Effectiveness of zonisamide in childhood refractory epilepsy

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INTRODUCTION

About 0.5%–0.8% of children have epilepsy, which is the most common cause of paediatric neurology clinic referral [1]. Approximately 80,000 new cases of epilepsy occur every year in children. Fortunately, many epileptic children will recover spontaneously and gradually, but severe complications develop in those with refractory seizures. Several studies have shown that about 10%–30% of people with epilepsy experience continuous seizure attacks, known as intractable epilepsy, despite adequate anticonvulsant medications. Refractory epilepsy is characterized by a lack of seizure control regardless of the use of three or four of the best frst-line drugs (taken in an adequate dose and for an adequate duration) [2–4]. Zonisamide (ZNS) is a newgeneration antiepileptic drug (AED) that has been used in refractory epilepsy for 20 years. First reported on in Japan in 1989, this synthetically produced drug has been used to treat epilepsy in children and adults [5]. A license for its use was taken for focal epilepsy in children older than 6 in Europe and in children older than 16 in the USA. In those over 16 years of age, ZNS has been approved for poly-therapy in refractory epilepsy and as a mono-therapy in focal epilepsy, while in those over 6 years of age, it has been approved for poly-therapy in focal and refractory epilepsy [6, 7]. ZNS is one of the benzisoxazole derivative new-generation AEDs. In animal models, it has been shown to have multiple effect mechanisms over neurotransmitters, such as voltagedependent Na channels, T type Ca channels, GABA and glutamate [8, 9]. The pharmacokinetics of ZNS is dose-dependent. After it is taken orally, its level peaks in the blood in 2–4, h and its half-life is 60 h. It is generally metabolized by the cytochrome p-450 system and is usually discharged in the urine [10, 11]. The efciency of ZNS has been shown in various seizure types and epileptic syndromes [12, 13]. It has been reported to be effective in epileptic syndromes such as infantile spasm, Lennox-Gastaut, Doose syndrome, and early infantile epileptic syndromes [14–16]. The present study examined the efciency and reliability of ZNS in focal or generalized refractory seizures in paediatric patients whose seizures continued despite multiple AED therapy.

	RGE Group	RFE Group	Total
Age range (average) (years)	1.5–17.5 (9.38 ± 4.46)	4–17 (11.34 ± 4.20)	1.5–17.5 (10.01 ± 4.40)
Gender n (%)			
Male	26 (56.5)	12 (54.5)	38 (55.9)
Female	20 (43.5)	10 (45.5)	30 (44.1)
Epilepsy Type n (%)			
Idiopathic	7 (58.3)	5 (41.7)	12 (17.65)
Structural	16 (72.73)	6 (27.27)	22 (32.36)
Genetic	6 (75)	2 (25)	8 (11.77)
Infectious	3 (75)	1 (25)	4 (5.88)
Metabolic	9 (64.29)	5 (35.71)	14 (20.59)
Epilepsy with unknown etiology	5 (62.5)	3 (37.5)	8 (11.76)
How many years of follow-up with epilepsy (average) (years)	1.5–16 (7.38 ± 3.87)	2.5–13 (6.88 ± 3.21)	1.5–16 (7.22 ± 3.66)
How many AEDs before ZNS (average)	2–4 (2.80 ± 0.58)	1–4 (2.45 ± 0.67)	1–4 (2.69 ± 0.62)
How many AEDs after ZNS (average)	2–5 (3.36 ± 0.64)	2–4 (2.90 ± 0.61)	2–5 (3.22 ± 0.66)
ZNS use in months (average) (months)	3–30 (9.76 ± 6.61)	3–30 (12.36 ± 7.28)	2–30 (10.60 ± 6.89)
ZNS dose (average) (mg/kg/day)	4–12 (7.03 ± 1.81)	4–11 (6.84 ± 2.05)	4–12 (6.97 ± 1.88)

MATERİALS AND METHODS

Sixty-eight refractory epilepsy patients who were 6 years of age or older and who had been followed up in a paediatric neurology centre, which is a referral centre for our region, between the years 2013 and 2019, were included in this retrospective study. The patient genders, ages, seizure types, underlying diseases, pre-treatments and post-treatment electroencephalography (EEG) fndings, treatment responses, ZNS usage durations and dosages, and any side efects that developed as a result of the ZNS therapy were assessed. The EEG fndings were classifed as generalized epileptic abnormality, focal epileptic abnormality or normal. Routine EEG evaluations were performed with electrodes placed according to the international 10–20 system. The patient responses to the treatment and EEG controls were assessed 3 months later at the earliest. The patients were followed up for 6–30 months. The pre-ZNS fnal states and post-ZNS fnal states were assessed. Seizure frequencies were determined according to seizure diaries of the patients. The responses of the patients to the treatment were determined according to an anamnesis and seizure diary that was collected from the family. The patient seizure types were classifed according to the ILAE 2017 epilepsy classifcation based on the anamnesis given by the families. The patients were grouped into two groups, namely refractory generalized epilepsy (RGE) or refractory focal epilepsy (RFE). The patients were divided into 4 groups according to their treatment responses, namely, termination of seizures,>50% reduction in seizures,

RESULTS

A total of 68 refractory epilepsy patients were included in the study. The patients were grouped in two groups, namely the AED RGE and RFE groups. There were 46 (67.65%) patients in the RGE group, while there were 22 (32.35%) patients in the RFE group (Table 1). The patient pre-ZNS antiepileptic usage time was 7.22±3.66 years on average. All of the patients were those who had used various AED therapies and whose seizures had continued, despite the use of multiple AED therapies before ZNS. Before ZNS, an average of 2.80±0.58 AEDs were used in the RGE group, while an average of 2.45±0.67 AEDs were used in the RFE group. ZNS was added to the protocol as an add-on therapy. Following ZNS therapy, the patients were followed up for 3–30 months (10.6±6.89 months). The average ZNS dose was 6.97±1.88 mg/kg/day (Table 1). Twelve (17.65%) of the patients were followed up for idiopathic epilepsy, 8 (11.76%) were followed-up for epilepsy with unknown aetiology. Twenty-two (32.36%) patients were followed up for structural abnormality, 8 patients (11.77%) were followed up for genetic disease (6 patients had tuberous sclerosis, 2 patients had Dravet syndrome), 4 patients (5.88%) were followed up for infectious sequel, 14 patients (20.59%) were followed up for metabolic group. The frequency of RGE was high in all the three groups (Table 1). In the structural abnormality group, 59.1% of the patients had cerebral palsy, while 27.27% had central nervous system developmental abnormalities, and 13.64% were trauma-tumour sequel. In the epilepsy with unknown aetiology group, 8 (36.37%) were being followed up for neuromotor-retarded development, but they had not yet received their primary disease diagnosis. All of these patients had received cranial MRI, and 32.4% were found to be normal. Of the remaining patients, sequel changes were found in the cranial MRI of 29.4%, and changes suggesting neurometabolic diseases were found in 20.6% (Table 2). Before ZNS therapy, on the EEGs of the patients who were diagnosed with RGE with clinical seizure semiologies, 60.9% were found to have generalized epileptic anomalies, while 8.7% were found to have normal EEGs. In those patients followed up for RFE, 95.5% were found to have focal epileptic anomalies. In control EEGs during ZNS therapy, there were normal fndings of 21.7% and 22.7% in the RGE and RFE groups, respectively (Table 3). During ZNS therapy, a more than 50% reduction in seizures was defned as a response to treatment. Seizure termination was defned as a full response. Of the 68 patients, 45 (66.2%) had a more than 50% reduction in seizures and 9 (13.2%) had seizure termination. However, 14 (20.6%) of the patients did not show any efects from ZNS therapy. When the sub-groups were assessed, a>50% reduction in seizures was found at a rate of 56.5% in the RGE group and at a rate of 86.4% in the RFE group, while termination of seizures was found at a rate of 15.2% in the RGE group and at a rate of 9.1% in the RFE group. Five of the 6 patients followed up for TSC were in the RFE group, while 1 was in the RGE group. Following ZNS use, seizures terminated in 3 (50%) of these patients, while a reduction in seizures was seen in 2 (33.3%), and no reduction was found in 1 (16.6%). During the follow-up, side efects were found in 4 (5.9%) patients; 2 of these patients were in the RGE group, while the other 2 were in the RFE group. The side efects were becoming matt in 1 patient, severe headache in 1 patient, loss of appetite in 1 patient and tooth decay in 1 patient.

	RGE Group n (%)	RFE Group n (%)	Total n (%)	p-value
Pre-ZNS EEG				
Generalized EA	28 (60.9)	1 (4.5)	29 (42.6)	
Focal EA	14 (30.4)	21 (95.5)	35 (51.5)	
Normal	4 (8.7)	-	4 (5.9)	
Post-ZNS EEG				
Generalized EA	22 (47.8)	1 (4.5)	23 (33.8)	
Focal EA	14 (30.4)	16 (72.7)	30 (44.1)	
Normal	10 (21.7)	5 (22.7)	22 (22.1)	
Seizure reduction				
Yes (≥%50 reduction)	26 (56.5)	19 (86.4)	45 (66.2)	
No (<%50 reduction/no reduction)	13 (28.3)	1 (4.5)	14 (20.6)	0.034
Total response (No seizure)	7 (15.2)	2 (9.1)	9 (13.2)	
ZNS: Zonisamide, EEG: Electroencephalography, EA: Epileptic anomaly				

MRI findings	RGE Group n (%)	RFE Group n (%)	Total n (%)
Normal	14 (30.5)	8 (36.4)	22 (32.4)
Sequel changes	10 (21.7)	10 (45.5)	20 (29.4)
Metabolic findings	14 (30.4)	-	14 (20.6)
Tubers	5 (10.9)	1 (4.5)	6 (8.8)
SSS developmental anomaly	3 (6.5)	3 (13.6)	6 (8.8)

	Idiopathic Epilepsy n (%)	Symptomatic Epilepsy n (%)	Epilepsy with unknown etiology n (%)	p-value
Pre-ZNS EEG				
Generalized EA	4 (33.3)	18 (37.5)	4 (50.6)	
Focal EA	7 (58.3)	27 (56.25)	3 (37.5)	
Normal	1 (8.3)	3 (6.25)	1 (12.5)	
Post-ZNS EEG				
Generalized EA	2 (16.7)	13 (27.08)	3 (37.5)	
Focal EA	4 (33.3)	29 (60.42)	3 (37.5)	
Normal	6 (50)	6 (12.5)	2 (25)	
Seizure reduction				
Yes (≥%50 reduction)	6 (50)	33 (68.75)	5 (62.5)	
No (<%50 reduction/no reduction)	4 (33.3)	7 (14.58)	2 (25)	0.51
Total response (No seizure)	2 (16.7)	8 (16.67)	1 (12.5)	2
ZNS: Zonisamide, EEG: Electroencephalography, EA: Epileptic anomaly				

ZNS is an efective new-generation AED for both focal and refractory epilepsy, but especially in focal epilepsies. In addition, although the number of cases is small, it is an alternative drug that can be used in refractory seizures in patients with TSC. ZNS is a molecule that can be safely used in the treatment of seizures resistant to multiple AEDs in children.

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