partial seizures treated with ZNS as add-on therapy. The ZNS dosage ranged from 100 mg once daily to 100 mg bid (twice daily) or 200 mg once daily on the

basis of clinical response. Three patients were affected by post-traumatic epilepsy, four by postanoxic damage, three were affected by stroke-related epilepsy, and ten by cryptogenic epilepsy. Three out of 20 patients (15%) experienced seizure freedom, and 16 out of 20 patients (80%) reported a reduction $>50\%$ in seizure frequency. No dropouts were reported in the responder group. Tosches and Tisdell³⁵ described 53 patients out of 60 patients identified (≥ 60 years, mean 76 years, range 60–97) treated with ZNS for ≥ 3 months. Thirty-seven patients were treated with ZNS as monotherapy (mean dose 200 mg/day, mean duration 28.2 months). Twenty out of 37 patients (54.1%) obtained seizure freedom, and a $\geq 50\%$ reduction in seizure frequency was achieved in further five patients (13.5%). The “add-on” group (16 patients, mean dose 268.8 mg/day, mean duration 35.3 months) showed seizure freedom in five patients (31.2%) and a $\geq 50\%$ reduction in seizure frequency in an additional seven patients (43.8%). The authors also reported positive neurological effects with the improvement of extrapyramidal tremor ($n=2$), improved awareness ($n=2$), mood ($n=1$), and also postherpetic neuralgia ($n=1$) and restless legs syndrome ($n=1$). In another retrospective study³⁶ of 417 old adults from the Columbia AED database comparing effectiveness of ten AEDs, including ZNS in older adults (>55 years), 30 patients with epilepsy (mean age 64 years) were taking ZNS (median dosage 300 mg/day). The authors reported a 12-month seizure-freedom rate of 22.2% for ZNS ($n=18$) similar to that obtained for the remaining AEDs except for lamotrigine and levetiracetam that showed seizure-freedom rates greater than 40% (54.1%, $n=85$ and 42.6%, $n=68$, respectively). The authors also compared 12-month retention rate (a combined evaluation of efficacy and tolerability) in 247 ($n=436$ subject–drug combinations) elderly patients newly treated with any AED over a period of 4 years. The highest retention rate was demonstrated for lamotrigine (78.6%, $n=126$), while ZNS, valproate, and levetiracetam showed a 12-month retention rate of 68.2% ($n=22$), 69.6% ($n=23$), and 72.5% ($n=102$), respectively. The lowest retention rate was seen with oxcarbazepine (23.5%, $n=34$). The subgroup evaluation of patients with refractory epilepsy ($n=250$ subject–drug combinations) showed a retention rate of 90% for valproate ($n=10$), followed by lamotrigine (77.8%, $n=63$), levetiracetam (71.8, $n=85$), ZNS (70%, $n=20$), and topiramate (66.7%, $n=15$).

Safety and tolerability

Pooled analysis of data from clinical studies

Recently, a pooled analysis of clinical data (five randomized, double-blind and two open-label clinical studies) specifically

performed to evaluate safety and tolerability profile of ZNS in older epileptic patients (≥ 65 years) compared to younger patients (18–65 years) has been published.⁴ In particular, Trinka et al analyzed data from 95 elderly patients and 1,389 younger adult patients and evaluated treatment-emergent adverse events (TEAEs). TEAEs were similar in both the groups (82% in elderly patients vs 84% in younger adult patients). In addition, the incidence of treatment-related TEAEs was less in older patients than in younger adults (56% vs 73%, respectively). Although these findings may be related to different titration schedule and dosages, the authors did not report any data regarding titration for both the groups. The greater part of TEAEs was mild to moderate in each group. Severe TEAEs were reported less frequently in elderly subjects compared with the younger group (11.6% vs 20.8%). Dizziness (15%), headache (13%), somnolence (12%), and fatigue (12%), followed by nasopharyngitis (8%), constipation (7%), diarrhea (6%), confusion (6%), pruritus (6%), nausea (6%), depression (5%), insomnia (5%), and loss of appetite (5%) were the most frequently reported TEAEs in the elderly group compared with the younger group. Peripheral edema of mild to moderate intensity occurred in 4% of elderly subjects vs 1% in the non-elderly adults group.

The main treatment-related TEAEs in elderly patients were dizziness (14%), sleepiness (9%), fatigue (8%), and pruritus (6%). Only three serious treatment-related TEAEs (pancreatitis, rib fracture, and status epilepticus) were reported in elderly patients treated with ZNS as add-on therapy. One death was considered treatment related due to pancreatitis. TEAEs leading to ZNS withdrawal occurring in $\geq 2\%$ of elderly patients were dizziness (4%), headache (2%), sleepiness (2%), and confusion (2%). Trinka et al did not report significant changes in the clinical laboratory parameters and body weight in the elderly group.⁴

Randomized controlled study

Recently, a 16-week Phase IV randomized placebo-controlled study investigated the safety, tolerability, and efficacy of ZNS as adjunctive treatment in elderly patients affected by refractory focal epilepsy concomitantly treated with one or two AEDs (NCT01546688 clinicaltrials.gov/show/NCT01546688, last updated June 30, 2014). The clinical data of 33 treated patients 18 patients in the placebo arm were reported. Serious adverse events were 6/33 (18.2%) with ZNS versus 1/18 (5.6%) with placebo, whereas other adverse events were found in 17 out of 33 (51.5%) elderly patients with epilepsy and in eight out of 18 (44.4%) patients in the placebo group. Serious adverse events reported in treated group were

cardiovascular insufficiency, pancreatitis, sudden death, rib fracture, convulsion, status epilepticus, vertebrobasilar insufficiency, and renal failure (1/33, 3.03% each).

Regarding the other adverse events, the most reported in the ZNS group were dizziness (5/33, 15.15% vs 2/18, 11.11% in the placebo group), somnolence (5/33, 15.15% vs 0/18, 0% in the placebo group), and headache (4/33, 12.12% vs 0/18, 0% in the placebo group).

Uncontrolled studies

In a retrospective 8-week open-label study³⁴ in 20 elderly patients (mean 64 years, range 49–89) with complex partial seizures under ZNS as add-on therapy, three patients discontinued ZNS (one for skin rash, one for visual hallucinations, and one for drowsiness). In addition, among 16 responder patients, five reported mild gastrointestinal upset and sleepiness without leading to ZNS discontinuation.

In a further retrospective open-label study³⁵ conducted in 60 elderly epileptic patients treated with ZNS (as monotherapy or add-on treatment), six patients (10%) discontinued ZNS, five due to unspecified adverse events (8.3%). The most frequent TEAEs were gastrointestinal upset, skin rash, and mild somnolence (2/60, 3.3% each) followed by anorexia, vision changes, headache, and lightheadedness (1/60, 1.7% each). In a retrospective analysis³⁶ comparing effectiveness of ten AEDs in old adults, the most frequent TEAEs leading to treatment discontinuation and/or to the dose change in more than 2% of patients in the ZNS-treated patients ($n=30$) were as follows: cognitive and gastrointestinal (10%–19.9%); allergies, dizziness, and headache (5%–9.9%); drowsiness, psychiatric effects, sleep difficulty, and vision (2%–4.9%).

Discussion

Seizures and epilepsy represent the third most frequent neurological disorder in the elderly. The incidence of epilepsy increases exponentially in people aged ≥ 65 years. The treatment of epilepsy in elderly patients can be challenging due to the fact that toxicity may be associated with concomitant treatments or medical conditions such as stroke, Alzheimer's, or Parkinson's disease. Several aspects may become complex treatment choices in elderly patients with epilepsy; therefore, physicians should pay attention in the management of seizures and epilepsy in this age-specific group. AEDs choice and dosing should consider the age-related physiological changes, comorbidities, concomitant treatment, and drug interactions. Although the primary goals of epilepsy therapy are similar in all ages, the abovementioned concerns become noteworthy issues managing epilepsy in older people. Thus,

drug selection needs to take into account not only efficacy but also tolerability and safety issues. Desirable characteristics of an AED for the management of epilepsy in aging are as follows: i) favorable safety profile; ii) absence of drug–drug interactions (concomitant treatment with AEDs and other medications); iii) weak influence on cognitive function; and iv) long half-life in order to allow one or two daily intakes.³⁸ Older patients with new onset epilepsy are often started on first-generation AEDs despite their poor tolerability. However, the second-generation AEDs are characterized by a better pharmacokinetic and tolerability profile and are best suited for the management of epilepsy in the elderly.²⁴ The pharmacokinetic profile of ZNS (long half-life, mild drug–drug interactions, and no induction or inhibition of the hepatic microsomal enzymes) can be considered favorable for the management of epilepsy in the elderly.^{15,29} This review showed several concerns. First, to offer the most recent estimation of the topic, we embraced abstracts from congress proceedings. Often, abstracts may not include significant aspects and are not subject to peer-reviewing processes. In addition, we derived data from the abstract itself and not from the posters. Therefore, some additional data regarding safety and efficacy of ZNS in elderly patients with epilepsy may have been missed by this approach. In addition, we cannot obtain comparisons regarding the frequency of adverse events between add-on and monotherapy studies. Although the few data obtained from the literature may be encouraging, we are far from obtaining generalizations regarding ZNS as AED in elderly population. Efficacy data from a single controlled study on efficacy of ZNS in elderly patients³² do not allow any conclusion because the data analysis is ongoing, and the sample size seems too small. ZNS is often well tolerated, but some authors suggested that its use may be limited by somnolence, psychiatric, and cognitive adverse effects.^{37,39} Psychiatric adverse events include depression, irritability, aggressive behavior, and psychosis, whereas cognitive adverse events comprise language impairment, cognitive slowing, memory impairment, and reduced mental concentration in a manner similar to topiramate.^{39,40} Although specific findings regarding psychiatric and cognitive profile of ZNS in older patients are lacking, cognitive and psychiatric adverse effects may be common during ZNS treatment, but they are related to specific risk factors (ie, past psychiatric history, symptomatic generalized epilepsy, number of concomitant AEDs, and ZNS serum levels)³⁹ with a low discontinuation rate in selected patients.⁴¹ The favorable ZNS pharmacokinetic profile, the lack of interaction, may represent the strength of the choice of ZNS in the elderly.

Although efficacy data are lacking, safety and tolerability of ZNS were recently evaluated in a pooled data analysis of five double-blind and two open-label studies conducted by Trinka et al⁴ in patients aged ≥ 65 years. In this analysis as well as in other uncontrolled studies, it has been reported that elderly patients treated with ZNS did not present more adverse events than the non-elderly. However, the relatively high frequency of cognitive and sedative adverse effects (ie, somnolence, headache, and dizziness) should be taken into account when ZNS is used in elderly patients.^{13,37} On the other hand, ZNS is effective in several disorders (ie, migraine, Parkinson's disease, obesity, and sleep disorders) that may affect elderly subjects.^{14,42–44} Therefore, ZNS may represent a useful option for the obese patients due to weight loss, for migraine, for patients affected by Parkinson's disease, and for sleep complaints. Recently, Eskandari et al⁴² showed a significant decrease of sleep apnea in a randomized placebo-controlled design independent of weight loss and probably due to carbonic anhydrase inhibition. On the contrary, treatment with ZNS should be avoided in patients with multiple or severe prior allergy/rash and renal stones. In a survey of experts for the treatment of symptomatic focal epilepsy in the elderly conducted in 2005, ZNS was recognized as first-line treatment by 39% and as second line by 56%.⁴⁵ Lamotrigine, levetiracetam, gabapentin, oxcarbazepine, and carbamazepine were considered as first-line AEDs by 98%, 95%, 71%, 61%, and 59%.⁴⁵

Conclusion

Based on our review, we conclude that, to date, there is no satisfactory evidence on the efficacy and tolerability of ZNS in the treatment of elderly patients with epilepsy, although the data from a limited number of studies are encouraging. Large controlled prospective studies are needed to establish the real role of newer generation AEDs, such as ZNS, in the management of epilepsy in the elderly.

Disclosure

VF is a former employee of Eisai s.r.l., Italy. AR, GDG, EAF, CF, and GV have no conflicts of interest to declare.

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