Brief Communication

Preventing Disturbing Migraine Aura With Lamotrigine: An Open Study

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Background.—Lamotrigine has been suggested as possibly effective for preventing migraine aura.

Objective.—To describe our experience with a series of patients with disturbing migraine aura treated with lamotrigine.

Methods.—The members of the Headache Group of the Spanish Society of Neurology were sent an ad hoc questionnaire to collect patients treated with lamotrigine due to disturbing migraine aura. The main outcome parameter ("response") was a >50% reduction in the mean frequency of migraine auras at 3 to 6 months of treatment.

Results.—A total of 47 patients had been treated with lamotrigine due to severe migraine aura. Three could not complete the protocol as a result of developing skin rashes. Thirty (68%) patients responded. These were 21 females and 9 males whose ages ranged from 19 to 71 years. Eight suffered from migraine with "prolonged" aura, 8 typical aura with migraine headache (but had frequent episodes including speech symptoms), 6 basilar-type migraine, 6 typical aura without headache, and 2 hemiplegic migraine. Fifteen had been previously treated, without response, with other preventatives. The mean monthly frequency of migraine auras in these 30 patients changed from 4.2 (range: 1 to 15) to 0.7 (range: 0 to 6). Response was considered as excellent (>75% reduction) in 21 cases (70% of responders). Auras reappeared in 2 months in 9 out of 13 patients where lamotrigine was stopped, and ceased as soon as this drug was reintroduced.

Conclusions.—Lamotrigine should be considered in clinical practice for the preventive treatment of selected patients with disturbing migraine auras. Lamotrigine seems worthy of a controlled trial as prophylaxis of migraine aura.

Key words: lamotrigine, migraine aura, migraine prophylaxis

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Migraine auras occur in about 15% of migraineurs, usually develop over 5 to 20 minutes, and last less than 60 minutes.[1] Patients with short and infrequent migraine auras usually require no pharmacological treatment but only diagnostic reassurance. There are a few migraine patients, however, for whom treatment of migraine aura would be welcomed. Those include patients with prolonged (>60 minutes) and/or frequent migraine auras, especially if the aura contains speech disturbances, posterior fossa symptoms, or profound hemiparesis. None of the current acute migraine medications are useful in the specific treatment of migraine aura. In fact, triptans have been reported to be inefficacious when given during migraine aura, both failing to abort the aura, and to prevent the subsequent pain[2] and ergotamine-containing medications should be administered with caution during the aura phase due to their potent vascular effects.[3] There have been

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several scattered reports showing some benefit with i.v. verapamil,[4,5] i.v. furosemide,[6] and intranasal ketamine[7] in the specific treatment of migraine with prolonged aura. In the biggest trial, intranasal ketamine reduced the duration and severity of neurologic deficits in only 5 out of 11 patients and induced significant adverse events.[7]

Experience in the prevention of migraine aura is also either scarce or negative. Beta-blockers remain the preventive treatment of choice for the most standard migraine patients. These drugs, however, have been incriminated as a potential contributor to migrainous stroke and are not recommended in disturbing migraine aura.[8-11] To our knowledge, there is no published specific experience for flunarizine with this indication. Regarding the two antiepileptic drugs with demonstrated antimigraine efficacy, valproic acid was reported as being useful in two patients with persistent migraine aura,[12] while in a recent open trial topiramate was not effective in preventing aura in 12 migraine patients.[13]

Lamotrigine has been tested in the prophylaxis of migraine headache in a placebo-controlled trial and proved to be of little value in reducing the frequency of migraine attacks.[14] This sodium channel blocker, however, was shown to be efficacious in preventing migraine aura in three different open trials including a total of 38 patients.[15-17] The aim of this open trial has been to explore further the possible efficacy of lamotrigine in the prevention of migraine aura in patients with disturbing migraine aura.

PATIENTS AND METHODS

After some neurologists had reported positive experiences with lamotrigine in patients with migraine aura at our Annual Meeting held in November 2002, the 88 active members of the Headache Group of the Spanish Society of Neurology were sent an ad hoc questionnaire to collect those patients treated with lamotrigine due to disturbing migraine aura. All patients gave verbal informed consent. Neurologists could include patients both retrospectively or also those treated prospectively until November 2003. To be eligible for this study patients should refer to a history of disturbing migraine aura, that is, the reason for their preventive treatment should obligatorily be the aura symptomatology, due to its high frequency or/and severity. Therefore, only patients meeting criteria for typical aura without headache, hemiplegic migraine, basilar-type migraine, persistent aura without infarction, and migraine-triggered seizure were included in this analysis.[1] Without exception, all had normal extensive laboratory determinations, including work up for an underlying coagulopathy, and neuroimaging (CT and usually MRI brain scans). Patients fulfilling criteria for typical aura with migraine headache were only included if, usually, the aura was prolonged, contained reversible aphasia and/or the episodes were frequent. All the patients had to have suffered from these migraine variants for at least 1 year and presented at least one attack per month in the last 3 months. Exclusion criteria included any prophylactic treatment of headache within the last 2 weeks prior to the beginning of the trial and previous treatment or contraindications to lamotrigine. There was no fixed dosing protocol, even though most investigators had begun with 25 mg at night and increased 25 mg per week usually until reaching a minimum dose of 100 mg. The main outcome parameter ("response") was a >50% reduction in the mean frequency of migraine auras at 3 to 6 months of treatment as compared to that of the 3 months prior to treatment. We considered response as "excellent" if reduction in the frequency of migraine auras >75%. Patients with a reduction in aura frequency <50% were considered as nonresponders.

RESULTS

A total of 47 patients had been treated with lamotrigine due to disturbing migraine aura. Three could not complete the protocol as a result of developing skin rashes. Thirty (68%) out of the 44 patients responded.

There was no clear difference in any available parameter (age, sex, diagnosis, dosage, etc.) between those responders and nonresponders; henceforth, we will focus on the analysis of the responders' group. They were 21 females and 9 males, whose ages ranged from 19 to 71 years. Eight patients in fact met diagnostic criteria for typical aura with migraine headache, but had frequent episodes including aphasia. Eight suffered from probable migraine with aura (all migraine with prolonged aura according to the previous IHS Classification), six basilar-type migraine, six typical

Summary of Clinical Data and Frequency of Migraine Aura at Baseline and During Treatment (Responders)

No.	Age	Sex	Daily Dose (mg)	Diagnosis	Frequency Before Treatment	Frequency After Treatment
1	69	F	100	Aura without headache	1/month	0/month
2	71	F	100	Aura without headache	3/month	0/month
3	53	F	100	Aura without headache	4/month	1/month
4	41	F	100	Aura without headache	5/month	0/month
5	60	F	50	Aura without headache	4/month	1/month
6	30	F	50	Migraine with prolonged aura	4/month	0/month
7	56	F	50	Migraine with typical aura	15/month	6/month
8	27	F	50	Migraine with prolonged aura	1/month	0/month
9	45	F	100	Migraine with prolonged aura plus aura-triggered seizures	1/month	0/month
10	30	F	50	Migraine with typical aura	10/month	1/month
11	25	F	200	Basilar-type migraine	4/month	0/month
12	27	M	50	Migraine with typical aura	3/month	1/month
13	29	M	100	Migraine with typical aura	3/month	0–1/month
14	44	M	100	Migraine with prolonged aura	3/month	0–1/month
15	41	F	200	Migraine with prolonged aura	10/month	1–2/month
16	55	M	200	Basilar-type migraine plus aura-triggered seizures	1/month	0/month
17	43	F	100	Migraine with typical aura	5/month	0/month
18	41	M	200	Migraine with typical aura	4/month	1/month
19	45	F	100	Migraine with typical aura	4/month	1–2/month
20	55	F	50	Migraine with typical aura	8/month	1–2/month
21	25	M	75	Basilar-type migraine	2/month	0/month
22	51	F	100	Basilar-type migraine	3/month	1–2/month
23	34	F	75	Migraine with prolonged aura	3/month	1–2/month
24	44	M	100	Sporadic hemiplegic migraine	2/month	0–1/month
25	38	F	100	Migraine with prolonged aura	2/month	0/month
26	34	M	100	Migraine with prolonged aura	3/month	1/month
27	20	M	300	Basilar-type migraine plus aura-triggered seizures	2/month	0/month
28	18	M	150	Familial hemiplegic migraine	3/month	0/month
29	45	M	150	Basilar-type migraine	4/month	1/month
30	45	F	100	Aura without headache	8/month	0/month

aura without headache, and two hemiplegic migraine (one familial and one sporadic). There was a history of occasional migraine-triggered seizures in three patients. Fifteen had been previously treated, without response, with β-blockers (n = 3), amitriptyline (n = 6), calcium antagonists (n = 10), valproic acid (n = 11), topiramate (n = 1), or carbamacepine (n = 4). The doses of lamotrigine ranged from 50 to 300 mg/day (mean = 110 mg daily; mode = 100 mg daily).

The mean monthly frequency of migraine auras in these 30 patients changed from 4.2 (range: 1 to 15) to 0.7 (range: 0 to 6) (Table). Response was considered as excellent in 21 cases (70% of the responders). Lamotrigine was stopped after 6 to 12 months in 13 patients. In four cases the auras did not come back, but this was followed by a recurrence of migraine auras within 2 months in nine patients. Lamotrigine was reintroduced in these nine patients with immediate response in all of them. Regarding the 17 patients left, 7 decided to remain on lamotrigine for more than 1 year (up to 4 years) due to their excellent response and for the remaining 10 no follow-up information is available as they have just completed the sixth month of treatment.

Demonstrative Clinical Case.—This 45-year-old woman began 20 years ago with very infrequent episodes of progressive hemianoptic visual disturbances, accompanied by paresthesias in one arm lasting 45 to 90 minutes. The episodes occurred on both

sides and included dysphasia when the left hemisphere was involved. She denied posterior headache. Complete laboratory determinations, including study of prothrombotic conditions, EEG, echocardiogram, carotid Doppler, transcranial Doppler, brain MRI, and MRI angiography were normal. During spring 2002, she experienced an increase in the frequency of these episodes to 8/month. In July 2002, she began taking valproic acid, 1 g/daily, with no response after 2 months. In October 2002, lamotrigine, up to a dose of 50 mg/12 h, was initiated with total disappearance of these episodes. Lamotrigine was tapered in August 2003. Fifteen days after lamotrigine had been stopped she again began to experience two to three similar episodes/week. Lamotrigine was reintroduced with no further episodes after a 6-month follow-up.

COMMENTS

The results of this trial concur with previous observations indicating a specific benefit of lamotrigine in preventing migraine aura.[15-17] Our data add further evidence to this potential beneficial effect of lamotrigine. First, this is the trial with the highest number of patients. Second, 36 out of the 38 reported patients previously treated with lamotrigine met criteria for migraine with typical aura, while only patients with disturbing, atypical migraine aura were included in this study, which makes it easier to test a specific benefit of lamotrigine on migraine aura.

Migraine is an unpredictable disease with a remarkable placebo effect. The fact that this is an open trial and partly retrospective obliges us to interpret the results with great caution. Nevertheless, the careful selection of patients with only severe auras, the fact that half of our responders had not shown any benefit with other preventatives and the prompt reappearance of the auras in most patients who stopped this treatment further support lamotrigine as a useful drug in this indication. These results do not agree with those reported in a double-blind, placebo-controlled, parallel study on the efficacy of lamotrigine in 53 migraine with and without aura patients.[14] In this trial there was no significant difference between active and placebo; however, the results for the 14 migraine with aura patients were not specifically given.

Is there any explanation for a specific effect of lamotrigine on migraine aura? Glutamate has been involved as the key neurotransmitter in the development and propagation of the neurophysiological correlate of the aura, the cortical spreading depression phenomenon.[18] Plasma and cerebrospinal glutamate levels are higher in migraine with aura that in migraine without aura.[19-21] Lamotrigine acts by blocking voltage-sensitive sodium channels, leading to an inhibition of the neural release of glutamate.[22-24] Therefore, if high glutamate levels were responsible for cortical spreading depression and the clinical symptoms of migraine aura, lamotrigine might suppress this phenomenon and thus prevent aura development. Lamotrigine also attenuates calcium influx via its effect on high-voltage-activated calcium channels and prevents calcium overload in neurons. The effective suppression of aura symptoms of lamotrigine may be due to the potent presynaptic and postsynaptic inhibition of glutamate, indicating that lamotrigine would act as a noncompetitive NMDA antagonist.[25,26]

In conclusion, lamotrigine should be considered in clinical practice for the preventive treatment of selected patients with disturbing migraine auras. Lamotrigine seems worthy of a controlled trial as prophylaxis of aura/migraine with patent aura.

REFERENCES

1. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 2nd edition. *Cephalalgia*. 2004(suppl 1):1-160.
2. Bates D, Ashford E, Dawson R, et al. Subcutaneous sumatriptan during the migraine aura. Sumatriptan Aura Study Group. *Neurology*. 1994;44:1587-1592.
3. Silberstein SD, McCrory DC. Ergotamine and dihydroergotamine: history, pharmacology and efficacy. *Headache*. 2002;43:144-146.
4. Yu W, Horowitz SH. Familial hemiplegic migraine and its abortive therapy with intravenous verapamil. *Neurology*. 2001;57:1732-1733.
5. Yu W, Horowitz SH. Treatment of sporadic hemiplegic migraine with calcium-channel blocker verapamil. *Neurology*. 2003;60:120-121.
6. Rozen TD. Treatment of a prolonged migrainous aura with intravenous furosemide. *Neurology*. 2000;55:732-733.

7. Kaube H, Herzog J, Kaufer T, Dichgans M, Diener HC. Aura in some patients with familial hemiplegic migraine can be stopped by intranasal ketamine. *Neurology*. 2000;55:139-141.
8. Prendes JL. Considerations on the use of propranolol in complicated migraine. *Headache*. 1980;20:93-95.
9. Gilbert GJ. An occurrence of complicated migraine during propranolol therapy. *Headache*. 1982;22:81-83.
10. Bardwell A, Trott JA. Stroke in migraine as a consequence of propranolol. *Headache*. 1987;27:381-383.
11. Mendizabal JE, Greiner F, Hamilton WJ, Rothrock JF. Migrainous stroke causing thalamic infarction and amnesia during treatment with propranolol. *Headache*. 1997;37:594-596.
12. Rothrock JF. Successful treatment of persistent migraine aura with divalproex sodium. *Neurology*. 1997;48:261-262.
13. Lampl C, Bonelli S, Ransmayr G. Efficacy of topiramate in migraine aura prophylaxis: preliminary results of 12 patients. *Headache*. 2004;44:174-176.
14. Steiner TJ, Findley LJ, Yuen AWC. Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. *Cephalalgia*. 1997;17:109-112.
15. Chen WT, Fuh JL, Lu SR, Wang SJ. Persistent migrainous visual phenomena might be responsive to lamotrigine. *Headache*. 2001;41:823-825.
16. D'Andrea G, Granella F, Cadaldicini N, Manzoni GC. Effectiveness of lamotrigine in the prophylaxis of migraine with aura: an open study. *Cephalalgia*. 1999;19:64-66.
17. Lampl C, Buzath A, Klinger D, Neuman K. Lamotrigine in the prophylactic treatment of migraine aura—a pilot study. *Cephalalgia*. 1999;19:58-63.
18. Lauritzen M. Pathophysiology of the migraine aura. *Brain*. 1994;117:199-210.
19. Castillo J, Martínez F, Leira R, Prieto JM, Lema M, Noya M. Changes in neuroexcitatory amino acids during and between migraine attacks. *Neurología*. 1994;9:42-45.
20. Martínez F, Castillo J, Rodríguez JR, Leira R, Noya M. Neuroexcitatory amino acid levels in plasma and cerebrospinal fluid during migraine attacks. *Cephalalgia*. 1993;13:89-93.
21. Cananzi AR, D'Andrea G, Perini F, Zamberlan F, Welch KMA. Platelet and plasma levels of glutamate and glutamine in migraine with and without aura. *Cephalalgia*. 1995;15:132-135.
22. Welch KMA, D'Andrea G, Tepley N, Barkley G, Ramadan NM. The concept of migraine as a state of central neuronal hyperexcitability. *Neurol Clin*. 1990;8:817-828.
23. Lang DG, Wang CM, Cooper BR. Lamotrigine, phenytoin and carbamazepine interactions on the sodium current present in N4TG1 mouse neuroblastoma cells. *J Pharmacol Exp Ther*. 1993;266:829-835.
24. Leach MJ, Lees G, Riddal DR. Lamotrigine. Mechanisms of action. In: Levy RH, Mattson RH, Meldrum BS, eds. Antiepileptic Drugs, 4th edition. New York: Raven Press; 1995:861-819.
25. Stefani A, Spadoni F, Siniscalchi A, Bernardi G. Lamotrigine inhibits Ca2+ currents in cortical neurons: functional implications. *Eur J Pharmacol*. 1996;307:113-116.
26. Wang SJ, Tsai JJ, Gean PW. Lamotrigine inhibits depolarization-evoked Ca influx in dissociated amygdale neurons. *Synapse*. 1998;29:355-362.