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Gabapentin in the treatment of migraine and epilepsy comorbid with mood and anxiety disorders

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Abstract This open prospective study asessed the use of gabapentin in migraine and epilepsy comorbid with mood and anxiety disorders. After a 4-week baseline period, gabapentin was used as adjunctive treatment in 14 adult patients with both epilepsy and migraine disorders for 3 months. The outcomes were compared with a control group of 14 sex-matched patients with the same disorders, not treated with gabapentin. Both groups were assessed on the Cornell dysthymia rating scale (CDRS), Beck depression inventory (BDI), and Hamilton anxiety scale. A total of 8 (57%) gabapentin-treated patients showed a significant improvement in migraine vs. 3 (21.4%) of the controls. In comparison with controls, the gabapentin-treated group had a significant decrease in CDRS and BDI scores ($p<0.05$). The results suggest a particular role for gabapentin in the treatment of patients with both epilepsy and migraine comorbid with mood and anxiety disorders.

Key words Gabapentin • Migraine • Epilepsy • Anxiety • Dysthymia • Pharmacotherapy

Introduction

Multiple actions of gabapentin – anticonvulsant, antinociceptive and psychoactive – underly its clinical efficacy in epilepsy [1, 2], migraine [3, 4], various psychiatric disorders including panic disorder and mood disorders [5] and neuropathic pain syndromes [6, 7]. They may be advantageous for the treatment of comorbid epileptic and nonepileptic conditions. Therefore, this open prospective study was designed to assess the value of gabapentin in epilepsy and migraine comorbid with psychiatric disorders.

Patients and methods

Patients with both partial epilepsy and migraine comorbid with mood and anxiety disorders were studied in a prospective, non-randomized fashion during a 4-week baseline and during a 3- to 6-month (mean, 5.1 months) period of adjunctive gabapentin treatment. The control group, not treated with gabapentin, consisted of age- and sex-matched patients with the same comorbid disorders. Inclusion criteria required that all patients before and during baseline period had migraine attacks incompletely controlled by their prophylactic migraine treatment, which consisted of propranolol (60–240 mg/day) in 8 gabapentin-treated and 7 control patients and magnesium (600 mg/day) in 6 and 7 patients, respectively. All patients had complaints indicating anxiety, dysthymia and/or depression. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) [8], the mental disorder in patients treated with gabapentin vs. patients in the control group was classified as dysthymic disorder in 7 vs. 7 patients, agoraphobia in 5 vs. 5, and dysthymic disorder associated with social phobia in 2 vs. 2 patients. Dysthymic disorders were comorbid in migraine with aura in 1 vs. 2 patients and in migraine without aura in 6 vs. 5 patients, agoraphobia was comorbid in migraine with aura in 1 vs. 1 patient and migraine without aura in 4 vs. 4, and dysthymic disorder associated with social phobia was comorbid in migraine without aura in 2 vs. 2 patients. The patients did not have any change of antiepileptic drugs (AEDs) in the 3 months prior to the study, in order to compensate for the possible effects of AEDs on these variables.

Frequencies of migraine attacks [9] and of partial seizures [10] were monitored throughout the study in both groups. The criterion for improvement of migraine with gabapentin treatment was defined as the frequency and severity of migraine attacks reduced by at least 50% in relation to the baseline. Both groups were assessed by interviewer-rated and self-rated scales of mood and anxiety: the Cornell dysthymia rating scale (CDRS) [11], Beck depression inventory (BDI) [12], Hamilton depression scale [13] and Hamilton anxiety scale [14]. Statistical significance was assessed by analysis of variance with replication, two paired *t* test, *t* test for two small samples and Fisher's exact test.

Results

Main demographic characteristics of patients treated with gabapentin were not different from controls (Table 1). The mean frequency of migraine attacks at baseline was similar in both groups (Table 1). The mean frequency of seizures at baseline was also similar in uncontrolled patients (4 gabapentin-treated patients and 5 controls. Antiepileptic drug regimens at baseline were similar in the two groups. A total of 7 patients in the gabapentin-treated group were on carbamazepine monotherapy (in dosages of 900–1200 mg/day) vs. 8 patients in the control group (900–1200 mg/day). In the experimental group, there were 4 patients taking carbamazepine and valproate (750–1500 mg/day) vs. 2 patients in the control group. Two patients in each group were taking carbamazepine (800–1100 mg/day) and lamotrigine (100–300 mg/day). Finally, 1 gabapentin-treated patient was taking phenytoin (200 mg/day) and clonazepam (3–4 mg/day), and 2 control patents were taking 150 and 200 mg phenytoin with 2.5 and 4.0 mg clonazepam.

Gabapentin was provided in 300-mg capsules. All patients began gabapentin treatment at 900 mg/day, titrated in 300-mg increments over a 3-day period. The initial dosage level was increased the following week to 1200 mg/day and was titrated over 6 weeks up to 2400 mg/day. If the patient was unable to tolerate a given dosage, the dosage was decreased to the previous tolerated dosage. The maintenance dosage was in the range of 600–2400 mg (mean, 1178±435 mg). Adverse events probably due to gabapentin were drowsiness in 3 and dizziness in 2 patients. The symptoms were transient and disappeared after the dosage reduction.

A significant improvement of migraine occurred in 8 (57.1%) of gabapentin-treated patients (Table 2). Reduction of seizure frequency by 50% or more in relation to baseline occurred in all 4 uncontrolled patients treated with gabapentin and in 3 of the 5 uncontrolled patients in the control groups; this difference was not statistically significant (Table 2). The seizure control remained stable in all other patients who were seizure-free at baseline.

The analysis of variance used in the assessment of mood and anxiety between gabapentin (GBP) and control groups showed significant between-groups effects ($p<0.01$). In comparison with the control group, the gabapentin-treated group had a significant improvement in mood and anxiety disorders (Table 3).

Table 1 Characteristicis of patients treated with gabapentin (GBP) and of controls

	GBP-treated group (n=14)	Control group (n=14)
Men, n (%)	3 (21)	3 (21)
Age, years		
Mean (SD)	23.8 (6.7)	24.7 (8.0)
Range	16–45	16–42
Duration of nonidiopathic epilepsy, years		
Mean (SD)	8.7 (4.7)	7.8 (7.3)
Range	4–21	3–23
Patients with seizures at baseline, n		
Uncontrolled	4	5
Controlled	10	9
Baseline seizure frequency for uncontrolled patients, mean (SD)[a]	6.2 (0.9)	6.5 (1.1)
Duration of migraine, years		
Mean (SD)	7.9 (5.4)	8.5 (7.3)
Range	4–20	4–18
Patients with migraine aura, n	2	3
Frequency of migraine attacks at baseline, mean (SD)[a]	2.2 (0.8)	2.1(0.6)

[a] Number per month

Table 2 Changes in seizure and migraine attack frequencies after treatment with gabapentin

	Gabapentin	Controls	Significance
Uncontrolled patients with seizures decrease ≥50%, n (%)	4 (28.6)	3 (21.4)	NS
Seizure frequency at end of study, mean (SD)[a]	4.3 (1.8)	5.2 (1.9)	NS
Patients with migraine attack decrease ≥50%, n (%)	8 (57.1)	3 (21.4)	$p<0.05$[b]
Migraine attack frequency at end of study, mean (SD)[a]	1.6 (0.6)	1.1 (0.8)	$p<0.05$[c]

NS, not significant
[a] Number per day; [b] Fisher's exact test; [c] *t* test for two small samples

Table 3 Comparison of outcome on mood and anxiety assessment between gabapentin and control groups. Values are means (SD)

Group	Baseline	After 3 months	Paired *t* test
Dysthymia (CDRS)			
Gabapentin	20.8 (3.6)	14.6 (4.0)	<0.001
Control	17.6 (2.6)	17.8 (3.1)	NS
Depression (Hamilton)			
Gabapentin	12.4 (3.0)	9.9 (2.9)	<0.001
Control	12.1 (2.4)	12.1 (2.7)	NS
Depression (Beck)			
Gabapentin	16.4 (3.6)	13.5 (4.4)	<0.01
Control	15.4 (3.7)	15.3 (3.9)	NS
Anxiety (Hamilton)			
Gabapentin	10.5 (1.4)	9.1 (2.5)	<0.05
Control	10.4 (3.0)	10.0 (2.1)	NS

NS, not significant; *CDRS*, Cornell dysthymia rating scale

Discussion

Comorbidity of migraine with epilepsy and psychiatric disorders [15] may require the chronic use of multiple drugs (such as anticonvulsants, antidepressants or other migraine prophylactic drugs) aiming to improve all comorbid disorders. The consequences may be drug interactions with adverse effects due to drug toxicity or worsening of seizure or migraine control. The present results demonstrated that gabapentin significantly improved both migraine and comorbid mood and anxiety disorders. The effect of comedication with other antiepileptic drugs, especially carbamazepine and valproate that also have psychotropic actions, cannot be completely excluded. However, a significant effect of these antiepileptic drugs on mood and anxiety in our patients is unlikely, since the effect was not apparent before gabapentin use and the dosage of these drugs was held constant even before baseline and throughout the study.

The present findings are in accordance with the recent double-blind study showing the favorable effect of gabapentin in migraine prophylaxis [3, 4]. However, in this open study, it cannot be excluded that the favorable effect of gabapentin may be in some part the result of the interaction with other antiepileptic drugs, especially valproate which is very effective in migraine prophylaxis [16]. The present study is in agreement with another open study showing the mood improvement of patients with partial epilepsy and dysthymia treated with gabapentin [17]. This effect is not dependent on the improvement of epilepsy since it was found in patients with controlled seizures [17] and, in this study, in some patients with uncontrolled seizures.

The positive effect of gabapentin on seizure control was not evident in this study since the number of patients with uncontrolled seizure at baseline period was small. However, anticonvulsant effect of gabapentin against partial seizures was proven in other studies including several hundreds of patients [1, 2, 18].

Multiple actions of gabapentin have been shown in studies using experimental animal disease models. Thus, gabapentin blocks the development of allodynia and hyperalgesia in postoperative [19] and other pain models [20]. The

broad spectrum of antinociceptive actions of gabapentin is associated with an anxiolytic-like effect [21]. The cellular mechanisms responsible for the antinociceptive and anxiolytic effects of gabapentin may be different from those related to its antiepileptic effects. In addition to the modulation of GABA and glutamate synthesis, increase in the concentration and probably the rate of synthesis of GABA in brain, high binding affinity to a subunit of voltage-sensitive Ca^{2+} channels, probably relevant for anticonvulsant action, they probably include the increase in serotonin concentrations in human whole blood [22]. Accordingly, recent clinical studies gave some evidence for the efficacy of gabapentin in trigeminal neuralgia [23], central post-stroke pain [24], post-herpetic neuralgia [25], migraine [3, 4] and other painful conditions [5]. Gabapentin is not metabolized and has no pharmacokinetic interactions with other drugs [1, 2], which makes it an attractive choice in the case of epilepsy comorbid with migraine or mood disorders. However, the question of optimal doses remains to be clarified. One recent study of resistant epilepsy [18] reported an increase in responders rate with increased dosage, namely from 44.9% to 76.0% of 1055 patients when the dosage was increased from ≤1800 mg/day to ≤3600 mg/day. The present study used maintenance dosages of gabapentin in the range of 600–2400 mg, mean 1178±435 mg. This is similar to 1200 mg/day in the study by Di Trapani et al. [3] and lower than 2400 mg/day of another recent study by Mathew et al. [4]. The latter studies reported an effective therapeutic action of gabapentin in the prophylactic treatment of migraine, at least a 50% reduction in the 3-month migraine rate in 30 of 63 patients [3] or in the 4-week migraine rate in 26 of 56 patients on gabapentin versus 5 of 31 patients receiving placebo ($p<0.008$) [4]. Further controlled studies including a greater number of patients are warranted to prove and to better define the use of gabapentin in the prophylaxis of migraine, and in migraine comorbid with mood and anxiety disorders.

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