8. Prophylaxis therapy with levetiracetam in elderly migraine patients: An updated open-label study

Vincenzo Pizza¹, Vincenzo Busillo², Anella Agresta¹
Antonio Agresta¹ and A. Capasso³
¹Neurophysiopathology Unit, S. Luca Hospital, Vallo della Lucania (SA)
²Neurology Unit, Maria SS Addolorata Hospital, Eboli (SA)
³Department of Pharmacy, University of Salerno, Italy

Abstract. In the last years, the hypothesis that cortical hyperexcitability may play a role in the physiopathology of migraine led to the therapeutic use of some antiepileptic drugs.

To evaluate the efficacy of levetiracetam as prophylactic treatment for migraine without aura in elderly patients.

We performed a small open-label trial treating 22 elderly patients (12F 10M) mean age 67.3 years (SD 5.03), range 60-79 years affected by migraine without aura (ICDH '04 criteria). The mean age of disease was 17.9 years (SD 13.4) range 2-45 years. At baseline: the frequency of attacks was 11.9/month (SD 5.3), range 6-25; the mean number of drugs for acute attacks was 11.9 (SD 5.7) tablets/month. All patients took concomitant medication for other chronic diseases. After recruitment Levetiracetam 500 mg/die was administered for 1 week and 1000 mg/die for six months.

The basal frequency of attack was 11.9 (SD 5.3) and 8.2 (SD 4.9), 5.3 (SD 3.9), 2.4 (SD 2.4) after 1, 3 and 6 months.
respectively [P=0.021; P<0.0001; P<0.0001]. The basal value of intaking drugs for acute attacks was 11,9 (SD 5.7) and 7,1 (SD 4.8), 3,9 (SD 3.2), 1,9 (SD 2.3) after 1, 3 and six months respectively [P=0.004; P<0.0001; P<0.0001] (T-test analysis). Levetiracetam was well tolerated (10 patients complained somnolence, lack of concentration, vertigo and gastralgia but none patient withdrew the study).

In our study levetiracetam showed a good efficacy in frequency and intensity reduction of headache attack and showed a very good tolerability despite all elderly patients took drugs for concomitant diseases.

**Introduction**

Migraine preventive therapy starts after a careful evaluation of severity and frequency of attacks, in order to improve patients quality of life and to reduce the quantity of analgesics to manage pain. Criteria for the evaluation according to the Italian Neurological Society Guidelines, are fixed to at least two migraine attacks per month or lasting four or more days per month, not completely responding to symptomatic therapy [1].

Several and various drugs are used for this purpose, such as beta-blockers, Ca-antagonists, tricyclic antidepressants and, more recently, anti-epileptics have been added to this list. Naturally, the choice of each of these drugs is based not only on their efficacy, but even on the expected adverse reactions and on possible concomitant diseases in patients.

Recently the employment of antiepileptic agents aroused a big interest. As well as in epilepsy, the neurophysiopathology of migraine was identified in a cerebral cortical hyperexcitability. Such diseases are sometimes comorbid [2] and even sharing some clinical features [3]. Thus suggests a common pathogenesis, involving membrane excitability and providing a plausible explanation for anti-epileptics mechanism of action. Nociceptive mechanisms mediated by GABA or glutamate or both are sites of action of antimigraine and antiepileptic drugs [4].

Among receptors with a prevailing inhibitory activity an important role is played by GABA receptors, in particular in the neurogenic inflammation process, as it has been proven in animal experimental models using valproate [5], an anticonvulsant drug currently used in the preventative treatment of migraine, also assayed as a symptomatic of second order in the therapy of cluster headache [6]. Good results have given in the treatment of primary headache also more recent anticonvulsant like gabapentin, lamotrigine, tiagabine, topiramate and others [7,8].

GABA-A receptors are located in trigeminal sensory neurons. Valproate is provided with two mechanisms of action, being able to inhibit GABA-
transaminase, which causes GABA degradation and, at the same time, to activate glutamic - decarboxylase, that induces GABA synthesis. Therefore, following its administration, GABA extracellular concentrations in the proximity of GABAergic endings are increased [9].

Valproate, in experimental animal models, blocks dural plasmatic extravasation induced by neurogenic inflammation due either to the electric stimulation of trigeminal fibres or to the intravenous administration of substance P. For this aspect preclinical data have been obtained later than clinical evidences, when the use of valproate in migraine therapy was already consolidated, but anyhow they bring a strong support to the hypothesis that the activation of trigeminal sensory neurons is an initial step in the neurogenic inflammation process and in the pathogenesis of primary headache pain.

About GABA-B receptors they have also been implicated with migraine pathogenetic mechanisms. The coupling between GABA and GABA-B receptors induces the activation of a specific Gi-protein, exerting an inhibitory effect on the enzyme adenylate-cyclase with the reduction of intracellular cAMP levels and decreased phosphorylation: Consequently it is produced a functional block of voltage-dependent Ca++ channels involved in the neurotransmitter release. GABA-B agonists, as baclofen, then, may negatively modulate, trough these mechanisms, the release of many neurotransmitters, GABA included. Baclofen indeed has shown to inhibit the activation of trigemino-vascular system at the level of the spinal trigeminal caudatus nucleus and therefore to be furnished of a distinguished anti-nociceptive activity, observed in many clinical trials on patients suffering from migraine or cluster headache [10,11].

Levetiracetam is a molecule studied and proposed in the ‘80s as having a nootropic and anxietyotic action and later an antiepileptic action too [12]. Although the mechanism of action remains unclear, the drug appears to have a selective action on anomalous neural activities, without binding to the main receptorial sites of other anti-epileptics [13], and it seems selectively to inhibit voltage-dependent N-type calcium channels [14]. Levetiracetam has got a good pharmacokinetic profile, doesn’t interact with other medicine and is well tolerated [15].

Recently Levetiracetam has been used in migraine treatment with satisfactory results. So, basing on these physiopathogenetic, pharmacodynamic and of clinical efficacy considerations, we studied the employment of levetiracetam in migraine preventive in a group of patients with advanced age (over 60), a condition in which patients often suffer from concomitant diseases, thus provoking the use of intercurring pharmacological poly therapies.
Methods

We performed a small open-label trial treating 22 elderly patients (12F 10M) (Fig. 1) mean age 67.3 years (SD 5.03), range 60-79 years affected by migraine without aura (ICDH ’04 criteria) consecutively observed at Headache Center in S.Luca Hospital of Vallo della Lucania (SA), Italy. The mean age of disease was 17.9 years (SD 13.4) range 2-45 years.

None of the patients had ever had a migraine preventive therapy and all of them suffered from migraine for at least one year and they were using other drugs for other diseases, except one. Particularly, 13 patients were using antihypertensives (sartans, ACE-inhibitors, beta-blockers and calcium antagonists), 2 anti-diabetics (sulfonilureas) and 8 anti-cholesterols (statins) 2 antidepressivi (citalopram) 7 antiaggreganti (ASA), 1 antiulcera (pantoprazolo). The sample underwent a careful clinical (general and neurological) and instrumental (cranial CT, EEG, routine hematochemical analyses) evaluation resulted normal and was monitored through a monthly diary for attacks in absence of drugs and during a 6-month therapy. The diary allowed to give full details of frequency of attacks and analgesics consumption for each patient.

The averages of these parameters were used as primary end points for the evaluation of drug efficacy through a t-test statistical analysis. Further evaluating parameters, secondary end points, were represented by reported adverse events and possible drop-outs.

All patients took concomitant medication for other chronic diseases. After recruitment Levetiracetam 500 mg/die was administered for 1 week and 1000 mg/die for six months.

Figure 1. Sex distribution.

![Sex distribution chart](image-url)
Results

At baseline the frequency of attacks was 11.9/month (SD 5.3); the mean number of drugs for acute attacks was 11.9 (SD 5.7) tablets/month. The frequency of attack was 8.2 (SD 4.9), 5.3 (SD 3.9), 2.4 (SD 2.4) after 1, 3 and 6 months respectively with a significant reduction \([P=0.021; \text{P}<0.0001}; \text{P}<0.0001 – \text{t-test analysis}] \) compared with basal values (Fig.2). The value of intaking drugs for acute attacks was 7.1 (SD 4.8), 3.9 (SD 3.2), 1.9 (SD 2.3) after 1, 3 and six months respectively with a significant reduction \([P=0.004; \text{P}<0.0001}; \text{P}<0.0001]\)(T-test analysis) compared with basal values (Fig.3). Primary end-points of clinical efficacy evaluation based on a reduction on frequency of attacks and of drug consumption for the attack were satisfied.

Figure 2. Frequency of attacks.

Figure 3. Intaking drugs for acute attacks.
Levetiracetam was well tolerated: 10 (45.4%) (Fig. 4) patients complained somnolence, lack of concentration, vertigo and a moderate gastralgia. None of the patients withdrew the study and finally, none of them reported adverse events from the concomitant usage with previous treatments.

So, secondary endpoints referred to the evaluation of drug tolerability were satisfied too.

![Figure 4. Adverse events.]

**Discussion**

Migraine therapy divides into preventive and attack therapy, on the basis of some clinical features, such as frequency, intensity and response to drugs. When necessary, a preventive therapy includes in its equipment a series of drugs belonging to deeply different classes, among them beta-blockers, antidepressants, calcium-antagonists and more recently anti-epileptics. Obviously the choice of a drug will take into consideration not only its probable efficacy, but also any concomitant disease or other drugs already used by patients. So, a drug with a good pharmacokinetic profile, in absence of significant interactions with other drugs and with a good tolerability profile could be indicated in those categories of patients in treatment with other drugs or carriers of comorbidities. Such conditions mostly occur in the advanced age, i.e. over 60 years, when poly therapies are frequently used for concomitant diseases. Levetiracetam is a pyrrolidine derivative, the earliest example of a new class of anticonvulsant drugs, structurally not correlated to other anti-epileptics generally used [16]. Although its exact mechanism of action remains unclear, it’s a effective antiepileptic drug and as well as others of the same class, which reported data of effectiveness in migraine, has a potential employment in this disease [17-21]. Its application in migraine
preventive treatment, in particular, was reported by some open studies and especially in pediatric populations. In five open studies on adult patients suffering from migraine with and without aura an effectiveness ranging 44 and 70% at doses of 1000 and 2000 mg/die was reported. About one third of patients referred vertigo, sleepiness and irritability as adverse events [22-26].

In the 2 open studied on a pediatric population, one prospective [27] and one retrospective [28], levetiracetam has seemed efficient even though the number of patients was low (20 and 19 children, respectively). The dosage used was 40 mg/Kg/die [27] and 125-750 mg/die [28]. Side effects reported in children were asthenia, sleepiness, vertigo and behavioural changes (irritability, hyperactivity and hostility) [27,28].

Although the mechanism of action doesn’t seem to be correlated to anyone of those known in excitatory or inhibitory transmission, the most relevant anti-migraine action seems to involve its direct effect on excitable membranes through N-type voltage dependent calcium channels inhibition. This mechanism can play an important role in antagonizing the neural state of hyperexcitability partly due to defective intracortical inhibitory processes highlighted in migraineurs and which can be a substrate for the higher susceptibility to migraine attacks [29]. In particular, a mechanism implicated in its anti-migraine activity could be provoked by its inhibitory effect on glutamate release through SV2A modulation [30].

In our casistic, not numerous but referred to a particular migraine population, that is patients over 60 years, the employment of levetiracetam has been proved to be efficient and safe. We noticed, in fact, a significant reduction of attacks and of drug consumption in every follow-up, that is 1, 3 and 6 months compared to the basal. In the same time, no one of the patients withdrew the study and they referred modest adverse events, sleepiness, loss in concentration, vertigo and gastralgia. 16 of 22 patients were using other drugs to treat concomitant diseases, such as hypertension, diabetes, dyslipidemia, depression and there weren’t any significant interaction in that sense. So it is possible to conclude that this drug can be considered an useful therapeutic instrument in migraine prophylaxis, especially in specific classes of patients, such as those in poly therapy and in advanced age.

Our data may be supported by evidence suggests the usefulness of levetiracetam in the prevention of migraine [22,23]. A recent study assessed levetiracetam as prophylaxis of transformed migraine. Mean headache frequency per month at baseline was 24.9 and a significant reduction of headache frequency was obtained in 1 month (19.4, P < .001), 2 months (18.4, P < .001), and 3 months (18.0, P < .001) [31]. The most common side effects reported in these initial clinical trials included fatigue or tiredness, somnolence, dizziness, and infection (common cold or upper respiratory tract
infection). Recently, the efficacy and safety of levetiracetam for pediatric migraine was evaluated in a population of 30 children or adolescents aged 6 to 19 years (mean 12.9 years). This was a 10-week, open-label study. Among the 19 patients who completed the study, 6 patients experienced at least a 50% reduction in headache frequency and severity; 8 had at least 75% improvement; 3 became headache-free; and 2 developed worsening headaches. In 16 of the participants, disability decreased and quality of life improved, evaluated by PedMIDAS. One patient reported delusions and violent behavior; 1 patient developed a seizure disorder; 5 patients did not comply; and 4 withdrew because of lack of efficacy [32].

The role of levetiracetam for prophylaxis of refractory migraines and other headache syndromes was first described by Krusz [22]. Thirty patients who had been treated with different neuron-stabilizing agents (anticonvulsants) were enrolled in an open-label study for prophylaxis therapy with levetiracetam. Each patient in this study tried up to two different agents, and 18 patients tried up to four different agents. Levetiracetam was started at 250 mg in the evening with weekly increases. Further dosage adjustments were made during active therapy, in some cases to 4500 mg daily in two or three doses. The patients kept headache diaries and rated the severity of a headache on a 0-10 numeric rating scale. Fourteen patients reported more than a 50% reduction in their migraine frequency and severity within three months of active therapy. Eight patients had no response or they discontinued levetiracetam treatment because of adverse effects.

In their study, Drake et al [23] showed levetiracetam as a promising agent in headache prophylaxis. They gave 62 patients levetiracetam, beginning at 500 mg twice daily and increasing as needed to 1500 mg twice daily. Headache frequency and severity of refractory migraines reduced with levetiracetam therapy but not during the first month of initiation of the treatment and not on levetiracetam less than 1500 mg/day. Ten patients discontinued levetiracetam because of adverse effects, including drowsiness, vomiting, headache, and tics [23].

One retrospective study of 19 pediatric patients (9 girls and 10 boys, mean age = 11.9 years) showed the efficacy and safety of oral levetiracetam in the treatment of migraine [33]. The dosage of levetiracetam used was 125–250 mg twice daily. The frequency of headache attacks before treatment was 6.3 per month and fell to 1.7 per month after treatment in this study ($p < 0.0001$). In 10 patients (52.6%), use of levetiracetam resulted in elimination of migraine. Seven patients (36.8%) had less severe and less frequent headaches, and 2 patients (10.5%) did not appear to have any benefit from levetiracetam. No adverse effects were reported in 82.4% of patients. However, 10.5% of patients discontinued treatment because of adverse effects, including somnolence, dizziness, and irritability.
Pakalnis et al [27] prospectively evaluated the tolerability and efficacy of levetiracetam in an open-label study in 20 pediatric patients, 6-17 years old, with migraine. Levetiracetam was started at 20 mg/kg/day, and later the dosage of levetiracetam was increased to 40 mg/kg/day if migraine frequency had not changed by at least 50% at the time of the second follow-up visit after two months. Eighteen out of 20 patients had a significant reduction in headache frequency (≥ 50% reduction in monthly headache frequency). The mean ± S.D. monthly headache frequency after levetiracetam treatment was 2.0 ± 1.9, which was significantly decreased from pretreatment (p < 0.001). Four of the treated patients were migraine free. Levetiracetam was well tolerated by most of the patients, and none of the patients discontinued the drug because of its adverse effects. The adverse effects included behavioral changes, irritability, aggressiveness, and mild memory problems. These limited data are insufficient to make a convincing case for the routine use of levetiracetam in adult and pediatric patients with headache.

Recent preliminary work has also shown the efficacy of i.v. levetiracetam in treating refractory headaches [34]. Levetiracetam is a potential candidate to treat status migrainosus, cluster, and other refractory headaches in the acute setting. Farooq et al [35] described a patient with status migrainosus who responded well to the i.v. levetiracetam. However, there are very limited data about the use of levetiracetam in acute headache patients, and it is not FDA approved for the treatment of status migrainosus.

In conclusion, in our study levetiracetam showed a good efficacy in frequency and intensity reduction of headache attack and showed a very good tolerability despite all elderly patients took drugs for concomitant diseases.

References

7. Freitag FG. Preventative treatment for migraine and tension-type headaches: do drugs having effects on muscle spasm and tone have a role? CNS Drugs. 2003; 17: 373-81.