Two cases of cluster headache effectively treated with levetiracetam

Dear Sir,

Cluster headache (CH), which is characterized by recurrent attacks of short-lasting excruciating pain accompanied by signs of autonomic dysfunction (ICHD-II) (Headache Classification Subcommittee of the IHS, 2004), is the most severe of the primary headache syndromes. CH is the most common of the trigeminal autonomic cephalalgias (TACs), whose pathophysiology has not been completely elucidated (Leone and Bussone, 2009).
The treatment of CH is still debated. Verapamil (a calcium antagonist) and lithium are the first-option drugs. Several drugs have been proposed as alternative treatments, but only some of these showed limited efficacy. Recently, a new-generation antiepileptic drug, topiramate (200 mg/day), was reported to ameliorate CH (Leone et al., 2003).
Here we describe two cases of CH that became unresponsive to classical treatment and were effectively treated with levetiracetam (LEV).

***Case 1:** A 35-year-old Caucasian man was referred to our clinic with a headache that had started two months earlier. The pain was unilateral, right-sided and localized in the orbital and periorbital region. The headache was of severe intensity, had a throbbing quality, and was associated with ipsilateral conjunctival injection and rhinorrhea. The patient presented three attacks per day, each lasting 20 minutes. He did not take any medications. His neurological examination was normal. Brain magnetic resonance imaging with gadolinium and angiography sequences was normal. The acute attacks were treated with sumatriptan subcutaneously; verapamil (360 mg/day) was prescribed for prophylactic treatment, and rendered him completely pain-free within six days. Two weeks later, verapamil was stopped. When headache reappeared four months later, verapamil (with corticosteroids) was started again, but without efficacy. After that, treatments with lithium (900 mg/day) and topiramate (200 mg/day) were tried, each for one month, but had no effect. We therefore decided to use LEV, first obtaining informed consent from the patient as LEV is off label for CH. The treatment was started at 500 mg/day, which was increased to 500 mg bid after three days. The patient was pain-free after one week. The LEV treatment was stopped after four months. Four months later, the headache reappeared and we again prescribed LEV. One week later the patient was pain-free. The LEV was again discontinued after four months. Eight months after terminating the LEV regime, the patient was still pain-free. No side effects from LEV were reported.*

***Case 2:** A 46-year-old Caucasian woman was referred to our clinic with a headache that had started one month earlier. The headache was unilateral, left-sided and localized in the periorbital area but also involved the temporal region. The intensity of the headache was severe. The pain had a throbbing quality and was associated with ipsilateral lacrimation and rhinorrhea. The patient presented five attacks per day that each lasted 15 minutes. Her neurological examinations were normal. Brain magnetic resonance imaging with gadolinium and angiography sequences and cardiologic examination were normal. She began acute treatment with sumatriptan subcutaneously and prophylactic treatment with verapamil (360 mg/day) for three weeks without any effect. Lithium (900 mg/day) and then topiramate (200 mg/day) were given, each for one month, but without effect. We decided to use LEV after obtaining informed consent from the patient. The titration and final dose used were the same as in case 1. The patient was pain-free after one week. LEV was stopped after four months. Six months after the end of the treatment, the patient was still pain-free. She experienced no side effects from LEV.*

The two patients we describe meet the IHS diagnostic criteria for episodic CH (Headache Classification Subcommittee of the IHS, 2004) and both showed complete benefit from the prophylactic treatment with LEV. The drug dose required to give complete pain relief was somewhat smaller than that usually needed to obtain the anticonvulsant effect (Abou-Khalil, 2008). This is not the first evidence of the efficacy of LEV in the prevention of CH, since our group previously treated three patients affected by chronic CH with a higher dosage (1000 mg bid) of LEV (unpublished data). In these latter cases, the time needed to obtain the therapeutic effect was longer: 35-40 days to obtain complete remission of symptoms. The different types of CH (chronic vs episodic) and the individual features of the patients could explain the difference between the two observations.
In the current patients, the prophylactic treatment was maintained for four months. This time was chosen arbitrarily, taking into account the persistence of episodes for several months in both patients, the favorable safety profile of LEV, and the good compliance of the patients (only patient 1 reported a transient mild somnolence).
The present results should be interpreted with caution, considering the episodic type of the headache and the high

placebo effects reported in trials of preventive medications in migraine. However, the ineffectiveness of the other prophylactic treatments and the persistence of the therapeutic benefit of LEV in CH relapses in both patients can hardly be attributed to a purely non-specific effect.
LEV is a novel antiepileptic drug that is approved for use in the treatment of partial seizures, with or without secondary generalization. It has a favorable pharmacokinetic profile and a low potential for drug interactions. (Abou-Khalil, 2008). This antiepileptic drug represents a safe and effective alternative prophylactic treatment in migraine with aura (Brighina et al., 2006). The ability of the drug to reduce the N-type activity of high voltage-gated calcium channels (Lukyanetz et al., 2002) could at least in part explain its efficacy in preventing migraine with aura attacks. Indeed, inhibition of the N-type calcium channels, as shown in experimental animals, is able to control the initiation and propagation of cortical spreading depression, the mechanism suggested to be at the basis of the aura phenomenon.
Calcitonin gene-related peptide (CGRP) has been found to be increased in external jugular blood when measured during attacks of migraine and CH (Fanciullacci et al., 1997) and it has also been found that CGRP receptor antagonists are effective in the treatment of migraine attacks. If CGRP plays a role in migraine and in CH, the factors determining the release of CGRP in the trigeminovascular system could represent a useful target for treatment of these headache forms.
Several studies have shown that CGRP release is regulated by voltage-gated calcium channels (Xiao et al., 2008) that mediate the influx of Ca2+ into cells in response to depolarization.
It is known that LEV significantly reduces N- and P/Q-type high voltage-activated Ca2+ currents (Lee et al., 2009). Studies demonstrate that LEV affects intraneuronal Ca2+ levels by partial inhibition of the currents of N-type Ca2+. So, it could be hypothesized that the efficacy of LEV in CH could be due to the reduced release of Ca2+ from intraneuronal stores.
If other studies confirm the efficacy of LEV in CH in larger series, we will have a new option for the treatment of this severe and sometimes incapacitating condition.

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References

Abou-Khalil B (2008). Levetiracetam in the treatment of epilepsy. Neuropsychiatr Dis Treat 4: 507-523.

Brighina F, Palermo A, Aloisio A, et al (2006). Levetiracetam in the prophylaxis of migraine with aura: a 6-month open-label study. Clin Neuropharmacol 29:338-342.

Fanciullacci M, Alessandri M, Sicuteri R, et al (1997). Responsiveness of the trigeminovascular system to nitroglycerin in cluster headache patients. Brain 120:283-288.

Headache Classification Subcommittee of the International Headache Society (2004). The International Classification of Headache Disorders: 2nd edition. Cephalalgia 24 (Suppl 1): 9-160.

Lee CY, Chen CC, Liou HH (2009). Levetiracetam inhibits glutamate transmission through presynapticP/Q-type calcium channels on the granule cells of the dentate gyrus. Br J Pharmacol 158:1753-1762.

Leone M, Bussone G (2009). Pathophysiology of trigeminal autonomic cephalalgias. Lancet Neurol 8: 755-764.

Leone M, Dodick D, Rigamonti A, et al (2003). Topiramate in cluster headache prophylaxis: an open trial. Cephalalgia 23: 1001-1002.

Lukyanetz EA, Shkryl VM, Kostyuk PG (2002). Selective blockade of N-type calcium channels by levetiracetam. Epilepsia 43:9-18.

Xiao Y, Richter JA, Hurley JH (2008). Release of glutamate and CGRP from trigeminal ganglion neurons: role of calcium channels and 5-HT1 receptor signaling. Mol Pain 4:12.