Journal of Pediatric Epilepsy 2 (2013) 125–129
DOI 10.3233/PEP-13051
IOS Press

Clinical trial of pregabalin as an add-on therapy in children with refractory epilepsy

M.K. Bakhshandeh Bali[a], Mahmoud R. Ashrafi[b], Seyedeh Mohadeseh Taheri Otaghsara[c], Mohammad M. Nasehi[d], Eznollah Azargashb[e,*], Parvaneh Karimzadeh[f] and Mohammad Ghofrani[f]

[a]*Pediatric Neurology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[b]*Children's Medical Center, Tehran University of Medical Sciences (TUMS), Tehran, Iran*
[c]*Brain and Spinal Injury Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran*
[d]*Pediatric Neurology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[e]*Department of Community Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[f]*Pediatric Neurology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

Received 21 February 2013
Revised 10 April 2013
Accepted 13 April 2013

Abstract. Epilepsy is the most common neurological disorder worldwide. One-third of epileptic patients do not respond after treatment with first- or second-line antiepileptic drugs. Pregabalin is a novel antiseizure drug with established anxiolytic and analgesic efficacy. In this study, we evaluated the efficacy and tolerability of pregabalin as an adjunctive therapy in a group of children with intractable epilepsy. From October 2011 to September 2012, 67 children with refractory epilepsy who visited the pediatric neurology clinic of Mofid Children's Hospital were enrolled in this study. The patients were treated with pregabalin. Reduction in seizure frequency and severity were compared after 1 and 6 mo of treatment initiation. During follow-up, >50% reduction in seizure frequency or severity was observed as a response to the drug. Of the 60 children who reached the last stage, 29 (48.3%) were boys and 31 (51.7%) were girls. The age of the children ranged between 6 mo and 16 yr, with a mean age of 71 ± 42.9 mo. Pregabalin reduced seizure frequency up to 2.41 ± 2.38 (48% decline) and 2.75 ± 2.38 (40.86% decline) after 1 and 6 mo of treatment initiation, respectively. There was a significant difference between seizure frequency at 1 ($P < 0.001$) and 6 mo ($P < 0.001$) after pregabalin initiation compared with the initial attacks. Increased appetite, frequent urination, hallucinations, and headache were the most common side effects in our patients, with a complication rate of 18.33%. Thus, pregabalin seems to be effective and well tolerated for seizure control in children with intractable epilepsies.

Keywords: Epilepsy, antiepileptic drugs, pregabalin

1. Introduction

Approximately 50 million people suffer from epilepsy worldwide, indicating that it is the most common neurological disorder. Only two-thirds of epileptic patients respond after treatment with first- or second-line antiepileptic drugs (AEDs) despite the presence of new-generation anticonvulsants. Multiple drug therapy using adequate AEDs with suitable safety and tolerability is another choice for the treatment of patients with epilepsy [1,2].

Pregabalin (PGB) is a novel AED, which has established anxiolytic and analgesic impressions in preclinical animal studies [3]. PGB is structurally similar to gamma-aminobutyric acid (GABA) but is inactive

*Corresponding author: Eznollah Azargashb, Department of Community Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel.: +98 936 111 9156; Fax: +98 212 290 9559; E-mail: dr.mkbakhshandehbali@yahoo.com.

against GABA receptors [4]. PGB has a favorable pharmacokinetic profile, including a linear dose-concentration curve, with an effective range of 150–600 mg/day; rapid and extensive absorption after oral consumption, which is not affected by food; high bioavailability of approximately 90%, which reaches peak plasma concentration 1 h after oral dosage; and a half-life of 6 h [5].

PGB does not cause relevant pharmacokinetic interactions with simultaneously administered anticonvulsants because of the lack of cytochrome P450 induction, protein binding, and pharmacokinetic interaction [6]. PGB has pharmacological features similar to those of gabapentin (GBP), with a 3-10-fold higher potency. Both these molecules connect the α2δ subunit of voltage-related calcium channels and carry out their actions through calcium channel turnover, which results in decreased calcium influx and consequently diminution of presynaptic neurotransmitter release [7,8].

Several randomized controlled trials have shown that PGB can be used as an adjunctive therapy for partial epilepsies, with favorable efficacy and tolerability [9]. However, limited literature is available on the efficacy of PGB as an adjunctive therapy in epileptic children experiencing different types of seizures. Thus, in this study, we evaluated the efficacy and tolerability of PGB as an adjunctive treatment in a group of children with intractable epilepsy.

2. Materials and methods

From October 2011 to September 2012, 67 children with refractory epilepsy who visited the pediatric neurology clinic of Mofid Children's Hospital were enrolled in this study. Inclusion criteria were children below age 18 years with epilepsy refractory to previous AEDs (>2 conventional and new AEDs). Exclusion criteria were children with neurodegenerative diseases or hypersensitivity to anticonvulsants.

After receiving written consent from patients, initial assessments such as disease history (type, onset, etiology, and frequency of seizure; previous treatment period; and AEDs used), physical examination (general and neurological), electroencephalography (EEG), and magnetic resonance imaging (MRI) were conducted.

Seizures were confirmed and quantified monthly by reports from parents, observation of videos taken by parents, and direct observation at the hospital before and after the treatment. EEG was done for all patients. Diffuse and continuous paroxysmal epileptic discharges were considered severely abnormal when epileptic discharges comprised >50% of the EEG and were considered mildly or moderate abnormal when paroxysmal epileptic discharges comprised 25% of the EEG. Next, children were given an initial dose of PGB capsule (5 mg/kg daily) that was divided in 2 or 3 doses in addition to the previous medication (>2 new, conventional, or concurrent AEDs listed in Table 1). The time required

Table 1
Patient characteristics

Characteristics	n (%)
Gender	
Male	29 (48.3)
Female	31 (51.7)
Age (mo)	
Mean ± SD	71 ± 42.89
Seizure type	
Tonic clonic	22 (36.7)
Simple partial	3 (5)
Complex partial	13 (21.7)
Infantile spasm	3 (5)
Myoclonic	3 (5)
Tonic	5 (8.3)
Atonic	2 (3.3)
Absence	1 (1.7)
Mixed	8 (13.3)
Electroencephalography quality	
Normal	4 (6.6)
Mild abnormal	17 (28.3)
Moderate abnormal	25 (41.6)
Severe abnormal	14 (23.3)
First month follow-up	
Unchanged	15 (25)
100% reduction	11 (18.3)
75–99% reduction	8 (13.33)
50–75% reduction	13 (21.3)
25–50% reduction	10 (16.6)
<25% reduction	3 (5)
Worsening	0 (0.0)
Daily seizure frequency	2.41 ± 2.38
Adverse effects	
Increased appetite	6 (10)
Increased urination	3 (5)
Hallucinations	1 (1.7)
Headache	1 (1.7)
Initial seizure frequency (daily)	
Mean ± SD	4.65 ± 3.77
Range	0.1–20
Seizure onset	
Mean ± SD	23.2 ± 24.3 mo
Range	15 day-10 yr
Magnetic resonance imaging	
Normal	20 (33.3)
Atrophy	16 (26.7)
Periventricular leukomalacia	5 (8.3)
Mesial temporal sclerosis	5 (8.3)
Focal lesion	3 (5)

(*continued*)

Table 1. Patient characteristics (Continued)

Characteristics	n (%)
Migrational disorder	3 (5)
Tuberous sclerosis	2 (3.3)
Cortical dysplasia	2 (3.3)
Cerebral calcification	2 (3.3)
Encephalomalacia	1 (1.6)
Basal ganglia lesion	1 (1.6)
Electroencephalography waves	
Spike	29 (48.3)
High voltage slow wave	12 (20)
Hypsarrhythmia	5 (8.3)
Sharp wave	8 (13.33)
Burst suppression	2 (3.33)
Six-month follow-up	
Unchanged	18 (30)
100% reduction	11 (18.3)
75–99% reduction	6 (10)
50–75% reduction	6 (10)
25–50% reduction	9 (15)
<25% reduction	8 (13.3)
Worsening	2 (3.3)
Daily seizure frequency	2.75 ± 2.38
Concurrent antiepileptic drugs	
Primidon	25 (41.6)
Na-valproate	18 (30)
Phenobarbital	15 (25)
Carbamazepin	11 (18.3)
Phenytoin	7 (11.6)
Topiramat	7 (11.6)
Others	18 (30)

to achieve an appropriate dose of the drug was 2–3 wk. Seizure periodicity and severity were evaluated within 3–4 wk from the initiation of PGB. According to the level of seizure response, PGB doses were adjusted to a maximum dose of 15 mg/kg daily. During follow-up, the mean seizure response frequency or severity reduced by ≥50%. All the ethical perspectives of this study were approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences. This study was registered in Iranian registry of clinical trial (IRCT; number: IRCT2012101510508N5). Data were analyzed using SPSS16, Wilcoxon, and Mann-Whitney *U* test. *P* value < 0.05 was considered statistically significant.

3. Results

This study enrolled 67 children, of which 60 reached the last stage. Details of patient properties are listed in Table 1. Of the 60 patients, 29 (48.3%) were boys and 31 (51.7%) were girls. The age of patients ranged from 6 mo to 16 yr, with a mean age of 71 ± 42.9 mo (Table 1). The age of seizure onset was from 15 days to 10 yr, with a mean age of 23.15 ± 24 mo. The initial seizure frequency varied from 3 seizures/month to 20 seizures/day, with a mean of 4.65 ± 3.77 seizures/day. Generalized tonic-clonic, partial, and mixed-type seizures were observed in 22 (36.7%), 16 (26.3%), and eight (13.3%) children, respectively (Table 1).

According to the seizure etiology showed in Table 1, 23 (38.3%), 30 (49.18%), and seven (11.7%) patients were classified as having idiopathic, cryptogenic, and symptomatic epilepsy, respectively. Brain MRIs of 20 (33.3%) patients were normal. In the remaining 40 patients, brain atrophy (16 [26.7%]), mesial temporal sclerosis (five [8.3%]), periventricular leukomalacia (five [8.3%]), migrational disorder (three [5%]), focal lesion (three [5%]), tuberous sclerosis (two [3.3%]), cortical dysplasia (two [3.3%]), cerebral calcification (two [3.3%]), encephalomalacia (one [1.6%]), and basal ganglia lesion (one [1.6%]) were the abnormal findings. EEG findings were normal, mild, moderate, and severely abnormal in four (6.57%), 17 (28.3%), 25 (41.66%), and 14 (23.33%) children, respectively (Table 1). Patients used 3–13 antiseizure medications (average, 7.28 ± 2.92) before the study. Primidone, sodium-valproate, phenobarbital, carbamazepine, phenytoin, and topiramate were the most commonly used concomitant drugs. PGB dosage ranged from 5–15 mg/kg/day, with a mean dosage of 14.3 ± 1.8 mg/kg/day.

After 1 and 6 mo of PGB initiation, seizure frequency decreased to 2.41 ± 2.38 (48% reduction) and 2.75 ± 2.38 (40.86% reduction), respectively. There was significant difference between seizure frequency at 1 ($P < 0.001$) and 6 mo ($P < 0.001$) after PGB initiation compared with the initial frequency of seizures. There was no significant difference in seizure frequency at 1 and 6 mo after treatment initiation ($P = 0.435$).

During the first month of follow-up, 15 (25%), 32 (53.33%), and 13 (21.66%) patients showed no change, decline of >50% (responder), and reduction of <50% (Fig. 1) in the severity and duration of seizure, respectively. During 6 mo of follow-up, 18 (30%), 23 (38.33%), 17 (28.3%), and two (3.3%) patients showed no change, decline of >50% (responder), reduction of <50%, and worsening in the severity and duration of seizure (Fig. 1), respectively.

During the first month of follow-up, the highest response to PGB was observed for partial (70.2%), generalized tonic (60%), and generalized tonic-clonic (40.9%) seizures. During the 6 mo of follow-up, the highest response to PGB was observed for partial (53.2%), generalized tonic (50%), and generalized atonic (40%) seizures.

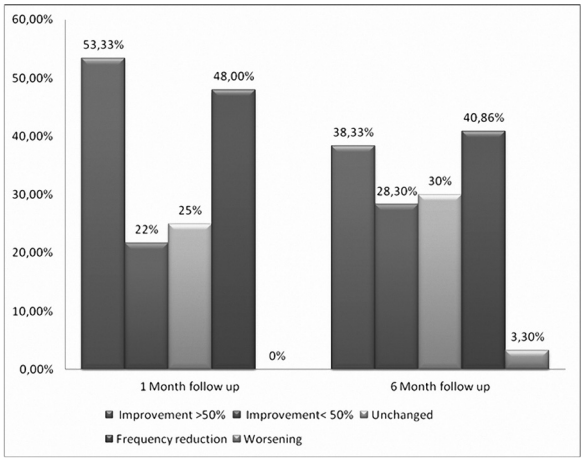

Fig. 1. Seizure reduction in the first and 6 mo follow-up. Frequency Reduction = Seizure frequency decline percent toward initial frequency; Improvement = Seizure severity reduction percent toward initial severity.

Myoclonic seizure showed no response to PGB during 1 or 6 mo of follow-up.

There was no significant correlation between drug dosage and seizure improvement ($P > 0.05$). Increased appetite (six [10%]), increased urination (three [5%]), hallucinations (one [1.7%]), and headache (one [1.7%]) were the most common side effects in our patients, with an overall complication rate of 18.33%.

4. Discussion

In our study, PGB reduced the seizure frequency up to 44.4% and showed >50% decline in seizure severity in 45.8% patients. PGB effectiveness in this study is in agreement with that observed in studies by Rivera-Casta et al. [1] and Arroyo et al. [10] who showed a remarkable seizure decline in clinical trials of PGB as an adjunctive therapy in patients with refractory epilepsy. In the study by Arroyo et al. [10], 43.5% patients with refractory epilepsy responded to PGB therapy; furthermore, this study showed a dose-dependent response to this drug, with a dose equal to 600 mg/day being quite effective. All responders in our study were given a PGB a dose of >10 mg/kg/day or <150 mg/day of the dose mentioned above. A possible explanation for this might be the difference in body weights, which were much lower in our children than in adults in the study by Arroyo et al. [10]. Rivera-Castaño et al. [1] showed that seizure frequency improved in >63.6% patients, which was even more significant than that observed in our study. However, the children included in our study had various types of seizure, whereas those included in the study by Rivera-Castaño et al. [1] had only partial epilepsy. Therefore, the difference in efficacy may be due to the greater therapeutic effect of PGB on partial seizures.

In our study, the drug efficacy was decreased 6 months after administration compared to the first month consumption. Löscher and Schmidt [11] showed that the efficacy of AEDs decreased over time due to receptor desensitization. Baulac et al. [12] compared the efficacy of lamotrigine and PGB in patients with refractory partial epilepsies in a 17 week trial and indicated that PGB decreased seizure intensity in 35.5% patients compared with lamotrigine in 21.4% of patients [12]. Lee et al. [5] reported a seizure frequency decline in 46.2% cases after 13 wk of PGB therapy, which is in accordance with the result of our study.

Elger et al. [13] showed PGB efficacy more remarkable than our outcome in patients receiving a fixed dose of PGB (600 mg/day); after 12 wk of treatment, seizure frequency decreased up to 49.3% in these patients. This difference may be due to our use of various doses of PGB (5–15 mg/kg/day), which require at least 2 wk to achieve a fixed level of drug availability in our patients. Contrary to the study by Rivera-Castaño et al. [1], which only analyzed patients with partial convulsions and showed a higher response, a study by Modur et al. [14] showed a significant response in the frequency and severity of seizures, up to 56%, in patients with multiple seizure types, which is far more effective than in our study. Three patients in our study who previously used gabapentin did not respond to PGB, which is in contrast to that observed in the study by Modur et al. [14] who showed PGB-induced seizure improvement despite a history of gabapentin usage.

Uthman et al. [15], Rivera-Castaño et al. [1], and Lee et al. [5] indicated that PGB is more effective against partial convulsions [16]. Briggs et al. [16] stated that various doses of PGB have good effectiveness against partial seizures, but only high dose of PGB (≥600 mg/day) can be used for the treatment of secondary generalized epilepsies. Novy et al. [17] showed that PGB was equally effective against tumor-induced partial and generalized convulsions.

All the complications in our patients occurred with a PGB dose of ≥150 mg/day. The rate of complications in this study was insignificant compared to rates of 64.7%, 50%, and 32.8% reported by Lee et al. [5], Baulac et al. [12], and Elger et al. [13], respectively. This difference may be due to a higher dose of PGB administered in these

three studies, which is necessary for the treatment of adults (at least 300 mg/day). Weight gain was the most common side effect of PGB in our patients, which was consistent with that observed in studies by Modur et al. [14], Arroyo et al. [10], and Baulac et al. [12] who reported a weight increase of approximately 5–7% in 24–50% patients. The most interesting finding of the present study was increased frequency of urination in three patients receiving PGB doses of >150 mg; this side effect was resolved after dose reduction.

In conclusion, pregabalin seems to be effective and well tolerated for seizure control in children with intractable epilepsies, with the highest effect on partial seizures and few but insignificant side effects.

Acknowledgments

We are very grateful to the Pediatric Neurology Research Center of Shahid Beheshti University of Medical Sciences, for supporting this study.

References

[1] Rivera-Castaño L, Leal-Cantu R, Abreu P, Guerrero M, Davila G. A 21-week open-label clinical trial of pregabalin as adjunctive therapy in partial seizures at multiple centers in Mexico (PREPS Mexico). Epilepsy Res 2012;100(1–2):74–9.

[2] Kwan P, Brodie MJ. Combination therapy in epilepsy: when and what to use. Drugs 2006;66(14):1817–29.

[3] Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004;45(Suppl 6):13–8.

[4] Briggs DE, Lee CM, Spiegel K, French JA. Reduction of secondarily generalized tonic-clonic (SGTC) seizures with pregabalin. Epilepsy Res 2008;82(1):86–92.

[5] Lee BI, Yi S, Hong SB, Kim MK, Lee SA, Lee SK, et al. Pregabalin add-on therapy using a flexible, optimized dose schedule in refractory partial epilepsies: a double-blind, randomized, placebo-controlled, multicenter trial. Epilepsia 2009; 50(3):464–74.

[6] Brodie MJ, Wilson EA, Wesche DL, Alvey CW, Randinitis EJ, Posvar EL, et al. Pregabalin drug interaction studies: lack of effect on the pharmacokinetics of carbamazepine, phenytoin, lamotrigine, and valproate in patients with partial epilepsy. Epilepsia 2005;46(9):1407–13.

[7] Miller R, Frame B, Corrigan B, Burger P, Bockbrader H, Garofalo E, et al. Exposure-response analysis of pregabalin add-on treatment of patients with refractory partial seizures. Clin Pharmacol Ther 2003;73(6):491–505.

[8] Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res 2007;73(2):137–50.

[9] Beydoun A, Uthman BM, Kugler AR, Greiner MJ, Knapp LE, Garofalo EA, et al. Safety and efficacy of two pregabalin regimens for add-on treatment of partial epilepsy. Neurology 2005;64(3):475–80.

[10] Arroyo S, Anhut H, Kugler AR, Lee CM, Knapp LE, Garofalo EA, et al. Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures. Epilepsia 2004;45(1):20–7.

[11] Löscher W, Schmidt D. Experimental and clinical evidence for loss of effect (tolerance) during prolonged treatment with antiepileptic drugs. Epilepsia 2006;47(8):1253–84.

[12] Baulac M, Leon T, O'Brien TJ, Whalen E, Barrett J. A comparison of pregabalin, lamotrigine, and placebo as adjunctive therapy in patients with refractory partial-onset seizures. Epilepsy Res 2010;91(1):10–9.

[13] Elger CE, Brodie MJ, Anhut H, Lee CM, Barrett JA. Pregabalin add-on treatment in patients with partial seizures: a novel evaluation of flexible-dose and fixed-dose treatment in a double-blind, placebo-controlled study. Epilepsia 2005;46(12): 1926–36.

[14] Modur PN, Milteer WE. Adjunctive pregabalin therapy in mentally retarded, developmentally delayed patients with epilepsy. Epilepsy Behav 2008;13(3):554–6.

[15] Uthman BM, Bazil CW, Beydoun A, Schulze-Bonhage A, Benabou R, Whalen E, et al. Long-term add-on pregabalin treatment in patients with partial-onset epilepsy: pooled analysis of open-label clinical trials. Epilepsia 2010;51(6):968–78.

[16] Briggs DE, Lee CM, Spiegel K, French JA. Reduction of secondarily generalized tonic-clonic (SGTC) seizures with pregabalin. Epilepsy Res 2008;82(1):86–92.

[17] Novy J, Stupp R, Rossetti AO. Pregabalin in patients with primary brain tumors and seizures: a preliminary observation. Clin Neurol Neurosurg 2009;111(2):171–3.