

New generation anti-epileptics for facial pain and headache

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Abstract

The prophylactic management of recurrent head and facial pains may be challenging because of lack of efficacy and/or bothersome adverse effects of available drug therapies. New generation antiepileptic drugs offer new perspectives in difficult cases. We will review the available published data and present our experience with lamotrigine in various head and facial pains such as migraine, cluster headache, neuropathic trigeminal pain, atypical facial pain, and chronic tension-type headache. Twenty-five patients were enrolled and followed for 18 months. The dose was gradually increased in steps of 25 mg up to the effective dose (mean 250 mg/d). Lamotrigine was most effective in trigeminal neuralgia and dysesthesia, but was of little utility in the other head or facial pains.

Key words : Lamotrigine ; facial pain ; tiagabine ; gabapentin ; topiramate ; headache.

Introduction

Prophylactic therapies are only partially effective in head and facial pains. Classical antiepileptic drugs, such as valproate and carbamazepine (CBZ), are among the most effective drug treatments. Valproate increases GABAergic transmission, but also serotonin (Mitsikostas *et al.*, 1994), and is efficient in migraine. CBZ blocks sodium channels and is the most helpful drug in trigeminal neuralgia. Both drugs may induce unacceptable side effects.

Many of the new generation antiepileptics have a more favourable efficacy/adverse effect profile in epilepsy. They have a variety of pharmacological actions, including effects on ion channels, glutamate release, GABA transmission, or carbonic anhydrase. Those targets may be relevant in head and facial pains. For instance, sodium channel blockade may reduce neuronal excitability and transmission in pain pathways (Cummins *et al.*, 2000), reduction of glutamate release, and increase of GABA activity may inhibit spreading depression (Scheller *et al.*, 1991) ; increased pH due to carbonic anhydrase inhibition may improve voltage-dependant Ca⁺⁺ channel fonction (Haan *et al.*,

2000). Lamotrigine (LTG) (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4 – triazine) is an anti-epileptic drug now marketed worldwide for the treatment of partial and generalized epilepsy. It acts by blocking voltage sensitive sodium channels, resulting in suppression of excessive release of excitatory amino-acids, chiefly of glutamate.

We here present the results of an open pilot study of lamotrigine in various headaches and facial pains and summarize the available published data on the use of the new antiepileptics, lamotrigine, gabapentin, tiagabine, and topiramate in these pain disorders.

Patients and methods

The lamotrigine (LTG) trial was carried out in the setting of a tertiary care headache clinic.

Twenty-five patients (age : 36-86 years ; mean : 60,9) affected by migraine with aura (IHS 1.2.1.) (n = 2) and without aura (IHS 1.1.) (n = 1), chronic tension-type headache (IHS 2.2.) (n = 2), chronic cluster headache (IHS 3.1.3.) (n = 4), neuropathic trigeminal pain (n = 12 ; 7 “idiopathic” neuralgia (IHS 12.2.1.), 3 post-herpetic (IHS 12.1.4.2.) and 2 post-traumatic trigeminal (IHS 12.1.1.), or atypical facial pain (IHS 12.8) (n = 4). All patients met the diagnostic criteria of the International Headache Society Classification (Cephalalgia, 1988).

Patients with migraine had at least 3 attacks per month during the last 3 months and had been resistant to various other preventive medications. We did not include patients with other causes of chronic or recurrent pains, cardiac, hepatic or renal disease, overt depression, pregnancy or risk of pregnancy, inability or unwillingness to cooperate. The starting dose of LTG was 25 mg/day as a single dose. It was augmented by 25 mg every two weeks up to the minimum effective dose with a maximal dosage of 200 mg b.i.d. (average daily dose : 200 mg ; range : 100-400).

Symptomatic treatment of acute pain was allowed. Frequency, intensity, and duration of pain as well as use of acute medications were recorded on a diary. The main efficacy measure was the

Table 1

	n = 25	mean dose mg/day (range)	No relief	Partial pain relief ($\geq 50\%$)	Total pain relief
Neuropathic trigeminal pain	7 idiopathic	200	2	1	4
	3 post-herpetic	(100-400)	0	0	3
	2 post-traumatic	(100-300)	0	1	1
Resistant migraine	3	300	2	1 (30%)	0
	(2 MA, 1 MO)	(150-400)	4	0	0
Cluster headache	4	200 (200-200)	4	0	0
Atypical facial pain	4	400 (100-400)	3	1	0
Chronic tension- type headache	2	200 (100-300)	2	0	0

reduction of pain frequency and intensity (on a 0-3 severity scale). Follow-up was performed by examining patients and collecting diary cards every 2 months.

At each visit, patients were questioned about the eventual occurrence of adverse events.

Results

The treatment period of 18 months was completed by all 25 patients. Table 1 summarizes the results expressed as the number of patients who had partial pain relief (reduction of pain frequency by at least 50%) or total pain relief.

As far as trigeminal neuralgia is concerned, 4 out of 7 patients were pain-free at dosages between 100 and 200 mg/day. One had partial relief, while only 2 patients were totally unresponsive. Among the 5 patients with trigeminal dysesthesias, 4 had total and 1 partial relief. Hence 83% of patients with neuropathic trigeminal pains got substantial relief from LTG.

Among the 3 resistant migraineurs, one patient who suffered from migraine without aura had a 30% decrease of attack frequency at a dose of 300 mg/day. The remaining 2 who had migraine with aura had no benefit on attack frequency from LTG. One of them, however, reported a disappearance of the aura with 300 mg of LTG per day, but no change of the headache.

The 4 patients with cluster headache and the 2 patients with chronic tension-type headache were completely unresponsive at doses of 200 and 300 mg/day respectively.

The 4 patients who suffered from atypical facial pain received up to 400 mg/day of LTG and only one of them reported a partial pain relief of 50%.

None of the treated patients had a significant decrease of pain intensity without reduction in frequency. Tolerance of LTG was excellent. No patient reported bothersome adverse effects.

Discussion and review of the literature

We have performed a small open trial to evaluate the possible efficacy of **lamotrigine** in different types of head and facial pains. Despite the obvious limitations of such a study, our results are comparable to previous reports (table 2) and confirm that LTG is particularly valuable in *trigeminal neuralgia* and other neuropathic trigeminal pains at a relatively small dosage (100-200 mg/day). In published studies, LTG had a significant effect in 48-100% of patients with trigeminal neuralgia. Patients who responded to LTG did so throughout the entire 18 month-follow-up study period which may be an advantage over other anti-epileptics used in the treatment of trigeminal neuralgia (table 3). Our study suggests in addition that LTG is also an efficient valuable drug in trigeminal dysesthesias secondary to Herpes Zoster infection or to trauma.

Gabapentin, a new anti-epileptic drug with GABA mimetic effects was effective in idiopathic trigeminal neuralgia and has a most favourable efficacy/adverse event profile. In 3 open-label trials (table 3), the mean effective dose varied between 1100 and 2400 mg/day. A randomised controlled trial (Rowbotham *et al.*, 1998) showed a high efficacy of gabapentin in the treatment of postherpetic pain (33% of pain reduction versus 9% in the placebo group) with negligible adverse events despite the high dose of 3600 mg/day used in 65% of patients.

Topiramate may also be useful in the treatment of trigeminal neuralgia as suggested by the retrospective study published by Haugh and Connor (2000). Six of the 8 patients who completed the study reported good to excellent relief with a mean dose of 175 mg/day and without serious adverse events.

From our data, it appears that lamotrigine is of little value in the prophylactic treatment of

Table 2
Lamotrigine and trigeminal neuralgia

	n M-F	duration of study (months)	mean dose mg/day	Drop-out	Partial pain relief ≥ 50%	Total pain relief	No relief	Comments
Canavero <i>et al.</i> J Neurol 244 (97)	21 7-14	6	400	0	10	7	4	idiopathic trigeminal neuralgia
Borre <i>et al.</i> Epilepsy 4 (97)	4 1-3	9	150	0	2	0	2	idiopathic trigeminal neuralgia
Zakrewska <i>et al.</i> Pain 73 (97)	14 8-6	1	400	1	11	0	2	idiopathic trigeminal neuralgia
Lunardi <i>et al.</i> Neurology 48 (97)	15 9-6	4	250	0	4	11	0	idiopathic trigeminal neuralgia
Leandri <i>et al.</i> J Neurol 247 (00)	18 4-14	10	200	0	1	16	1	trigeminal neuralgia due to MS

Table 3
Gabapentin and trigeminal neuralgia

	n M-F	duration of study (months)	mean dose mg/day	Drop-out	Partial pain relief ≥ 50%	Total pain relief	No relief	Comments
Sist <i>et al.</i> Neurology 48 (97)	2 0-2	10	900 2400	0 0	1	1	0	assessment with diaries
Merren <i>et al.</i> Southern Med J (98)	7 2-5	19	1500	0	1	5	1	due to MS ; assessment with diaries and self assessment
Valzania <i>et al.</i> Neurology 50 (98)	7 3-4	3	1100	0	3	1	3	idiopathic trigeminal neuralgia

migraine. This conflicts with the results obtained by D'Andrea *et al.* (1999) (table 4) who found a prophylactic benefit of LTG in 80% patients, but all of those had migraine with aura.

Our results are in line, however, with those found in a double blind placebo-controlled parallel study of 77 patients (Steiner *et al.*, 1997). In the latter, no differences were found between LTG and placebo. Interestingly, in our study 1 of 2 patients with migraine with aura reported disappearance of the aura after LTG, without change in headache. As suggested by D'Andrea *et al.* (1999), this might suggest that LTG is able to inhibit spreading depression which is thought to be responsible for the migrainous aura (Lauritzen, 1994) and that pathogenic factors might be separate for the aura and the migraine headache (Goadsby, 2001).

Topiramate has been studied in several open label trials with moderate efficacy in migraine prophylaxis (table 5). Controlled randomised trials are underway.

Gabapentin was effective in migraine prophylaxis in a few small studies (table 6). In one of them (Merren, 1998), monthly attack frequency decreased significantly (more than 50%) in more than 80% of patients who completed the study.

Tiagabine, an other anticonvulsivant drug with GABA-mimetic effects, has been studied as a migraine prophylactic agent in only one study (Freitag *et al.*, 1999): 69% of treated patients improved on a mean regimen of 12 mg/day.

Although there is no published data on its efficacy in *cluster headache*, we used LTG (mean dose : 200 mg/day) in four patients suffering from a resistant form of this disorder. None of them improved. Other anticonvulsivants agents like sodium valproate have been used in severe cluster headache (Mathew, 1994), but its effect and clinical utility seem limited. One patient who suffered from chronic cluster headache since 2 years, became symptom-free with a dose of 1800 mg/day of gabapentin (Ahmed, 2000). No other cases have been published since.

Topiramate induced a remission in 14 out of 18 cluster headache patients at a low mean dose of 77 mg/day in the open label study of Wheeler and Carrazana (2000).

We found no effect of LTG in 2 patients suffering from *chronic tension-type headache*, despite a high dose of 300 mg/day. Although this allows no definitive conclusion because of the small number of patients, it is worth mentioning that we had

Table 4
Lamotrigine and migraine

	n M-F	duration of study (months)	mean dose mg/day	Drop-out	Partial pain relief ≥ 50%	Total pain relief	No relief	Comments
Steiner <i>et al.</i> Cephalalgia 17 (97)	77 14-63	3	200 placebo	14/37 10/40	0 0	0 0	23 30	MO (?) ou MO + MA
D'Andrea <i>et al.</i> Cephalalgia 19 (99)	24 6-18	3	100	3	6	13	2	MA
Lampl <i>et al.</i> Cephalalgia 19 (99)	15 8-7	4	100	0	4 (85%)	0	11	MA ; effect on aura symptom

Table 5
Topiramate and migraine

	n M-F	duration of study (months)	mean dose mg/day	Drop-out	Partial pain relief ≥ 50%	Total pain relief	No relief	Comments
Edwards <i>et al.</i> Cephalalgia 20 (00)	30 1-29	6	200 placebo	4 3	7/15 7/15	0 0	4 5	
Potter <i>et al.</i> Cephalalgia 20 (00)	40 1-39	5	200 placebo	3 2	5/19 2/21	0 0	11 17	MA – M0
Wilson <i>et al.</i> Cephalalgia 20 (00)	34 3-31	2	100	0	19	0	15	↓ frequency ≥ 50%
Von Seggern <i>et al.</i> Cephalalgia 20 (00)	69 13-56	6	100	20	20	0	49	↓ frequency ≥ 50%

Table 6
Gabapentin and migraine

	n M-F	duration of study (months)	mean dose mg/day	Drop-out	Partial pain relief ≥ 50%	Total pain relief	No relief	Comments
Cerbo <i>et al.</i> J Neurol Sci 150 (97)	15 6-9	3	900 1200	7/10 3/5	3 1	0 0	0 1	
Merren <i>et al.</i> Southern Med J 91 (98)	14 4-10	19	1200	3	8	3	5	
Di Tanpani <i>et al.</i> Headache (00)	22 5-17	3	1200	0	17 (75%) (65%)	0	5	MA MO

similar negative results in tension-type headache with sodium valproate (Lenaerts *et al.*, 1996).

Out of the four patients who suffered from *atypical facial pain* (IHS 12.8.) one reported partial pain relief of 50%, while the 3 others were not ameliorated despite a daily 400 mg dose of LTG. To the best of our knowledge, no trials have been performed up to now with the new generation antiepileptics in atypical facial pains.

Conclusions

Notwithstanding the methodological limitations of small open label studies, our results indicate therapeutic benefit of lamotrigine in trigeminal neuropathic pain including idiopathic trigeminal

neuralgia and post-herpetic or post-traumatic dysesthesias which is in line with previously published results. There is, however, no suggestion of a favourable effect of LTG in other head or facial pains such as migraine or cluster headache.

We have scrutinized published studies of new generation anti-epileptics in head and facial pains. Although double-blind, randomised, controlled trials are scarce, it appears that most new anticonvulsants may have a role in the management of trigeminal neuralgia (lamotrigine, gabapentin, topiramate). Topiramate may also be useful in resistant cluster headache and, as gabapentin and possibly tiagabine, in migraine. Further placebo controlled and comparative studies, however, are necessary to determine their exact place in the pharmacological armamentarium for facial pains and headache.

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