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ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Safety and Efficacy of Zonisamide in Refractory Epilepsy Patients: Clinical Experience from a Tertiary Center

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Tedaviye Dirençli Epilepsi Hastalarında Zonisamidin Etkinliği ve Güvenilirliği: 3. Basamak Merkezin Klinik Deneyimi

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Summary

Objectives: Zonisamide (ZnS) is a new generation antiepileptic agent used in the treatment of epilepsy patients with partial and generalized seizures. In this study, we aim to investigate the safety and efficacy of ZnS in the treatment of patients with refractory epilepsy who were being followed.

Methods: Forty-five refractory epilepsy patients who received ZnS treatment were included in this study. Patients who received ZnS treatment for less than six months were excluded. Age, sex, types of seizures, examination findings, magnetic resonance imaging and electroencephalography findings, concurrent use of non-ZnS antiepileptic drugs, decrease in the seizure frequency and side effects of the drug were recorded.

Results: Thirty-nine patients, whose mean age was 34.3±9.3 years, were evaluated. Complex partial seizures (CPS) and generalized tonic-clonic seizure (GTCS) were observed in 74.4% of the patients, whereas 10.3% had GTCS alone, 7.7% had CPS alone, 5.2% had GTCS and myoclonia and 2.6% of them had absence and myoclonia. In the follow-up, treatment was observed to be discontinued in 19 of the 39 patients due to drug side effects, or where there was an increase, or no change, in seizure frequency. Twenty patients responded to treatment. Seizure frequency was decreased by 25% in one patient; 50% in five patients, and 75% in seven patients. Three patients were seizure-free. Although there was no change in seizure frequency, seizure duration was shortened in four patients. Treatment-responsive patients were using ZnS at doses that ranged from 100 to 400 mg/day for 7 to 80 months.

Conclusion: ZnS is a safe, tolerable and effective option for the additional treatment of refractory epilepsy patients at our center.

Keywords: Antiepileptic drug; epilepsy; zonisamide.

Özet

Amaç: Zonisamid (ZNS), parsiyel ve jeneralize nöbetleri olan epilepsi hastalarının tedavisinde kullanılan yeni nesil bir antiepileptik ajandır. Bu çalışmanın amacı hastanemiz takipli dirençli epilepsi hastalarının tedavisinde ZNS'nin güvenilirliğini ve etkinliğini araştırmaktır.

Gereç ve Yöntem: Çalışmaya, ZNS tedavisi altında olan, 45 dirençli epilepsi hastası dahil edildi. Altı aydan kısa süre ZNS tedavisi altında olan hastalar dışlandı. Yaş, cinsiyet, nöbet tipleri, muayene bulguları, manyetik rezonans görüntüleme, elektroensefalografi bulguları, eş zamanlı kullanılan ZNS dışı antiepileptik ilaç sayısı, nöbet sıklığında azalma ve ilaç yan etkileri kaydedildi.

Bulgular: Yaşları ortalama 34.3±9.3 yıl olan 39 hasta değerlendirildi. Hastaların %74.4'ünde kompleks parsiyel nöbet (KPN) ve jeneralize tonik klonik nöbet (JTKN), %10.3'ünde yalnızca JTKN, %7.7'sinde yalnızca KPN, %5.2'sinde JTKN ve miyokloni, %2.6'sında ise JTKN, absans ve miyokloni mevcuttu. İzlemde 39 hastanın 19'unda, ilaç yan etkisi, nöbet sıklığında değişme olmaması ya da artış olması nedeniyle tedavinin sonlandırıldığı görüldü. Yirmi hasta tedaviye yanıt vermişti. Nöbet sıklığı; bir hastada %25; beş hastada %50; yedi hastada %75 oranında azalmıştı. Üç hastada nöbetsizlik sağlanmıştı. Dört hastada ise nöbet sıklığında bir değişiklik olmamasına rağmen nöbet süresi kısalmıştı. Tedaviye yanıtlı hastalar 7–80 ay arasında değişen sürelerde 100–400 mg/gün değişen dozlarda ZNS kullanmaktaydı.

Sonuç: Zonisamid, merkezimizde dirençli epilepsi hastalarının ekleme tedavisinde güvenli, tolere edilebilir ve etkin bir seçenek olmuştur.

Anahtar sözcükler: Antiepileptik ilaç; epilepsi; zonisamid.

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Introduction

Zonisamide (ZnS), 1,2-benzisoxazole-3-methanesulfonamide, which has a unique chemical structure, is one of the benzisoxazole-derivative ofnew generation antiepileptic drugs. This sulfonamide, which was discovered in the 1970s and found to have potent anticonvulsant activity. ıt has less drug interactions andits... and its mechanism of action is wide and diverse.[1–4] ZnS is thought to inhibit the spread of seizures by blocking voltage-gated sodium and T-type calcium channels.[4–6] It has been reported to inhibit secondary glutamate release by modulating GABA-mediated neuronal inhibition.[7] ZnS is also a weak inhibitor of carbonic anhydrase, which can alter dopamine, 5-HT and acetylcholine metabolism.[4,8] It is used orally and is almost completely absorbed independently from food intake, and its absolute bioavailability is known to be about 100%. It has a pharmacokinetic effect, depending on dose. ZnS binds to plasma proteins by 40–50%, metabolizes in the liver and is eliminated by the kidneys. Approximately 50% of the elimination is achieved by CYP3A4-mediated metabolism. Acetylation is responsible for 20% of the metabolism. Metabolites are deprived of anticonvulsant activity.[4,9,10]

ZnS was incidentallydiscovered in 1974 during the routine tests of 1,2-benzisoxazole derivatives synthesized for the treatment of psychiatric disorders. Japan approved its clinical use in 1989, South Korea in 1992, the US in 2000, and Europe in 2005.[4] Turkey approved the use of ZnS in 2008, as an adjunctive treatment for epilepsy patients with partial and generalized seizures. Approval was given for its use in monotherapy on February 20, 2013. common side effects are somnolence, dizziness, loss of appetite, nausea and vomiting, headache, weakness of concentration, fatigue, agitation, psychosis, and diplopia.[4]

This study aims to investigate the safety and efficacy of ZNS in refractory epilepsy patients who are followed in the epilepsy clinics of our center.

Materials and Methods

Forty-five refractory epilepsy patients, who were treated with ZnS in the Epilepsy Polyclinics of Health Sciences University Bakırköy Prof. Dr. Mazhar Osman Mental and Neurological Disorders Training and Research Hospital, were retrospectively evaluated between October 2015 and May 2017. Six patients, who were receiving ZNS treatment for less than six months, were excluded from this study given that the duration of the treatment could be insufficient. All of the patients who were receiving ZNS were under polytherapy. Age, sex, parental consanguinity, febrile convulsion history, age of seizure onset, seizure type, neurological examination findings, cranial magnetic resonance imaging (MRI) findings, electroencephalography (EEG) properties (normal, generalized and/or focal anomalies), the number of antiepileptic drugs used aside from ZNS, seizure frequency before and after the ZNS treatment, and side effects were recorded. This study was approved by the Local Ethics Committee of the Health Sciences University Bakırköy Prof. Dr. Mazhar Osman Mental and Neurological Disorders Training and Research Hospital.

Results

Of the 39 patients included in this study, 43.6% (n=17) were female and the mean age was 34.3±9.3 (19–56 years). Complex partial seizures (CPS) and generalisedtonic–clonic seizure (GTCS) were observed in 74.4% of the patients (n=29) whereas 10.3% (n=4) had GTCS alone, 7.7% (n=3) had CPS alone, 5.2% (n=2) had GTCS and myoclonia and 2.6% of them (n=1) had GTCS, absence, and myoclonia.

Of the patients, 20.5% (n=8) had a history of febrile convulsions, while parental consanguinity (the first-degree consanguinity was determined in four patients, second-degree consanguinity in one patient, and distant consanguinity in two patients) in 17.9% (n=7) of the patients. There was mental retardation in 33.3% (n=13) of the patients. The mean age of onset, when the first complaints started, was found to be 9.5±10.8 years (1–40 years).

In EEG, focal neuronal hyperexcitability findings were observed in 35.9% of the patients (n=14), generalised epileptiform anomalies were observed in 15.4% (n=6), generalized retardation was observed in 15.4% (n=6), generalized retardation and focal neuronal hyperexcitability findings were observed in 17.9% (n=7), focal retardation and focal neuronal hyperexcitability were observed in 7.7% (n=3) and multifocal neuronal hyperexcitability findings were observed in 7.7% (n=3).

Cranial MRI revealed that 35.9% (n=14) of the patients had normal findings, 25.6% (n=10) had unilateral mesial temporal sclerosis (MTS), 12.8% (n=5) had neonatal hypoxic ischemic findings, 7.7% (n=3) had postoperative encephalo-

Table 1. Clinical and demographic characteristics of the patients

	n	%
Gender		
Female	17	43.6
Male	22	56.4
Age (years), (Mean±SD)	34.3±9.3	–
Seizure types		
CPS and GTCS	29	74.4
GTCS	4	10.3
CPS	3	7.7
GTCS and myoclonia	2	5.2
GTCS, absence seizures and myoclonia	1	2.6
Febrile convulsion history		
Yes	8	20.5
No	31	79.5
Parental consanguinity		
Yes	7	17.9
No	32	82.1
Magnetic resonance imaging		
Normal	14	35.9
Unilateral MTS	10	25.6
Neonatal hypoxic ischemic findings	5	12.8
Postoperative Encephalomalacia	3	7.7
Cortical dysplasia	2	5.1
Arachnoid cyst	2	5.1
Leukodystrophy	1	2.6
Two-sided MTS	1	2.6
Ischemic stroke-related lesion	1	2.6
Electroencephalography		
Focal neuronal hyperexcitability	14	35.9
Generalized epileptiform discharge	6	15.4
Generalized retardation	6	15.4
Generalized retardation and focal neuronal hyperexcitability	7	17.9
Multifocal neuronal hyperexcitability	3	7.7
Focal retardation and focal neuronal hyperexcitability	3	7.7

CPS: Complex partial seizure; GTCS: Generic tonic–clonic seizures; MTS: Mesial temporal sclerosis; Mean: mean; SD: Standard deviation.

malacia, 5.1% (n=2) had arachnoid cyst, 5.1% (n=2) had cortical dysplasia, 2.6% (n=1) had leukodystrophy, 2.6% (n=1) had bilateral MTS and 2.6% (n=1) had ischemic stroke-related sequel lesion. Our patients were receiving valproic acid (VPA), carbamazepine (CBZ), levetiracetam (LEV), lamotrigine (LTG), oxcarbazepine (OXC), clonazepam (CLZ), lacosamide (LCM), phenobarbital (PB), topiramate (TPM), and vigabatrin (VGB) medications. The clinical and demographic characteristics of the 39 patients included in this study are summarized in Table 1.

Zonisamide was started as the second drug in 12.8% (n=5) of patients, the third in 61.5% (n=24), the fourth in 23.1% (n=9) and the fifth drug in 2.6% (n=1). Four of the patients, for whom ZNS was started as the second drug, were using CBZ and one was using VPA; 11 of the patients, for whom ZNS was started as the third drug, were receiving CBZ + LEV, three were using VPA + CBZ, three were using VPA + LEV, two were using VPA + LTG, one was using CBZ + LTG, one was using VPA + OXC, one was using VPA + CLZ, one was using CBZ + CLZ, and one was using LEV + LTG; two of the patients, for whom ZNS was started as the fourth drug, were receiving VPA + CBZ + LEV, one was receiving CBZ + LEV + LCM, one was receiving VPA + CBZ + VGB, one was receiving CBZ + LEV + LTG, one was receiving CBZ + LEV + PB, one was receiving CBZ + LEV + TPM, one was receiving CBZ + LCM + TPM, and one was receiving VPA + LCM + TPM; and the patient, for whom ZNS was started as the fifth drug, was using LTG + OXC + LCM + PB.

Drug side effects were defined in four of the 39 patients (10.2%). The treatment of three patients was discontinued due to side effects. Diplopia, drowsiness during the day, and psychosis were observed as side effects. Diplopia was observed in two patients. One of these patients was female, and the remaining patient was male. Their seizure types were CPS and GTCS, and drugs other than ZNS were VPA + CBZ + LEV and LTG + OXC + LCM + PB. The treatment of one of these two patients was terminated due to side effects. The other patient's ZnS treatment continued, as the duration of diplopia was short, and improvements were observed in seizure control. The treatment of one of our patients was discontinued due to excessive daytime drowsiness. This patient was male, the seizure type was CPS and GTCS, and the treatment was CBZ + LEV + PB. In another patient, ZnS treatment was discontinued due to psychotic findings despite complete seizure control. This patient was male, the seizure type was CPS and GTCS, and the treatment was CBZ + LEV.

Out of the patients whose treatment was discontinued due to the side effects, treatment of the four of the remaining

Table 2. Antiepileptic drugs used by the patients for whom ZnS treatment was initiated*

Antiepileptic drugs	n=39	n=20
CBZ	4	2
VPA	1	1
CBZ + LEV	11	8
VPA + LEV	3	3
VPA + CBZ	3	–
VPA + LTG	2	2
CBZ + LTG	1	1
VPA + OXC	1	1
VPA + CLZ	1	1
CBZ + CLZ	1	–
LEV + LTG	1	–
VPA + CBZ+LEV	2	–
CBZ + LEV + LCM	1	–
VPA + CBZ + VGB	1	–
CBZ + LEV + LTG	1	–
CBZ + LEV + PB	1	–
CBZ + LEV + TPM	1	–
CBZ + LCM + TPM	1	–
VPA + LCM + TPM	1	–
LTG + OXC + LCM + PB	1	1

*In the first column, the number of patients, for whose treatment ZnS was added, is given. In the second column, the number of patients continuing to ZnS treatment is given. ZnS: Zonisamide; CBZ: Carbamazepine; VPA: Valproic acid; LEV: Levatiracetam; LTG: Lamotrigine; OXC: Oxcarbazepine; CLZ: Clonazepam, LCM: Lacosamide; PB: Phenobarbital; TPM: Topiramate; VGB: Vigabatrin.

36 patients was discontinued due to the increase in seizure frequency and treatment of 12 patients was terminated because there was no change in seizure frequency. Of the patients whose seizure frequency was observed to be increased, one patient was female and three patients were male and their seizure types were CPS and GTCS. The drugs used by these patients were CBZ + LEV + LCM, VPA + CBZ + VGB, CBZ + LEV + LTG and CBZ. The seizure types of 12 patients with no change in seizure frequency were CPS + GTCS (n=8), CPS (n=2) and GTCS (n=2). Three of these patients were using VPA + CBZ, two were using CBZ + LEV while the others were using CBZ, CBZ + CLZ, LEV + LTG, VPA + CBZ + LEV, CBZ + LEV + TPM, CBZ + LCM + TPM and VPA + LCM + TPM.

There were 20 patients who benefited from the ZnS treatment. Decrease was observed in the seizure frequency by 25%, 50% and 75% in one patient (2.7%), five patients (13.8%), and seven patients (19.4%), respectively and three patients (8.3%) were seizure free. Although the number of seizures in four patients (11.1%) did not change, the seizure duration was shortened. Consequently, these patients continued their treatment. In 51.3% of the refractory epilepsy patients, who received ZnS additional treatment for at least six months, seizure frequency was decreased by 25–100% or seizure duration was shortened. The rate of seizure freepatients was 8.3%. The ages of these three patients were 24, 27 and 28 years. The seizure types of the patients with ongoing ZnS treatment were CPS + GTCS in 14 patients, GTCS in two patients, GTCS + myoclonia in two patients, CPS in one patient and GTCS absence + myoclonia in one patient. The seizure types of two of the three patients with complete seizure-free were CPS + GTCS, and the seizure type of the remaining one patient was GTCS. The most commonly used combination was + CBZ + LEV in 20 patients who continued on ZnS treatment (n=8). The medications used by the patients with complete seizure resolution were ZNS + VPA + CBZ, ZnS + LEV + LTG, and ZnS + VPA + LEV. This combination was used in 11 of all the patients, and eight patients (72.8%) had noside effects. Of the 29 patients, for whose treatment ZnS was added as the second and third drug, 19 (65.5%) were on treatment, while only one (10%) of the 10 patients, for whose treatment ZnS was added as the fourth and fifth drugs, were observed to continue the treatment. The twenty patients who responded to treatment were using ZnS for an average of 41.5±24.3 (7–80) months, at a mean dose of 270±92.3 (100–400) mg/day. In Table 2, the antiepileptic drugs used by the patients, for whose treatment ZnS was added and who continue the treatment, are given.

Discussion

Epilepsy, a disease that has a considerable effect on the quality of life of. Itrequires long-term follow-up and the treatment is very difficult. The main goal of treatment management is to provide seizure control while preventing the side effects of the drugs.[11] newly diagnosed patients are generally respond well to initial antiepileptic treatment. However, about one-third of patients are resistant to treatment.[5] In 2010, refractory epilepsy was described by ILAE as the failure to achieve seizure control and sustained seizure freedom despite receiving at least two antiepileptic drugs, which are appropriately chosen according to seizure type and tolerated in the required time and dose, as monotherapy or polytherapy.[12] For patients with refractory epilepsies, as well as seizure control, drug side effects are

another problem. This situation further complicates compliance to the treatment.[13] The efficacy and safety of ZnS have been widely proven in controlled clinical trials. It is also reported that ZNS has a low drug-drug interaction potential with other antiepileptics, and it has been proposed as a treatment option for the seizure control.[4,14,15]

Our study revealed that seizure frequency was observed to be decreased by 25–100%, or seizure duration was shortened in 51.3% of the refractory epilepsy patients who are using, taking de olabilirZnS additional treatment for at least six months. seizure free patients rate waswas found to be 8.3%. In the literature, the rate of patients whose seizure frequency decreased after ZnS is between 40.9% and 79.7% (defined as the rateof patients with seizure frequency decreased by ≥50% compared to baseline), whereas the rate of patients who achieve seizure freeis between 15% and 43.6%.[16–19] In a study by Dash et al.,[20] in which ZnS was used as monotherapy or alternative monotherapy in 20.92% of patients and as additional therapy in 59.85% of patients, the response rate was reported to be 78.6% and about 41.22% of the patients were seizure-free after 24-week ZNS treatment. In a study by Lee et al.[21] including 1744 patients who received ZnS treatment, 755 patients (43.29%) were reported to be seizure-free and a significant reduction was reported in the seizure frequency of 322 patients (18.41%). In our patients, ZnS was initiated as the additional treatment for refractory epilepsy patients and as the third antiepileptic drug in the majority of cases. There was no patient for whom ZnS was started as monotherapy.

Zonisamide treatment was discontinued in a few cases due to side effects. Two patients had diplopia, one patient had excessive drowsiness, and one hadpsychosis. The side effects reported in the literature include loss of appetite, weight loss, fatigue, drowsiness, dizziness, headache, aggressive behaviors, psychosis, sleep disturbance, rash and diplopia.[18,18,20] Side effects were seen in 10.2% of our patients. Dash et al. reported 17.4% of the patients using ZnS have side effects. The seizure types of the patients who developed side effects were CPS and GTCS. The patient, whose treatment was discontinued due to excessive drowsiness, was using CBZ + LEV + PB combination. Phenobarbital is known to have a side effect of excessive drowsiness. As there was only one patient who had this situation in our study, it is difficult to comment. However, ZnS may cause hypersomnia when used with PB. Psychotic findings occurred as a result of the addition of ZnS to the CBZ + LEV combination but this combination was the most commonly used combination in our study and 72.8% of the patients benefited from the treatment, and no side effects were observed. The age of the three patients for whom eizure free wereounger than the mean age. In these patients, ZnS was added as the third drug. Taking the whole study into consideration, 65.5% of the patients, for whom treatment ZnS was added as the second and third drug, were observed to continue the treatment, while 10% of the patients, for whom treatment ZnS was added as the fourth and fifth drugs, were observed to continue the treatment. When an examination was performed of the patients with side effects, ZnS was observed to be started as the third, fourth and fifth drug in one patient, two patients, and one patient, respectively. Here, the increase in the number of medications received also reflects the resistance of the patient's seizure. Thus, the rate of response to the treatment decreases at this time.

Zonisamide is a weak inhibitor of carbonic anhydrase. Carbonic anhydrase inhibition is 100–200 times weaker than acetazolamide.[22] However, this mechanism is not thought to contribute to the antiepileptic effects of ZnS. Carbonic anhydrase inhibitors increase the risk of nefrolithiasis. Although ZnS-related kidney stones have been reported in the literature, kidney stones have not been found in some placebo-controlled studies carried out in the USA and Europe.[15,23] On the other hand, only two patients were observed to have ZnS-related kidney stones in 1,008 disease phase II and III trials carried out in Japan, and both of these patients were reported to have a history of nephrolithiasis in their families.[24] Kidney stones are thought to be associated with high doses and long-term treatment.[25] In a study carried out in the USA (mean ZnS dose was 500 mg/day), kidney stones were reported in four of 113 patients, after 96-week treatment.[26] It may not be necessary to discontinue treatment for patients with asymptomatic kidney stones. In a study by Richards et al.,[27] ZnS treatment was continued in three patients who developed kidney stones, and the patients remained asymptomatic in the follow-up regarding kidney stones. In our study, no kidney stones were observed in our patients.

In conclusion, our study revealed that ZnS is a safe, tolerable, and effective alternative drug in the additional treatment of refractory epilepsy patients with partial and generalised seizures at our center.

Ethics Committee Approval

Local ethics committee approval was obtained.

Peer-review

Externally peer-reviewed.

Conflict of interest

The authors declare that they have no conflict of interest.

Authorship Contributions

Concept: D.A.; Design: S.A.B.; Data collection &/or processing: H.S., B.T.G; Analysis and/or interpretation: H.S.; Literature search: S.Ş., S.A.; Writing: S.Ş.

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