



Seizure response and adverse effects of Zonisamide in primary generalized epilepsy- a six month open label study

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Abstract

Context: Valproate is not favored in women in the childbearing age with primary generalized epilepsy (PGE) due to adverse reaction and teratogenicity. Levetiracetam which is an alternative is not as effective. We have limited literature on Zonisamide (ZNS) in PGE.

Aims: To look at seizure control and tolerability of ZNS in PGE.

Settings and Design: We did a prospective observational study in patients 13 years and above with PGE, in females who have not completed their family, and males not controlled or intolerant to valproate attending the outpatient department.

Methods and Material: We excluded patients with psychogenic nonepileptic seizures, renal failure, renal stone, allergy to sulphonamides, pregnant and lactating mothers. They were followed up for a period of 6 months using Engel score for seizure frequency, Liverpool Adverse Event Profile and Naranjo's algorithm. A responder was a patient with 50% reduction in seizure frequency. Patients were seizure-free if they had no seizures on completion of the evaluation period.

Statistical analysis used: Descriptive statistics was applied.

Results: The dose of ZNS ranged from 50 to 300 mg (mean-161.6; SD- 58.3). At six months, ZNS was used as monotherapy in 80 % and as an adjuvant in 6 patients (20%). Majority (93%) attained >50% reduction in seizure frequency. More than 50% seizure frequency reduction was seen with GTCS (84.6%), myoclonus (100%) and absence (100%). Twenty patients (67%) developed adverse reactions, which included tiredness (66%), difficulty in concentration (33%) and headache (20%).

Conclusions: Zonisamide is an alternative to valproate and levetiracetam in PGE especially in women in the child bearing age group and in men who do not respond to valproate or are intolerant of valproate and levetiracetam

Keywords: Therapy, outcome assessment, adverse drug reaction, anticonvulsant, Zonisamide, Primary generalised epilepsy.

Introduction

Primary generalized epilepsy (PGE) are a group of epileptic syndromes with combinations of generalized seizure types, with normal background activity and generalized epileptiform discharges on EEG^[1]. There is weak evidence base to guide the treatment of PGE. Very few studies have been published on monotherapy for effective control of GTCS in adults and children^[2]. Carbamazepine and phenytoin may control GTCS in some patients with PGE. They are ineffective and may exacerbate other seizure types in PGE such as myoclonic and absence seizures^{[3][4]}. Broad spectrum antiepileptic drug (AED)s are effective in controlling primary generalized epilepsy. Among them, valproate is found to more effective than lamotrigine and topiramate in IGE^[5]. Valproic acid is generally recommended as the drug of the first choice, based on lower level of evidence^{[3][6]}. Valproate has adverse effects like weight gain, obesity, insulin resistance syndrome, hair loss, polycystic ovarian disorder^[7]. Valproate has a high potential for teratogenicity including major congenital anomalies like spinal tube defect^[8] and causes cognitive dysfunction in children of mothers taking valproate during pregnancy^{[9][10]}. Levetiracetam is an alternative for valproate in primary generalized epilepsy, especially in women. Often levetiracetam is not as effective as valproate. We need an alternative to valproate and levetiracetam.

Zonisamide (ZNS) is a novel antiepileptic drug (AED) which is a sulfonamide derivative. It has multiple mechanisms of action, including an effect on voltage-dependent T-type Ca²⁺ channels. Zonisamide can be an effective alternative because of its efficacy against all three PGE seizure types and the lack of endocrine and metabolic side effects frequently reported with valproate. Japanese studies had shown that ZNS is efficacious in PGE^[11]. A retrospective study showed >50% reduction in seizure frequency with Zonisamide in JME^[12]. A case study showed complete resolution of generalized spike and wave discharges on electroencephalogram^[13]. These data suggest the possible use of zonisamide in PGE. Due to lack of

literature from India and paucity of data world over we decided to look at seizure control profile and tolerability of zonisamide in PGE.

Subjects and Methods

We did a prospective observational study in the outpatient Department of Neurology, Government Medical College, Thiruvananthapuram, Kerala, India during the period of June 2011- June 2012. We included all female patients with PGE who have not completed their family, and all male patients with PGE not controlled or intolerant to valproate. We included drug naïve patients as well as patients on medications like valproate or carbamazepine. We excluded patients with psychogenic nonepileptic seizures, renal failure, renal stone, allergy to sulphonamides, pregnant and lactating mothers. We estimated the sample size from 80% seizure control reported earlier^[12].

Institutional ethics committee approval was obtained prior to the study. Confidentiality and anonymity of patient's details were maintained during and after the study. Consecutive patients were initiated on Zonisamide after obtaining written informed consent from patients or their guardians if the subject were less than 18 years of age. Baseline data included the seizure type, the age of onset of epilepsy, family history of epilepsy and sociodemographic data. A 6-month historical baseline seizure count was obtained. Zonisamide was started at an initial low dose of 50 mg once daily and the dose was titrated per the seizure control, up to a maximum of 300 mg once daily. They were followed up monthly for a period of six months. We tried to taper off valproate and carbamazepine during the initial six weeks. Patients or caregivers maintained seizure diary. The frequency of seizures, adverse drug reactions or intolerability to the drug were recorded with a monthly follow-up for a period of six months. Seizure burden was scored using Engel system that scores seizure frequency and disability on a quasi-logarithmic scale ranging from 0 to 12^[14]. Adverse effects were noted with the help of Liverpool Adverse Event Profile (LAEP)^{[15][16][17]}. Their

severity and relationship to study medication were recorded using Naranjo's algorithm^[18]. Neurologic, physical examinations including body weight and vital signs were recorded on follow-up.

The primary endpoint was the percentage reduction in seizure days per month (all seizures) from baseline period. We took 50% reduction in seizures from the baseline as responder rate. We considered patients to be seizure-free if they had no seizures on completion of the evaluation period. Patients who discontinued prematurely while being seizure-free were considered as non-seizure-free. Descriptive statistics was used for data analysis.

Results

We recruited 30 patients with PGE attending the Neurology outpatient department of Government Medical College, Thiruvananthapuram. The age ranged from 13 to 28 years (mean 16 years). The majority of the patients were females (73%). Most of them (53.3%) belonged to below poverty line as per Government records. Students constituted 67% followed by housewives 20% and manual laborers 13%. Only 26% of patients were married. The minimum age of onset of seizures observed in the study was 4 years and the maximum was 20 years. The majority of the patients had their seizure onset in the age interval 10-15 years.

We had patients with a combination of myoclonus and GTCS (66%), followed by GTCS alone (13%) followed by GTCS and absence, absence alone and a combination of absence, GTCS and myoclonus in 7% each. The most common PGE syndrome was Juvenile Myoclonic Epilepsy (60%) followed by Juvenile Absence Seizures (13%). The family history of epilepsy was seen in 20% of the patients. At baseline, 60% were on monotherapy with valproic acid, 27% on dual medication, 7% on triple medication and another 7% on four AEDs. Electroencephalogram (EEG) showed bilateral

generalized frontally dominant epileptiform anomalies in 10 patients. Activation during hyperventilation (HV) was seen in 2 patients, intermittent photic stimulation (IPS) in 2 patients and both HV and IPS evoked activity in 4 patients. Six patients showed bursts of 3 Hz generalized spike-wave complexes. EEG was normal in 14 patients.

The dose of ZNS ranged from 50 to 300 mg (mean-161.6; SD- 58.3). The starting dose of ZNS was 50 mg and one patient (3.33%) was seizure free with this dose. The majority (36.67%) responded to a dose of 200 mg. The maximum dose given was 300 mg (6.67 %).

At the end of six months, ZNS was used as monotherapy in 80 % of subjects and as an adjuvant in 6 patients (20%). After administering zonisamide, 93% of patients attained >50% and 73% attained > 75% seizure control.

Since patients with primary generalized epilepsy usually present with multiple seizure types, seizure control profile for each type of epilepsy was analyzed separately. Of the patients with GTCS, 53.84% had >75% reduction in seizure frequency. (Table 1) Only 15.4% of patients had <50% seizure reduction. All patients with myoclonic seizures attained >50% seizure control and 80 % of patients had >75% seizure control. All the 6 patients who presented with absence seizures had 100% seizure reduction.

Half of the patients (46%) lost 2 kg body weight but was not statistical significance. Twenty patients (67%) developed adverse reactions to Zonisamide. LAEP scores ranged from 20 to 67. Most common adverse effects reported included tiredness (66%), difficulty in concentration (33%) and headache (20%).(Table 2)

Table 1: Reduction of individual seizure types

Percentage Seizure reduction	25-50%*	50-75%*	75-100%*
GTCS(Nos. 26)	4(15.4%)	8(30.8%)	14(53.84%)
Myoclonic(Nos. 20)	0	4(20%)	16(80%)
Absence(Nos. 6)	0	0	6(100%)

Table: 2 Naranjo's score of the reported ADRs

ADRs	Possible*	Probable*	Definite*	Total*
Tiredness	5	15	-	20
Concentration	10	-	-	10
Sleepiness	2	8	-	10
Headache	2	4	-	6
Nervousness	2	-	-	2
Stomach upset	-	2	-	2
Dizziness	-	2	-	2
Memory problems	-	1	-	1
Total	21	32		53

Discussion

We found zonisamide to be effective in PGE with no life-threatening ADRs. The majority (60%) of our patients had JME. The majority of our patients had GTCS with myoclonus since we were treating only patients 13 years or more. Another study which included pediatric patients had GTCS with absence in 48%, GTCS with myoclonus in 31%, and absence alone in 20%^[19]. Age of onset of seizure was lower since we had 6 patients with Juvenile absence than in series having JME^[20]. Family history was present in our patients too^[21].

With slow titration we could convert 80% patient to zonisamide monotherapy with 93% of patients attained >50%. The similar good response has been reported^[12]. At six months 84.6% of patients with GTCS, and 100% of patients with myoclonic seizure had >50% seizure control. Cent percent of absence seizure had >75% seizure control. Good control of GTCS, Myoclonic and absence seizures in PGE have been reported earlier^[12]. Seizure freedom was seen in absence seizure in half of the treated patients^[22]. The adverse drug reaction in the current study was similar to the previous experience^[12]. There was no change in body weight in our experience, however, weight loss has been reported earlier^[12]. It does not cause polycystic ovarian disease. Thus it is an alternate medication to be tried in PGE especially in women. In previous studies, zonisamide was given more often to women due to the favorable safety profile^[12]. We had more women since the present study focused on women who have not yet completed their family.

One of the major limitations of the study was the small number of patients and the restricted period of monitoring of adverse drug reactions. The short

period also caused an increase in ADR as tolerance develops to many of them over time. We need to look at the long-term seizure control and adverse effects of zonisamide. Another important limitation of this study is that it has been an observational study. For better assessment of the efficacy of ZNS, controlled large double-blind clinical trials would be desirable. Safety of zonisamide in pregnancy has to be explored. Its role in valproate resistant PGE has to be looked at.

Conclusion

ZNS is found to achieve seizure control in PGE and is effective in all the three types of seizures. It was found that ZNS is an effective alternative to valproate in young adolescent females and in women who have not completed their family.

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