Vigabatrin in pediatric patients with refractory epilepsy

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New generation antiepileptic medications have improved seizure outcome in patients with intractable epilepsy. We studied the efficacy and side effect profile of vigabatrin (VGB) in pediatric patients with intractable seizure disorder.

We reviewed the database of our short-term video-EEG monitoring laboratory to screen patients with intractable epilepsy who were on VGB either alone or in combination for three months or more. We subsequently reviewed the medical records of these patients to abstract clinical information regarding age, sex, seizure type, epilepsy syndrome, efficacy and side effects of VGB.

Of 111 patients, 75 (68%) were male and 36 (32%) female. Seizure onset was during the newborn period in 12 patients (11%), during the first year of life beyond the newborn period in 47 patients (42%), between 1-5 years in 23 patients (21%), and above five years in the remaining 29 patients (26%). Fifty-four patients (48.6%) had partial onset seizures with or without secondary generalization; 49 patients (44.1%) had primary generalized seizures; 8 patients (7.2%) had two or more types of seizure. Fifty-three percent of patients had mental retardation, and 35% had abnormal findings on physical/ neurological examination. Of 98 patients, 70 (71.4%) had abnormal magnetic resonance imaging (MRI) findings. Ninety-seven percent of patients had been on polytherapy before VGB was added to treatment. VGB reduced seizure frequency by at least 50% in 33.3% of patients with partial seizures, and in 30.6% of patients with primary generalized seizures. Six of the responders with partial seizures had complete resolution of their seizures. Most common side effects included visual field defects, increased appetite and obesity.

Vigabatrin seems to be more effective in partial seizures in childhood intractable epilepsy. Patients should be closely monitored regarding side effects of VGB.

Key words: vigabatrin, intractable epilepsy, efficacy, side effect.

New generation antiepileptic medications have improved seizure outcome in patients with intractable epilepsy[1,2]. Vigabatrin (VGB) acts by inhibiting the enzyme γ-aminobutyric acid (GABA) transaminase which catalyzes the inactivation of GABA irreversibly and leads to an increase in the levels of the inhibitory neurotransmitter GABA in presynaptic terminals within the central nervous system[3,4]. VGB is found to be an effective anti-epileptic drug in the treatment of refractory infantile spasms and partial seizures[1,2]. VGB is generally well tolerated; the most common adverse effects are headaches and drowsiness, which are usually self-limiting, and weight gain. The other side effects include anxiety, emotional lability, behavioral disturbances including psychosis, irritability, tremor, abnormal gait, speech disorder, increased appetite, dyspepsia and visual field constriction[2,5]. We studied the efficacy and side effect profile of VGB in pediatric patients with intractable seizure disorder.

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Material and Methods

We reviewed the database of our video-electroencephalography (EEG) laboratory between 1994-2002 and found 111 patients with refractory epilepsy who had been on VGB either alone or in combination with other antiepileptic drugs (AED) for three months or more. We reviewed the medical records of these patients retrospectively. For missing information, parents were interviewed by telephone. We abstracted age, gender, age of seizure onset, seizure type, etiology, intelligence scores, neurologic deficits, family history for epilepsy and other neurological disorders, parental consanguinity, period of the treatment with VGB alone or in combination with other AED, dosage of VGB received, side effects, seizure outcome on VGB, magnetic resonance imaging (MRI) of the head, and EEG characteristics of the patients. Seizures were classified according to the International Classification of Seizures[6] based on review of videotaped attacks, or clinical descriptions by parents. Clinical response to the treatment was evaluated by comparison of mean seizure frequency in the three months preceding and following VGB treatment initiation, respectively. The medication was considered as "effective" when all seizures had ceased, as "partially effective" when seizure frequency was decreased by >50%, as "not effective" when seizure frequency was decreased by <50%, unchanged or worse.

Results

Patient Characteristics

Of 111 patients, 75 (68%) were male and 36 (32%) female. The mean age of the patients at the time of video-EEG monitoring was 10.05±5.53 years (range 6.5 months-19 years, median: 11 years). The mean age of seizure onset was 2.89±3.68 years (range: newborn period-16 years, median: 1 year). Age at seizure onset was during newborn period in 12 patients (11%), during the first year of life beyond the newborn period in 47 patients (42%), between 1-5 years old in 23 patients (21%), and above five years of age in the remaining 29 patients (26%) (Fig. 1).

In 27% (n: 30) of the patients, parents were relatives. Thirty-three (29.7%) patients had positive family history for epilepsy and/or

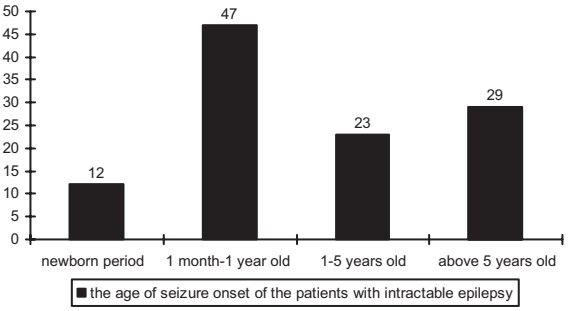

Fig. 1. Graph showing age at onset of seizures.

mental retardation. The most common cause was hypoxic and/or infectious insults during perinatal period, seen in 27 patients. Other etiologic factors included malformations of central nervous system, intracranial mass lesion (hamartoma/tumor), meningitis, encephalitis, head trauma, inborn metabolic disorders, chromosomal abnormalities, and acute myeloid leukemia (Table I). Fifty-nine (53%) patients had mental retardation, and 35% (n: 39) had abnormal findings on physical/neurological examination such as abnormal tone, hemiparesis, quadriparesis, microcephaly, dysmorphic facial features, and autistic features with or without dysmorphic features. Of 98 patients, 70 (71.4%) had abnormal MRI findings (Table II).

Seizure Types and Epilepsy Syndromes

Fifty-four patients (48.6%) had partial onset seizures with or without secondary generalization; 49 patients (44.1%) had primary generalized seizures; and 8 patients (7.2%) had two or more types of seizure (Fig. 2). Of 98 patients with MRI, 13.3% (n: 13) of patients had idiopathic epilepsy, 15.3% (n: 15) had cryptogenic epilepsy, and 71.4% (n: 70) had symptomatic epilepsy (Table I). There were six patients with infantile spasms developed secondary to cerebral dysgenesis in four patients, hypoxic damage in perinatal period in one patient, and sequelae of meningitis and encephalitis in one patient. There were three patients with tuberosclerosis.

AED Treatment and Efficacy

Ninety-seven percent (n: 108) of patients had been on polytherapy before VGB was added to treatment. Only three patients (2.7%) were maintained on VGB monotherapy, and one of these showed improved seizure control.

Table I. Seizure Etiology of the Patients

Idiopathic	13 (13.3%)
Cryptogenic	15 (15.3%)
Symptomatic	70 (71.4%)
a-Hypoxic/infectious insults during perinatal period	27 (24.3%)
b-CNS malformation	9 (8.1%)
c-Intracranial mass (hamartoma/tumor)	9 (8.1%)
d-Meningitis-encephalitis	7 (6.3%)
e-Head trauma	4 (3.6%)
f-Chromosomal abnormality	2 (1.8%)
g-Inborn metabolic disorders	2 (1.8%)
h-Extracranial malignancy	2 (1.8%)
i-Intrauterine infection	2 (1.8%)
j-Intracranial malignancy	2 (1.8%)
k-Others (febrile convulsion, vaccine related, etc.)	25 (25.5%)

CNS: Central nervous system.

Table II: Cranial MRI Findings of the Patients Classified According to Response to Vigabatrin Treatment

Cranial MRI findings	Total (n=98)	No. of patients responsive to VGB (n=31)	No. of patients unresponsive to VGB (n=67)
1-Normal	28	8	20
2-Mesial temporal sclerosis	15	3	12
3-Atrophy	14	4	10
4-Cortical dysplasia	9	5	4
5-Intracranial mass	9	1	8
6-Findings related with hypoxic ischemia	8	3	5
4-Infarct	6	3	3
8-Hydrocephalus	6	4	2
9-Sequelae of meningitis-encephalitis	2	0	2
10-White matter lesions	1	0	1

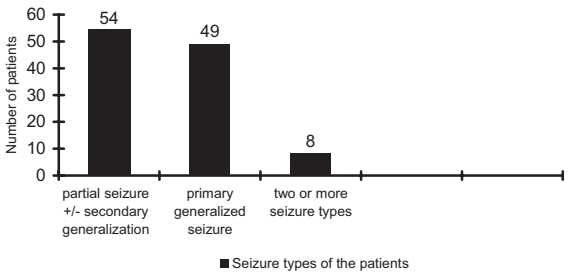

Fig. 2. Distribution of seizure types among patients with childhood-onset intractable epilepsy.

The mean age at the introduction of VGB was 8.34±4.92 years (range: 3 months-18.5 years, median: 9 years). The mean duration of epilepsy in patients was 5.23±4.35 years (3 months-14 years, median: 4 years). The mean duration of the treatment with VGB alone or in combination with other AED was 23.76±22.41 months (range 3-120 months, median: 12 months). The mean dosage of VGB received was 48.38±26.57 mg/kg/day (range: 10-125 mg/kg/day, median: 40 mg/kg/day) (Table III). The patients who achieved 50% or more reduction in seizure frequency received VGB at a mean dosage of 61.49±28.37 mg/kg/day (range: 20-125 mg/kg/day, median: 60 mg/kg/day).

There was no statistically significant difference in the efficacy of VGB in seizure control between the patients with partial epilepsy and those with primary generalized epilepsy (p=0.768). VGB reduced seizure frequency at least 50% in 33.3% of patients with partial seizures, and in 30.6% of patients with primary generalized seizures (Table IV). Six of the responders with partial seizures had complete resolution of their seizures. Also, there were no statistically significant differences between responders and non-responders for the age

Table III. Patient Profile in the Study Group

Total patient number	111
Male	75
Female	36
Age of introduction of VGB treatment	Mean 8.34±4.92
Duration of VGB treatment	Mean: 23.76±22.41 months
Dosage of VGB	Mean: 48.38±26.57 mg/kg/day
Treatment status with VGB	
as monotherapy	3
as add on	108

VGB: Vigabatrin.

Table IV. Efficacy of Vigabatrin (VGB) in Patients with Partial and Generalized Seizures

Seizure type	No. of patients responsive to VGB	No. of patients unresponsive to VGB	Total
Partial seizure +/– secondary generalization	18 (33.3%)	36 (66.7%)	54
Primary generalized seizure	15 (30.6%)	34 (69.4%)	49

of seizure onset, age of VGB introduction, dosage of VGB, or intelligence scores (p values were 0.51, 0.62, 0.75, and 0.63, respectively). However, the duration of epilepsy was found to be statistically effective on clinical response to the treatment (p=0.011). The mean duration of epilepsy when VGB was started in responders and non-responders was 4.13±4.47 years (median: 21 months) and 5.9±4.15 years (median: 5 years), respectively.

Vigabatrin reduced infantile spasms in four patients by 50% or more. The mean dosage of VGB received by the patients with infantile spasms was 74.47±29.61 mg/kg/day (range: 50-125 mg/kg/day, median: 62.39 mg/kg/day). No patient with tuberosclerosis improved.

Seven patients with poor seizure control [intracranial dysembryoblastic neuroepithelial tumor (DNET) lesion, n: 2; hypoxic-ischemic findings, n: 1; infarct lesion, n: 1; cystic lesion, n: 1; sequelae lesions of meningitis-encephalitis, n: 1; mesial temporal sclerosis on cranial MRI, n: 1] subsequently underwent evaluation for epilepsy surgery and improved following surgery.

Side Effects

The side effect profile of VGB observed during the treatment of the patients is shown in Table V. The most common side effects included visual field defects, increased appetite and obesity. Four patients with an age range

Table V. Side Effect Profile of Vigabatrin Observed during Treatment of Patients with Intractable Epilepsy

Side effects	Number of patients	Number of patients in whom VGB was discontinued due to side effects
1-Increase in appetite and weight	5	–
2-Visual field defect	4	1
3-Rash	3	1
4-Drowsiness	2	1
5-Behavioral issues	2	–
6-Nausea and vomiting	1	1
7-Alopecia	1	–
8-Increased liver enzymes	1	–
9-Hirsutism	1	–

between 4 months and 10 years receiving VGB as an adjunct AED at a dosage of 30-70 mg/kg/day for a period ranging between 12 months and 54 months were diagnosed to have visual field defects; one had to discontinue VGB. Electroretinography (ERG) was performed in one patient with visual field defect and it was abnormal.

Statistical Analysis

Chi-square test and Mann-Whitney test were performed.

Discussion

The previous studies on the efficacy of VGB suggest that 40-60% of patients who have partial onset seizures with or without secondary generalization achieve 50% reduction in seizure frequency[7-15]. VGB is found to be an effective drug to reduce infantile spasms particularly due to tuberosclerosis and Down syndrome in 50% of patients[7,8,16,17]. For generalized epilepsies except infantile spasm, VGB is less efficacious[7,13]. VGB can exacerbate myoclonic seizures and is ineffective for absence seizures[15,18].

In this study, we suggest that VGB might be more effective in pediatric patients with partial onset seizures with or without secondary generalization; the majority of the patients with symptomatic infantile spasms improved. We also suggest that the efficacy of VGB is high in the patients with short duration of epilepsy irrespective of seizure type or etiology. In our EEG laboratory, the patients with intractable epilepsies on polytherapy were studied, so the study group did not reflect the general childhood epilepsy population. In Turkey, some of the new generation AEDs like zonisamide or levetiracetam are difficult to obtain, the number of medical centers carrying out vagal nerve stimulation for the treatment of epilepsy is low, and the compliance of children to a ketogenic diet is insufficient. However, according to our findings, we recommend that VGB should be considered when intractable partial seizures fail to respond to any other medication. It may be the first choice of AED in the treatment of infantile spasms.

We observed that seven patients unresponsive to the medical treatment improved postoperatively. Patients with poor seizure control in spite of appropriate medical treatment should be evaluated for surgery.

In this study, the most common side effects observed during the treatment with VGB included visual field defects, increased appetite and obesity. Increased appetite and weight gain could be managed with low caloric intake[5]. Bilateral permanent binasal visual field defects have been reported in association with the usage of VGB in up to 65% of children[19-21]. The concentric contraction of visual fields does not improve when the medication is discontinued[22]. The visual changes are explained by the accumulation of GABA in the Mueller cells and the GABA transaminase inhibition of the rod bipolar cells in the peripheral retina[23]. In some studies, it is suggested that the cumulative effect of the drug may cause permanent visual field defect while others suggest that an idiosyncratic response may play a role[19,20,24]. Although there is not yet sufficient data in the literature to determine the exact point at which the visual field changes start, it is recommended that children with an intelligence score of nine years old should have a visual field examination before VGB is initiated and every six months thereafter[25]. Perimetric evaluation is the most sensitive test for identifying VGB toxicity causing visual field defect[23]. In a previous study, visual evoked potentials (VEPs) and ERGs were found to be abnormal in children with visual field defect, and the authors suggested that traditional electrophysiological testing (VEP, ERG) may be useful in evaluation of VGB toxicity in children in whom perimetric monitoring is not feasible[26]. We found visual field defects in four patients and the medication had to be discontinued in one of them. ERG was performed in one patient with visual field defect and it was also abnormal.

As in previous studies, we also suggest that VGB is an effective AED in the treatment of refractory partial seizures and infantile spasms. The patients should be followed for the side effects of VGB, especially for visual field constriction.

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