Subcutaneous histamine versus sodium valproate in migraine prophylaxis: a randomized, controlled, double-blind study

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Histamine has a selective affinity for H3-receptors and it may specifically inhibit the neurogenic edema response involved in migraine pathophysiology. The objective of this study was to evaluate the therapeutic potential of subcutaneous administration of histamine in migraine prophylaxis, compared with oral administration of sodium valproate, in an open clinical trial. Ninety-two patients with migraine were selected under criteria established by the International Headache Society and enrolled in a 12-week double-blind controlled clinical trial to evaluate the efficacy of subcutaneous administration of histamine (1–10 ng twice a week; $n = 46$) compared with oral administration of sodium valproate (500 mg daily dose; $n = 46$). The variables studied were headache intensity, frequency, duration, analgesic intake and migraine disability assessment (MIDAS). Two-tailed Student's *t*- test was used to compare means and the Mann–Whitney *U* and ANOVA tests were used. The data collected during the 4th, 8th and 12th weeks of treatment revealed that histamine caused a significantly greater reduction ($P < 0.001$) in intensity and duration of migraine attacks as well as in analgesic intake. No difference was detected in the frequency of attacks or in MIDAS. The present study provides evidence of the superior efficacy of histamine applied subcutaneously in migraine prophylaxis when compared with sodium valproate taken orally. Subcutaneously applied histamine may represent a novel and effective therapeutic alternative in resistant migraine patients.

Introduction

Epidemiological data suggest that preventive medication may be indicated for a large proportion of persons suffering from migraine (about 50%), but only about 10% of those individuals are receiving preventive therapy [1]. In recent years, there has been a proliferation of pharmacological agents used in migraine prophylaxis [2,3]. The cause and pathophysiology of migraine are not well understood [4], but prolonged treatment with [beta]-blockers, valproate, topiramate, methysergide, or amitriptyline reduced the number of potassium-evoked cortical spreading depressions and elevated the electrical stimulation threshold for their induction in rats [5]. Divalproex, is an antiepileptic drug (AED) that has received Food and Drug Administration approval for migraine management [6–9]. In 1991, we carried out an initial study [10] that provided evidence for the beneficial effects of histamine in migraine prophylaxis. Our data showed that subcutaneous administration of low doses (1–10 ng) of histamine induced significant relief from migraine symptoms, with no secondary effects. The possible mechanisms of histamine migraine prophylaxis, can be explained by histamine control of mast cells; the antidromic stimulation of trigeminal nerve endings induces the release of substance P and other neuromodulatory peptides, which in turn stimulate the release of histamine from mast cells. In meningeal blood vessels, activation of H1-receptors (H1-R) by histamine, results in vasodilatation and plasma protein extravasation, causing neurogenic inflammation [11]. Work by Krabbe and Olesen [12] and by Lassen *et al*. [13] showed that on migrainous subjects, intravenous administration of relatively high doses of histamine (0.5 μg/kg per minute for 20 min) caused an immediate headache during the infusion, followed by a delayed migraine attack which was abolished by pre-treatment with the H1-R antagonist, mepyramine. However, degranulation of mast cells and neuropeptide release from C fibers endings are inhibited by the histamine at low-concentration interaction with H3-receptors (H3-R), and probably reflects a local

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feedback circuit between C-fiber nerve endings and mast cells, which control neurogenic inflammation [14–17]. Therefore, it is reasonable to assume that the administration of low doses of histamine, to achieve and maintain low-circulating concentrations, may lead to a selective interaction of histamine with H3-R. Histamine could constitute a new therapeutic drug in migraine prophylaxis that acts by limiting the excessive inflammatory response involved in migraine pathophysiology.

The objective of this study is to evaluate the therapeutic potential of the subcutaneous administration of histamine in migraine prophylaxis, compared with sodium valproate by undertaking an open clinical trial.

Methods

This was a 12-week randomized, controlled, double-blind study [18,19] in 92 patients diagnosed with recurrent migraine unresponsive to available abortive (acetaminophen, ergotamine, dexamethasone, and sumatriptan) and/or prophylactic agents (propranolol, amitriptyline, and verapamil), patients were identified and recruited from the general population visiting neurologists and physicians of other specialities and the migraine diagnosis was independently confirmed by a second member of the research team [20–22]. The procedure was explained to them and they were invited to take part in the study. All participants signed a letter of consent in accordance with the Helsinki statement. The patients were male or female adults between the ages of 18 and 65 years, all having a history of migraine for several years. Pregnant women, patients suffering daily headaches, as well as patients whose radiological tests, including computer-assisted tomography, revealed any pathology were excluded from the study. Selected patients underwent a 1-month period of prophylactic agent washout, during which headache frequency was monitored. Based on histamine-placebo controlled studies [10], they were then divided into two groups for treatment in randomized blocks of three, double-blind fashion: the histamine study group ($n = 46$) and the sodium valproate control group ($n = 46$). This randomization was carried out by a research collaborator who throughout the duration of the study had no contact with the patients and prepared vials containing either 10 ng/ml subcutaneous histamine or oral placebo (flour) for the histamine group and 250 mg oral sodium valproate twice per day or subcutaneous placebo (Evan's solution = phenol 0.4%, isotonic sodium chloride) for sodium valproate group. The vials were numbered and identical in appearance, which allowed the blinding to be effective as neither the patients nor the physicians were able to identify the vehicle or active drug. The regimen began with the administration (back region of the upper arm) of 0.1 ml volume of subcutaneous histamine which was consecutively increased (by 0.1 ml) until reaching 1.0 ml. Continuous repetition of this protocol, beginning again with 0.1 ml volume administration was carried out for a period of 12 weeks. A dose of 250 mg oral sodium valproate was administered twice a day, during the first week, each subject received 500 mg/day of sodium valproate; after the first week, subjects received four tablets of sodium valproate (1000 mg/day). During treatment, patients were allowed to take 500 mg acetaminophen tablets if they had moderate or severe headache with an intensity value of two on a scale of 1–3, and lasting for more than 8 h. The variables studied [18] were: (i) headache frequency, measured by numbers of attacks per month, (ii) intensity of pain (scale from 1 to 3), (iii) duration of pain, measured by hours of headache per attack, (iv) intake of rescue analgesics, measured by the number of acetaminophen tablets (500 mg) taken per month, and (v) Migraine Disability Assessment (MIDAS) [23]. Values for the parameters studied were collected over a period of 4 weeks before initiation of treatment (baseline), and efficacy and safety assessments were carried out every 30 days for 3 months. Serum levels of sodium valproate were routinely checked and the investigator had the option to decrease the dose to 500 mg/day for the remainder of the 12 weeks of the trail if deemed necessary because of intolerance. Patients were instructed to keep a daily record of events. The relationship between an adverse event and study treatment was assessed by the investigator as none, possible, probable, or definite. Patients who abandoned the study were still taken into account in the final statistical analysis: average descriptive statistics and standard deviations were applied to data obtained. Two-tailed Student's *t*-test was used to compare means and the Mann–Whitney *U* and ANOVA tests were used as a multivariable study in the inferential statistics. With an α at 0.5% and β at 80%, $P < 0.05$ was considered significant [24]. The study was approved by the Ethical and Scientific Committee of our hospital.

Results

A total of 86.3% patients were female and the mean age was 32 years ± 9.7 (range 16–50). Headache duration was 15 years and headache frequency was 3.8 headaches per month. Forty-six patients (50%) were randomized to histamine, and 41 completed the treatment. Forty-six (50%) were randomized to sodium valproate, and 40 completed the treatment. The treatment groups were similar at baseline based on demographic and clinical characteristics (Table 1); for all variables studied,

Table 1 General and clinical characteristics of patients (before undergoing period washout of prophylactic agents)

Feature	Histamine ($n = 46$)	Sodium valproate ($n = 46$)
Age [mean years (SD)]	32.6 (9.76)	31.5 (8.59)
Male	7	8
Female	39	38
Years of migraine (mean ± SD)	15.3 (6.23)	14.70 (8.42)
Migraine type		
with aura	4	6
Without aura	42	40
Age at onset, mean years (SD)	17.38 (10.16)	18.00 (8.82)
Baseline MIDAS, mean score (SD)	66.0 (10.6)	68.7 (8.2)
Frequency of headaches per 30-day period at baseline, mean score (SD)	4.4 (2)	4.0 (0.8)
Intensity of headache at baseline[a]	3	3
Duration of headache (hours), mean score (SD)	39 (3)	37 (8)
Tablets/month of rescue, mean score (SD)	18 (13.2)	21.6 (10.40)

[a]Intensity of headache. Scales 1–3: (1-minimum), (2-moderate), and (3 severe); SD, standard deviation; MIDAS, Migraine Disability Assessment.

the statistical analysis of data collected, showed no significant differences between baseline values obtained for the histamine and the sodium valproate treated groups ($P > 0.05$). By the beginning of the 4th week of treatment, analysis of the temporal course of events showed a significant decrease (with respect to basal values) in the magnitude of all parameters studied, as a result of the histamine or sodium valproate administration schema followed ($P < 0.001$). For values found for the 8th week of treatment, comparison between both groups (Fig. 1), revealed that histamine treatment exerted a significant ($P < 0.001$) higher reduction (comparatively with sodium valproate) on intensity, duration of migraine attacks, as well as on the use of rescue medication. Eighty-seven percent of patients receiving histamine reported a 53% reduction in headache intensity $P < 0.001$ (mean, 3 ± 0.6 before treatment vs. 1 ± 0.5 after treatment), whereas 58% of patients receiving sodium valproate reported a 33% reduction (mean, 3 ± 0.8 before treatment vs. 2 ± 0.7 after treatment. Eighty-four percent of patients receiving histamine reported an 82% reduction in headache duration $P < 0.001$ (mean, 39 ± 3 h of headache per attack; before treatment vs. 6 ± 8 h of headache per attack; after treatment), whereas 54% of patients receiving sodium valproate reported a 17% reduction (mean, 37 ± 8 h before treatment vs. 20 ± 0.5 h after treatment). In rescue medication, 83% of patients receiving histamine reported a 53% reduction in the number of tablets ingested $P < 0.001$ (mean, 18 ± 13.2 acetaminophen tablets per month before treatment vs. 5 ± 3.7 acetaminophen tablets per month after treatment), whereas 77% patients receiving sodium valproate reported a 25% reduction (mean 21.6 ± 10.40 acetaminophen tablets per month before vs. 11.25 ± 9.40 acetaminophen tablets per month after treatment). No difference was observed between frequency and MIDAS. Eighty-seven percent of patients receiving histamine reported a 39% reduction in headache frequency $P > 0.05$ (mean, 4.4 ± 2 attacks per month before treatment vs. 1.8 ± .7 attacks per month after treatment), whereas 62% of patients receiving sodium valproate reported a 28% reduction (mean 4 ± 0.8 attacks per month before treatment vs. 2.2 ± 0.5 attacks per month after treatment). Eighty percent of patients receiving histamine reported a 49% reduction in MIDAS (mean, 66 ± 10.6 before treatment vs. 42 ± 6 after treatment), whereas 70% of patients receiving sodium valproate reported a 45% reduction $P > 0.05$ (mean, 68 ± 8.2 before treatment vs. 38 ± 6.5 after treatment). After 12 weeks of treatment, the effects of histamine and sodium valproate remained identical to the values found at the 8th week. The treatment group reported transitory burning and itching at the injection site, but no significant ($P > 0.05$) differences in these side effects between the two groups developed to impede the blinding of the assay or the planned order of events. There were no modifications in arterial tension or cardiac frequency in either group for the duration of the study, nor were there any alterations in the laboratory analyses performed at the beginning and end of the study.

Eleven patients left the study because they were not satisfied with the speed of the results. Six of these patients stopped taking sodium valproate during the first weeks because of the side effects, the most common of which was nausea (37%). Other side effects included tremor (34%), weight gain (24%), and alopecia (12%) and the dose was reduced to 500 mg/day for the remaining patients to continue the study without adverse events. Five patients from the histamine group abandoned the study even though they did not present any side effects.

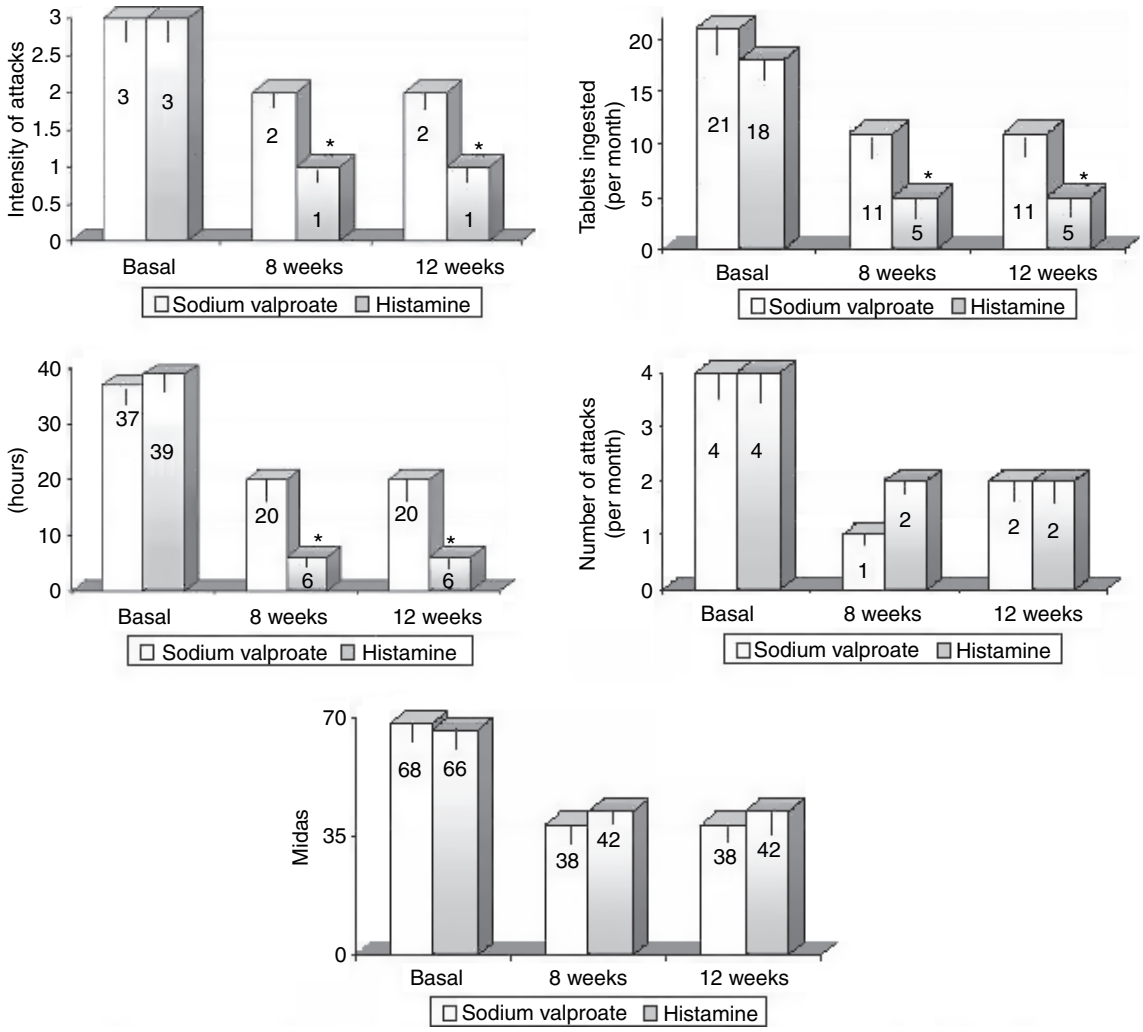

Figure 1 Effects induced (in 92 patients with recurrent migraine) by the subcutaneous administration (twice a week, during 12 weeks) of histamine ($n = 46$) and sodium valproate ($n = 46$) on the intensity, duration, and frequency of migraine attacks; Migraine Disability Assessment (MIDAS), as well as on the consumption of 500 mg acetaminophen tablets used as rescue medication during headache. Data correspond to mean values [plus standard error of the mean (SEM)] obtained during a 4-week period prior to initiation of treatment (basal), and to 8 and 12 weeks of treatment $^*P < 0.001$.

Discussion

It has been demonstrated that high concentrations of histamine activate H1-R, producing vasodilatation and release of nitric oxide [25], which conduces to neurogenic edema and is responsible for the acute phase of migraine [11–17]. Our data reveal that the administration of histamine, at very-low doses (0.1–1 ng), induces a significant relief of migraine symptoms without complications. This finding may be explained on the grounds of the control of mast cells by histamine acting at H3-R, which involves neuropeptide-containing nerves, and presumably, reflects the operation of a local C fiber nerve ending/mast cell feedback loop controlling neurogenic inflammation. Altogether the results obtained in this and in placebo-controlled previous studies [10], show that histamine is a safe drug with therapeutic potential in migraine prophylaxis, exercising specific mechanisms on pathophysiological processes involved in this disease. Although there are well-designed placebo-controlled studies that demonstrate the effectiveness of several prophylactic medications in patient populations with less headache burden, tolerability continues to be an issue for many patients as reflected by the high-discontinuation rates (13–21%) [26,27]. Tolerability issues may be one reason that prophylactic medications are vastly underutilized for those with migraine, even when the patients meet the frequency or disability criteria for the use of prophylactic medications [28–31]. Migraineurs do not mind using more than

one preventive agent at a time if greater efficacy can be achieved. Agents that can affect weight and/or cause sedation may be important factors as to why patients (especially females) would not want to take a preventive medication. For patients with more than one disease, treatment should be modified to include all conditions. For example, both migraine and epilepsy can be managed with a mood-stabilizing AED, such as divalproex [32]. Caution must be exercised with the use of divalproex sodium in women of childbearing potential. Migraineurs in this population want to be involved in the decision-making process of choosing a migraine preventive, and want their physician to explain in depth the side effect profile of the particular preventive agent chosen [33]. Low concentrations of histamine (1–10 ng) has become a therapeutic alternative in our medical consultations in patients presenting recurrent migraine who do not respond to diverse antimigraine drugs and it is our treatment of choice in migraine patients over 60 years of age who have hypotension or cardiac rhythm alterations, and in whom the usual drugs are contraindicative (β-adrenergic), or in patients having developed secondary gastritis and cannot tolerate further oral drug therapy [34]. The reason why migraine patients are not receiving migraine prevention may be due to lack of recognition of migraine-related disability by physicians, but there is also a barrier created by the patient to taking daily medication. Twice-weekly, subcutaneous application has been accepted in our practice by patients, who have not been satisfied with the daily administration of other medications.

A cross-over study was not carried out, because of the fact that the use of drugs having a prolonged therapeutic effect does not lend itself well to such a study. Sample size and the fact that the patients in the study were recruited from the general population and not from a headache specialty clinic are limitations of the present study.

References

1. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache* 2001; **41:** 646–657.
2. Lohman JJ, Van der Kuy-de Ree MM. Patterns of specific antimigraine drug use-a study based on the records of 18 community pharmacies. *Cephalalgia* 2005; **25:** 214–218.
3. Silberstein SD. Preventive treatment of headaches. *Current Opinion in Neurology* 2005; **18:** 289–292.
4. Cutrer FM. Pathophysiology of migraine. *Seminars in Neurology* 2006; **26:** 171–180.
5. Sanchez-Del-Rio M, Reuter U, Moskowitz MA. New insights into migraine pathophysiology. *Current Opinion in Neurology* 2006; **19:** 294–298.
6. Cutrer FM, Moskowitz MA. Wolff Award 1996. The actions of valproate and neurosteroids in a model of trigeminal pain. *Headache* 1996; **36:** 579–585.
7. Mathew NT, Saper JR, Silberstein SD, *et al*. Migraine prophylaxis with divalproex. *Archives of Neurology* 1995; **52:** 281–286.
8. Klapper J. Divalproex sodium in migraine prophylaxis: a dose-controlled study. *Cephalalgia* 1997; **17:** 103–108.
9. Silberstein SD, Collins SD. Safety of divalproex sodium in migraine prophylaxis: an open-label, long-term study. Long-Term Safety of Depakote in Headache Prophylaxis Study Group. *Headache* 1999; **39:** 633–643.
10. Millán-Guerrero RO, Isais CM, Antonio OA, Pacheco-Carrasco MF. Histamine as a therapeutic alternative in migraine prophylaxis: a randomized, placebo-controlled, double-blind study. *Headache* 1999; **39:** 576–580.
11. Akerman S, Williamson DJ, Kaube H, Goadsby PJ. The role of histamine in dural vessel dilation. *Brain Research* 2002; **956:** 96–102.
12. Krabbe AA, Olesen J. Headache provocation by continuous intravenous infusion of histamine: clinical results and receptor mechanisms. *Pain* 1980; **8:** 253–259.
13. Lassen LH, Thomsen LL, Olesen J. Histamine induce migraine vía the H1 receptor support for the NO hypothesis of migraine. *Neuroreport* 1995; **6:** 1475–1479.
14. Dimitriadou V, Rouleau A, Dam Trung Tuong M, *et al*. Functional relationship between mast cells and C-sensitive nerve fibres evidenced by histamine H3-receptor modulation in rat lung and spleen. *Clinical Science* 1994; **87:** 151–163.
15. Arrang J-M, Garbarg M, Schwartz J-C. Auto-inhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. *Nature* 1983; **302:** 832–837.
16. Arrang J-M, Garbarg M, Lancelot J-C, *et al*. Highly potent and selective ligands for histamine H3 receptors. *Nature* 1987; **327:** 117–123.
17. Ishikawa S, Sperelakis N. A novel class (H3) of histamine receptors on perivascular nerve terminals. *Nature* 1987; **327:** 158–160.
18. International Headache Society committee on clinical trials in migraine. Guidelines for controlled trials of drugs in migraine. *Cephalalgia* 1991; **11:** 1–12.
19. Lipchik GL, Nicholson RA, Penzien DB. Allocation of patients to conditions in headache clinical trials: randomization, stratification and treatment matching. *Headache* 2005; **45:** 419–428.
20. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgia and facial pain. *Cephalalgia* 1988; **8**(Suppl. 7)**:** 1–96.
21. Olesen J, Bousser M-G, Diener H-CH, Dodick D, First M, Goadsby PJ, *et al*. Second Headache Classification subcommittee members. International classification of headache disorders, 2nd edn. *Cephalalgia* 2004; **24**(Suppl. 1)**:** 1–160.
22. Eriksen MK, Thomsen LL, Olesen J. Sensitivity and specificity of the new international diagnostic criteria for migraine with aura. *Journal of Neurology, Neurosurgery and Psychiatry* 2005; **76:** 212–217.
23. Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical utility of an instrument assessing migraine disability: the Migraine Disability Assessment (MIDAS) questionnaire. *Headache* 2001; **41:** 854–861.

24. Hulley SB, Gove S, Cummings SR. Elección de los individuos que participarán en el estudio: especificación y muestreo. In: Hulley SB, Cummings SR, eds. *Diseño de la Investigación Clínica*. España: Harcourt Brace, 1997: 21–55.
25. Thomsen LL, Olesen JB. Nitric oxide in primary headache. *Current Opinion in Neurology* 2001; **14:** 315–321.
26. Brandes JL, Saper JR, Diamond M, *et al*. Topiramate for migraine prevention: a randomized controlled trial. *Journal of the American Medical Association* 2004; **291:** 965–973.
27. Silberstein SD, Neto W, Schmitt J, Jacobs D. Topiramate in migraine prevention: results of a large controlled trial. *Archives of Neurology* 2004; **61:** 490–495.
28. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. *Neurology* 2002; **58:** 885–894.
29. Lipton RB, Diamond S, Reed M, Diamond ML, Stewart WF. Migraine diagnosis and treatment: results from the American Migraine Study II. *Headache* 2001; **41:** 638–645.
30. Buchanan TM, Ramadan M. Prophylactic pharmacotherapy for migraine headaches. *Seminars in Neurology* 2006; **26:** 188–198.
31. Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD; BOTOX CDH Study Group. Botulinum toxin type a for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. *Headache* 2005; **45:** 315–324.
32. Silberstein SD, Lipton RB, Breslau N. Migraine: association with personality characteristics and psychopathology. *Cephalalgia* 1995; **15:** 358–369.
33. Meador KJ, Baker GA, Finnell RH, *et al*. In utero antiepileptic drug exposure. Fetal death and malformations. *Neurology* 2006; **67:** 407–412.
34. Millan-Guerrero R, Trujillo-Hernández B, Tene CE. Histamina subcutánea en profilaxis de migraña. Efectos iniciales y seguimiento a largo plazo. *Neurología* 2006; **21:** 55–59.

