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RAPID COMMUNICATION

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An open-label pilot study on the efficacy and tolerability of levetiracetam in the prophylaxis of migraine

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Abstract A preliminary, open label study was conducted on 20 patients with migraine without aura and with high headache frequency to assess the efficacy and tolerability of the new antiepileptic drug levetiracetam. Patients were treated with levetiracetam for three months. The drug was started at a dose of 500 mg and slowly increased within 10 days to the target dose of 2000 mg/day. After 3 months of treatment, 11 (57.9%) of 19 patients who completed the study had a reduction of at least 50% in headache frequency. The intensity of migraine attacks was significantly reduced as was the use of symptomatic drugs. A 3-month carry-over effect was found in about two-thirds of the 11 patients reporting a positive treatment response. Levetiracetam was well tolerated and no patient discontinued the drug due to side effects. This preliminary study supports the potential role of levetiracetam as a new preventive treatment for migraine without aura. The promising results obtained should be confirmed by further research with a double-blind controlled design.

Key words Levetiracetam • Migraine without aura • Prophylaxis • Open label study

Introduction

Levetiracetam is a new antiepileptic drug indicated as adjunctive therapy for the treatment of partial seizures with or without generalization [1]. This molecule was originally studied in the 1980s as a drug active at a cognitive level and as an anxiolytic; thereafter, clinical tests began on its use in epilepsy [2]. In animal models, levetiracetam did not confer protection against single seizures induced by electrical current. However, the drug protected against secondarily generalized activity from focal seizures induced by chemotactants, mimicking some features of complex partial seizures with secondary generalization. Levetiracetam also showed an inhibitory effect in the rat kindling model of human complex partial seizures [3, 4].

Although the mechanism of action of levetiracetam remains unknown, the drug seems to exert a selective action on abnormal neuronal activity, without apparently binding to the principal receptor sites or uptake sites used by other antiepileptic drugs [5]. Recently, selective inhibition by levetiracetam was demonstrated on N type voltage-dependent Ca^{2+} channels [6]. Levetiracetam is not extensively metabolized in humans: 66% of an administered dose was excreted unchanged in urine while the remaining 24% was converted to an inactive metabolite by hydrolysis of the acetamide group by an enzyme not related to the

hepatic P-450 cytochromes (CYP) [7, 8]. Levetiracetam presents a good pharmacokinetic profile, does not have significant interactions with other drugs, and is well tolerated [9, 10].

Based on the observation that certain antiepileptic drugs, by stabilizing neuronal hyperexcitability, are efficacious as preventive drugs for migraine, we conducted a preliminary open study to assess the efficacy and tolerability of levetiracetam in the prophylaxis of migraine.

Patients and methods

The study enrolled 20 outpatients (7 men, 13 women; mean age, 43.5 years; SD=13.2 years) referred to the Headache Centre of the University of Perugia. All patients had migraine without aura, diagnosed according to the 1988 criteria of the International Headache Society (IHS) [11], for at least one year. Patients were included only if they were older than 18 years, had a frequency of at least 4 attacks per month but no more than 15 days per month with headache, and an intake of symptomatic drugs for migraine attacks not exceeding that defining analgesic abuse according to the current IHS criteria [11]. The patients should have tried at least 2 prophylactic treatments for a minimum of 3 months each unsuccessfully. Exclusion criteria were: the presence of other headache types, including a concomitant tension-type headache; headache beginning after age 50 years; analgesic abuse; the presence of other neurological, psychiatric, or systemic diseases; pregnancy and breastfeeding; inability to correctly complete a diary or to properly take medication; and use of other prophylactic drugs. The protocol was approved by the Ethics Committee of the Region of Umbria and all patients gave written informed consent.

Data collection was based on diary cards, in which patients recorded the number, duration, intensity (mild, moderate, or severe) of attacks, accompanying symptoms, and use of symptomatic drugs for migraine attacks. During the initial screening at baseline, the inclusion and exclusion criteria were verified, followed by general physical and neurological examinations. The patients received a diary in which to record headache characteristics. At the second 1-month visit levetiracetam was started at the dosage of 500 mg at night for 5 days, and slowly increased by 500 mg every 5 days, up to the target dosage of 2000 mg/day in 2 administrations. After the titration period, no further changes in levetiracetam dosage were made. Each patient was re-evaluated every 30 days for 3 months to review the headache diary and monitor eventual adverse events. Further visits were made 1 and 3 months after discontinuing levetiracetam, at which time the headache diary was also reviewed.

Statistical analysis

Analysis of variance and least significant difference tests were used to compare the number of headache attacks, attack duration, and number of symptomatic drugs used by the patients during attacks in the study period. The percentage of patients with headache frequency reduced by at least 50%, that of patients who resorted to symptomatic antimigraine drugs and the percent variations of headache intensity were also calculated. Fisher exact test was used to compare the percent variations in headache intensity at baseline and at different times of the study. A value of $p<0.05$ was considered to be statistically significant.

Results

The study enrolled 20 patients with migraine without aura (Table 1). Of these, 19 (95%) completed the study and one failed the screening. At baseline, patients had headache of moderate or severe intensity for a mean of 10.7 days per month. The mean number of drugs taken for the single migraine attack was 9.3 (SD=2.9).

After 3 months of treatment, 11 (57.9%) of the 19 patients who completed the study reported a reduction of at least 50% in the number of days per month with headache (Fig. 1). Headache frequency was also significantly reduced ($p<0.001$) (Table 2). A significant decrease in the intensity of migraine attacks was also observed from the first month of treatment compared to baseline conditions ($p<0.005$) (Fig. 2), as was the administration of drugs for the acute attack ($p<0.001$) (Fig. 3).

All 11 patients reporting a positive treatment response were followed for at least 3 months after discontinuing levetiracetam. A short-term carry-over effect (1 month after drug suspension) occurred in 9 (81.8%) of these patients and a more sustained relief (3 months after drug suspension) occurred in 7 (63.6%) of them.

The side-effects referred by all patients were somnolence (68.4%), asthenia (47.3%), and postural instability (31.5%); all were of mild entity and well tolerated.

Table 1 Characteristics of the 20 patients with migraine without aura at study entry

Men, n (%)	7 (35)
Women, n (%)	13 (65)
Age, years[a]	43.5 (13.2)
Days with headache, n/month[a]	10.7 (1.9)
Headache intensity, n (%)[b]	
Moderate	35 (31.6)
Severe	76 (68.4)
Drug intake for acute attacks, n/month[a]	9.3 (2.9)

[a] Values are mean (SD)

[b] Calculated on the basis of the total number of attacks experienced in the first month of observation without treatment (n=111)

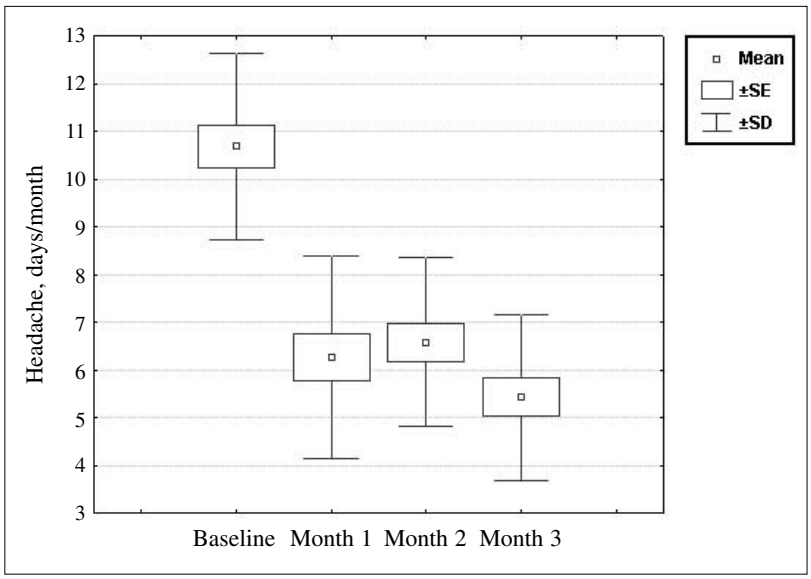

Fig. 1 Number of days with headache per month at baseline and during the three-month treatment with levetiracetam

Table 2 Changes in headache frequency, days per month with headache and symptomatic drug intake during levetiracetam treatment. Values are mean (SD)

	Baseline	Month 1	Month 2	Month 3
Headaches, n/month	8.1 (2.7)	3.3 (2.9)**	3.6 (3.3)**	2.8 (1.3)**
Days with headache, n/month	10.7 (1.9)	6.3 (4.5)*	6.6 (3.1)*	5.4 (3.0)*
Drug intake for acute attacks, n/month	9.3 (2.9)	5.0 (2.9)**	4.8 (2.3)**	4.9 (1.9)**

*p<0.005 vs. baseline; **p<0.001 vs. baseline

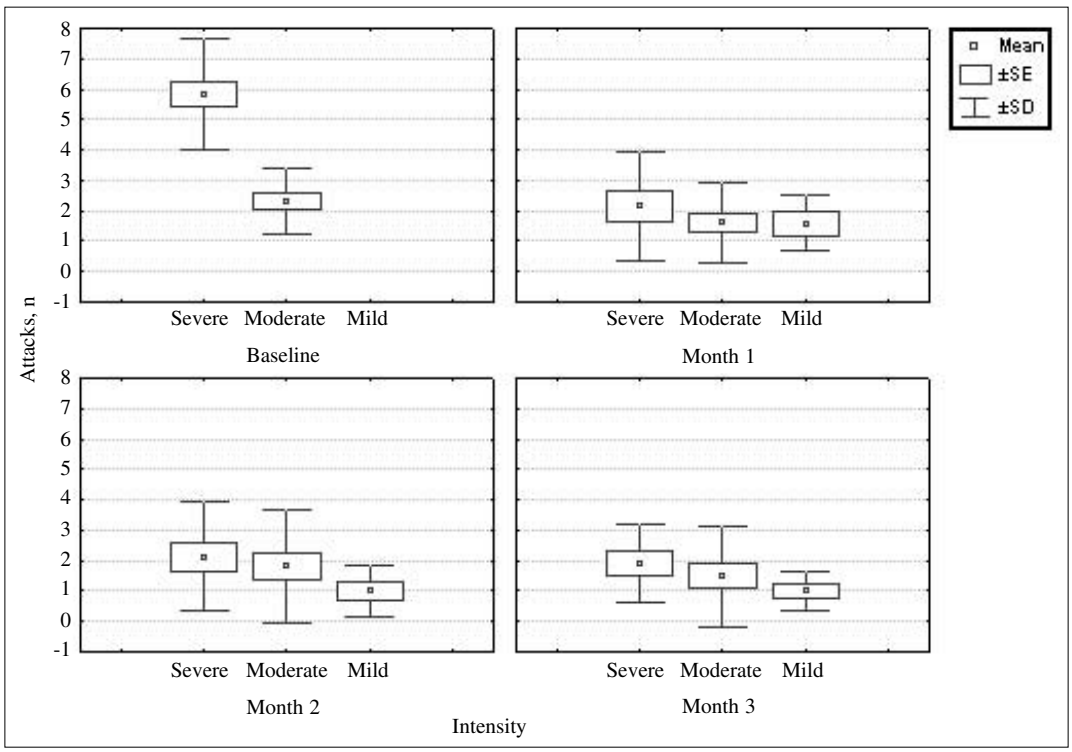

Fig. 2 Number of attacks of severe, moderate, and mild intensity per month at baseline and during the three-month treatment with levetiracetam

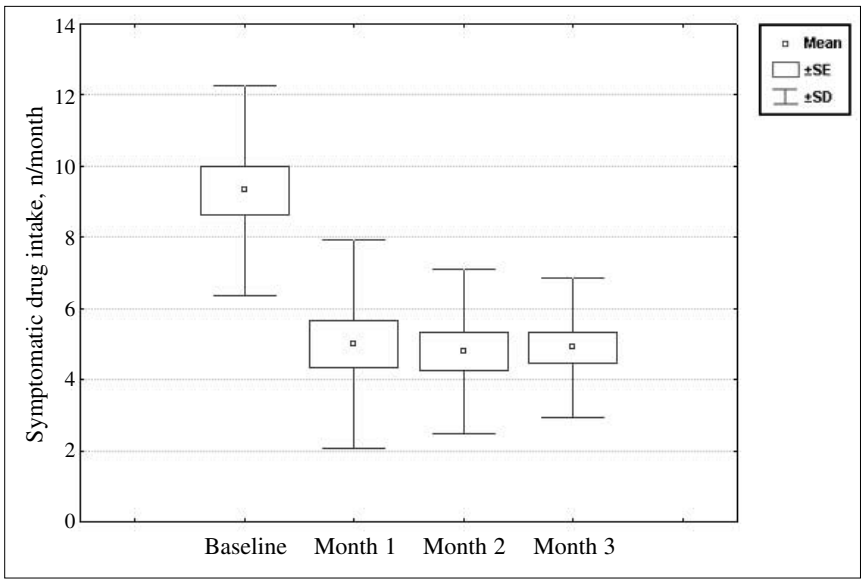

Fig. 3 Number of symptomatic drugs taken by the patients per month at baseline and during the three-month treatment with levetiracetam

Discussion

Levetiracetam, a pyrrolidine derivative belonging to the class of anticonvulsant agents, is structurally unrelated to other available anticonvulsants. Although its mechanism of action is only partially known, its efficacy as an antiepileptic drug, together with the positive results obtained with other drugs of the anticonvulsant class in migraine prophylaxis, render this drug a potential therapeutic option for the preventive treatment of migraine.

Two studies on the use of levetiracetam in the prophylactic treatment of migraine are available in the literature as abstracts [12, 13]. The first one was an open study conducted on 30 patients who had previously failed at least two other agents and had levetiracetam added to their current preventive treatment [12]. Fourteen of these patients (46.7%) reported more than 50% reduction in their migraine frequency and intensity within 3 months of active therapy. Dosage was adjusted from 2000 to 4500 mg per day in two or three doses. The authors concluded that levetiracetam could be a potential strategy in the treatment of refractory headaches [12]. A second study with the same design reached similar conclusions [13]. No serious events were reported and the rate of mild, moderate and transitory adverse events was 16.1% [13].

In our preliminary study, the short-term 12-week treatment with levetiracetam at the dosage of 2000 mg per day reduced the frequency and intensity of migraine more than 50% in a slightly higher percentage (57.9%) of patients than that reported in previous studies. This had as counterpart a significant reduction in symptomatic drug use for migraine attacks. In our research, the percentage of side effects was greater than that recorded in the second unpublished study [13], however, they were all mild and transitory and did not induce discontinuation of the drug by any of the patients. Somnolence was the most frequent side effect referred by the patients, occurring in 68.4%.

Previous experiences suggest that successful short-term prophylactic treatment of migraine may sometimes be followed by a continued respite from headaches once the treatment has been discontinued ("carry-over effect"). This has been clearly shown for sodium valproate, although the maintenance response was sustained in only a minority of patients [14]. A short-term carry-over effect seems to be evident in our study of levetiracetam in 81.8% of patients reporting a positive treatment response, and a successful sustained (3 month) treatment effect was present in about two-thirds of them. The results of this preliminary study confirm previous reports on the effectiveness of levetiracetam as a therapeutic strategy in the prophylactic treatment of migraine, considering the good tolerability and the absence of pharmacological interactions.

Because the mechanism of drug action does not seem related to any known mechanisms involved in excitatory or inhibitory neurotransmission, the most relevant antimigraine action should involve its direct effect on excitable membranes, through the inhibition of N type voltage-dependent Ca^{2+} channels. This mechanism could play an important role in antagonizing the state of neuronal hyperexcitability, in part attributed to deficient intracortical inhibitory processes evident in migraineurs, which may be the substrate for the greater susceptibility to migraine attacks [15].

Confirmation of these and previous promising results with double-blind controlled studies is warranted.

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