Original Paper

European Neurology

Eur Neurol 2008;59:237–242
DOI: 10.1159/000115637

Received: May 16, 2007
Accepted: August 31, 2007
Published online: February 8, 2008

Subcutaneous Histamine versus Topiramate in Migraine Prophylaxis: A Double-Blind Study

R.O. Millán-Guerrero[a] R. Isais-Millán[b] S. Barreto-Vizcaíno[a] I. Gutiérrez[a]
L. Rivera-Castaño[c] B. Trujillo-Hernández[a] L.M. Baltazar[a]

[a]Department of Neurology, Unidad de Investigación Médica en Epidemiología Clínica, Hospital General de Zona UMF No 1 IMSS Colima, Colima, [b]Instituto Tecnológico y de Estudios Superiores de Monterrey, Monterrey, [c]Department of Neurology, Hospital CIMA, Chihuahua, México

Key Words
Migraine prophylaxis · H3 receptor · Subcutaneous histamine

Abstract
Background: Histamine has a selective affinity for H3 receptors and it may specifically inhibit the neurogenic edema response involved in migraine pathophysiology. ***Objective:*** To evaluate the therapeutic potential of subcutaneous administration of histamine in migraine prophylaxis, compared with oral administration of topiramate. ***Methods:*** Ninety patients with migraine were selected in a 12-week double-blind controlled clinical trial to evaluate the efficacy of subcutaneous administration of histamine (1–10 ng twice a week) compared with oral administration of topiramate (100 mg daily dose). The variables studied were: headache intensity, frequency, duration, analgesic intake and Migraine Disability Assessment. ***Results:*** The data collected during the 12 weeks of treatment revealed that headache symptoms improved in both the histamine and topiramate groups, which was evident within the first month after the initiation of treatment, with statistically significant ($p < 0.001$) reductions in headache frequency (50%), Migraine Disability Assessment score (75%), intensity of pain (51%), duration of migraine attacks (45%), as well as in the use of rescue medication (52%). ***Conclusion:*** The present study provides evidence of the efficacy of subcutaneously applied histamine and orally administered topiramate in migraine prophylaxis. Subcutaneously applied histamine may represent a novel and effective therapeutic alternative in resistant migraine patients.

Introduction

Migraine affects approximately 10–14.7% of the general population and is 2–3 times more common in women than in men [1, 2]. Prophylactic migraine treatment is recommended when headache frequency is greater than 2 times per week [3–5]. Antiepileptic drugs such as magnesium valproate, gabapentin, and topiramate are among the diverse drugs used in migraine prophylaxis. Magnesium valproate has an efficacy percentage of 50%, gabapentin of 46%, and topiramate of 26–47% [6–11]. Topiramate, at a dose of 100 mg/day has demonstrated efficacy

Study presented at the 8th Headache Congress of the European Headache Federation, April 2006, Valencia, Spain.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0014–3022/08/0595–0237$24.50/0

Accessible online at:
www.karger.com/ene

Rebeca O. Millán-Guerrero, MD
J. Jesús Ponce No 538
Lomas de Circunvalación CP 28010
Colima, Col. (México)
Tel./Fax +52 1312 314 17 57, E-Mail millanrebeca@hotmail.com

in migraine prevention in several clinical trials. Despite the diversity of drugs used in migraine prophylaxis, there is a 10–30% therapeutic failure rate with periodic migraine attack persistence, high drug consumption [12] and a significant deterioration in quality of life. As yet, few of the drugs employed in migraine prophylaxis act on specific mechanisms related to migraine pathophysiology [13–15]. In spite of the fact that the cause and pathophysiology of migraine are not well understood, they appear to involve a relationship between brain metabolic and cerebrovascular dysfunction. This activates pain pathways which cause a series of events ending in neurogenic inflammation, an important component in migraine that is perhaps genetically determined [16]. Topiramate is reported to have multiple action mechanisms that could contribute to migraine prophylaxis. In 1991, we carried out an initial study [17] 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. These findings can be explained by histamine's control of mast cells, acting on H3 receptors which engage the nerves containing neuropeptides. This probably reflects a local feedback circuit between C-fiber nerve endings and mast cells, which control neurogenic inflammation [18–22]. Histamine could constitute a new therapeutic drug in migraine prophylaxis, and the objective of this study was to evaluate in a clinical trial the therapeutic potential of subcutaneous administration of histamine in migraine prophylaxis compared with oral administration of topiramate.

Methods

This was a 12-week randomized, controlled, double-blind study [23, 24] in 90 patients diagnosed with relapse of headache who were unresponsive to available abortive (acetaminophen, ergotamine, dexamethasone, sumatriptan) and/or prophylactic agents (propranolol, amitriptyline, verapamil), without sustained pain-free response, with an attack frequency of 3–5 per month, a severity of 2–3, and overuse of acute pharmacotherapy. Patients came from multiple physicians and neurologists and their diagnoses were independently confirmed by a second member of the research team [25–27]. 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, those with a history of nephrolithiasis, and 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. They were then divided into two groups for treatment in randomized blocks of three, in a double-blind fashion: the histamine study group (n = 45) and the topiramate control group (n = 45). 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, and 100 mg oral topiramate or subcutaneous placebo (Evan's solution = phenol 0.4%, isotonic sodium chloride). The vials were numbered and identical in appearance, which allowed the blinding to be effective since neither the patients nor the physicians were able to identify the vehicle or active drug. The treatment consisted of subcutaneous (back region of the upper arm) administration of histamine (10 ng/ml in Evan's solution) 1–10 ng twice a week. The regimen began with the administration of 0.1-ml volume of either subcutaneous histamine or placebo, 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) and 100 mg topiramate (50 mg/day for the first week, followed by weekly increases of 25 mg) or subcutaneous placebo twice a week was carried out for a period of 12 weeks. During treatment, patients were allowed to take 500 mg acetaminophen tablets if they had moderate or severe headache with an intensity value of 2 on a scale of 1–3, and lasting for more than 8 h. The variables studied [23] were: (1) headache frequency, measured by numbers of attacks per month; (2) intensity of pain (scale from 1–3); (3) duration of pain, measured by hours of headache per attack; (4) intake of rescue analgesics, measured by the number of acetaminophen tablets (500 mg) taken per month, and (5) Migraine Disability Assessment (MIDAS) [28]. 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 a period of 12 weeks. 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 analysis.

Statistical Analysis

Average descriptive statistics and standard deviations were applied to data obtained. The Wilcoxon rank-sum test was used to assess the statistical significance of differences between treatment groups in baseline characteristics (age, years since onset, age at onset); two-tailed Student's t test was used to compare mean of the MIDAS variable to determine if a difference exists between two groups, and the evaluation of statistical significance for differences found between values for both groups during the aforementioned weeks of treatment was performed using a Mann-Whitney U rank sum test. In order to analyze the temporal course of each treatment (for each variable studied), a Friedman repeated-measures ANOVA on ranks test was used to evaluate the statistical significance of differences between basal values and values found for the 4th, 8th, and 12th weeks of treatment. With an alpha at 0.5 and beta at 0.20, $p < 0.05$ was considered significant [29]. Statistical analysis of data was carried out using the Statistical Package for Social Sciences program v10.0. The study was approved by the ethical and scientific committee of our hospital.

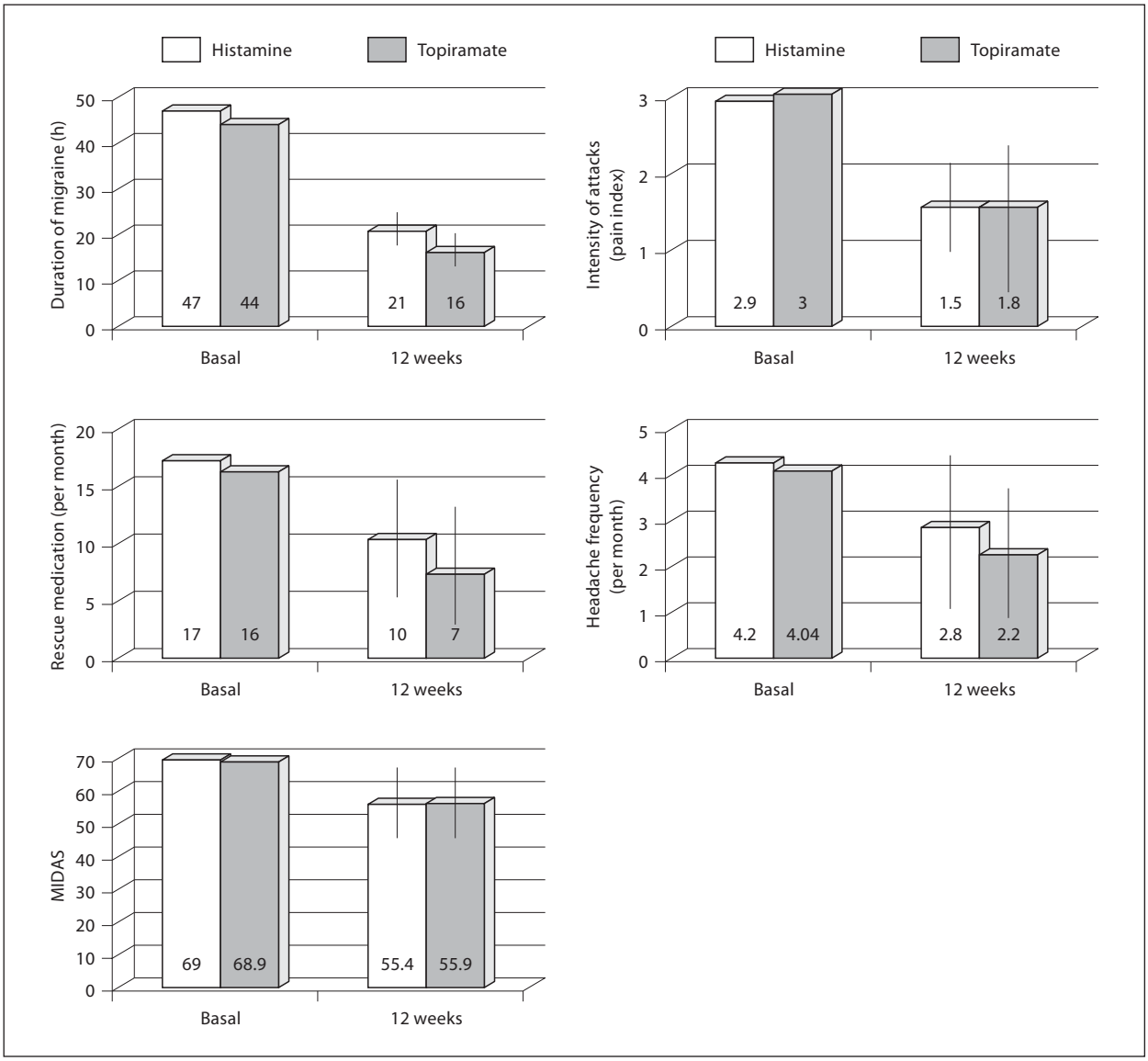

Fig. 1. Effects induced by the subcutaneous administration (twice a week, during 12 weeks) of histamine (n = 45) and topiramate (n = 45) on the intensity, duration, frequency of migraine attacks, MIDAS, and on the consumption of 500-mg acetaminophen tablets used as rescue medication during headache in 90 patients with recurrent migraine. Data correspond to mean values (SEM) obtained during a 4-week period prior to initiation of treatment (basal), and after 12 weeks of treatment ($p < 0.001$).

Results

From the total of 90 patients enrolled and randomized into the 2 groups (histamine n = 45; topiramate n = 45), 40 in the histamine group and 35 in the topiramate group completed the study. A total of 86% of the patients were female (40 female/5 male in the histamine group and 44 female/1 male in the topiramate group) and mean age was 32 years ± 10.4 (range 18–60). Headache duration was 14 ± 9.3 years and frequency of migraine attacks was 4.12 (95% CI 1.23–1.89) per month. The treatment groups were similar at baseline based on demographic and clinical characteristics (table 1) for all variables studied. The statistical analysis of data collected showed no significant differences between the baseline values obtained for the histamine and the topiramate treatment groups ($p > 0.05$). We compared the response of one group to its baseline and the differential response of one group to the oth-

er. Analysis of the temporal course of events showed that by the beginning of the 4th week, there was a significant decrease (with respect to basal values) in the magnitude of all parameters studied, as a result of the schema followed for the administration of histamine ($p < 0.001$) or topiramate ($p < 0.001$). The same was found for values at the 8th, and 12th weeks of treatment (fig. 1). Histamine and topiramate group comparison revealed that histamine showed no significant differences for any of the variables analyzed with confidence intervals. Comparison between both groups (table 2) revealed a significant ($p < 0.001$) reduction in duration of migraine attacks: Sixty-four percent of patients receiving histamine reported a 45% reduction in duration of migraine attacks $p < 0.001$ (mean 47.4, 95% CI 17.8–22.7 h of headache per attack before treatment vs. 21.08, 95% CI 8.1–6.3 h of headache per attack after treatment), whereas 66% of patients receiving topiramate reported a 43% reduction ($p < 0.001$; mean 44.1, 95% CI 18.1–22.5 h of headache per attack before treatment vs. 16, 95% CI 7.2–8.4 h of headache per attack after treatment). Regarding rescue medication, 74% of patients receiving histamine reported a 52% reduction in the number of tablets ingested ($p < 0.001$; mean 17.2, 95% CI 10.1–9.2 acetaminophen tablets per month before treatment vs. 10.8, 95% CI 4.2–5.1 acetaminophen tablets per month after treatment), whereas 58% of patients receiving topiramate reported a 34% reduction ($p < 0.001$; mean 16.8, 95% CI 8.5–4.5 acetaminophen tablets per month before treatment vs. 7.5, 95% CI 5.2–4.1 acetaminophen tablets per month after treatment. For pain intensity, topiramate treatment exerted a significant reduction: 87% of patients receiving topiramate reported a 51% reduction in headache intensity ($p < 0.001$; mean 2.9, 95% CI 1.3–0.2 before treatment vs. 1.5, 95% CI 0.5–0.2 after treatment), whereas 60% of patients receiving histamine reported a 53% reduction in the intensity of pain ($p < 0.001$; mean 3, 95% CI 1.8–0.5 before treatment vs. 1.8, 95% CI 0.6–0.3 after treatment. No difference was observed between headache frequency and MIDAS. Sixty-six percent of patients receiving histamine reported a 50% reduction in headache frequency ($p < 0.001$; mean 4.20, 95% CI 1.2–1.8 attacks per month before treatment vs. 2.8, 95% CI 1–1.2 attacks per month after treatment); 60% of patients receiving topiramate reported a 55% reduction ($p < 0.001$; mean 4.04, 95% CI 1.3–1.6 attacks per month before treatment vs. 2.2, 95% CI 0.8–1.1 attacks per month after treatment). In MIDAS, 56% of patients receiving histamine reported a 75% reduction ($p < 0.001$; mean 69.04, 95% CI 10.2–15.8 before

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

Feature	Histamine (n = 45)	Topiramate (n = 45)
Age, years	32.81 (9.93)	32.16 (10.9)
Sex, m/f	5/40	1/44
Years of migraine	14.82 (9.01)	14.92 (10.02)
Migraine type		
With aura	3	5
Without aura	42	40
Age at onset, years	16.23 (9.21)	17.05 (8.82)
Baseline MIDAS score	69.04 (6.21)	67.12 (6.16)
Frequency of headaches per 30-day periods at baseline	4.20 (1.6)	4.04 (1.2)
Intensity of headache at baseline[1]	2.92 (0.5)	2.90 (0.6)
Duration of headache, h	47.12 (21.3)	44.40 (21.4)
Rescue medication tablets/month	17.8 (9.44)	16.3 (8.47)

Values are expressed as mean (SEM) except for sex and migraine type.

[1] Scale 1–3 (1 – minimum, 2 – moderate, 3 – severe).

Table 2. Efficacy response measures – comparison of treatment groups

Variable	Histamine 1–10 ng (n = 45)			Topiramate 50 mg/day (n = 45)			F	Significance
	baseline	12 weeks	p	baseline	12 weeks	p		
Number of attacks per month	4.20 (100)	2.8 (50), CI 1–1.2	<0.001	4.04 (100)	2.2 (55), CI 0.8–1.1	<0.001	1.6	0.42
Headache duration, h	47.4 (100)	21.08 (45), CI 6.3–8.1	<0.001	44.1 (100)	16 (43), CI 7.2–8.4	<0.001	1.9	0.16
Intensity of attacks (1–3 scale)	3 (100)	1.8 (53), CI 0.3–0.6	<0.001	2.9 (100)	1.5 (51), CI 0.2–0.5	<0.001	1.3	0.24
Tablets ingested per month	17.2 (100)	10.8 (52), CI 4.2–5.1	<0.001	16.8 (100)	7.5 (34), CI 4.1–5.2	<0.001	2.4	0.12
MIDAS	69.04 (100)	55.4 (75), CI 9.8–11.2	<0.001	CI 4.5–8.5 68 (100)	55 (78), CI 10.8–11.1	<0.001	2.3	0.12

Figures in parentheses are percentages. F values from ANOVA between groups (4–12 weeks; d.f. = 1.89).

treatment vs. 55.4, 95% CI 11.2–9.8 after treatment), and 62% of patients receiving topiramate reported a 78% reduction ($p < 0.001$; mean 68, 95% CI 11.2–9.6 before treatment vs. 55, 95% CI 11.1–10.8 after treatment). After 12 weeks of treatment, the effects of histamine and topiramate were identical to the values found at the 8th week.

Twenty-two percent (10/45) of the study patients in the topiramate group receiving 100 mg/day withdrew early from the trial after the first 3 weeks due to adverse events which complicated the blinding. The most common adverse effect was paresthesia (47%), and other side effects included dizziness (34%), and fatigue (24%). One patient presented with the complications of cognitive dysfunction, psychiatric/behavioral disturbances, somnolence and fatigue. The dose was then reduced to 50 mg/day in the remaining patients in order to continue the study without adverse events. Eleven percent (5/45) of patients in the histamine group withdrew without adverse events, because they were not satisfied with the speed of the results even though they did not present any side effects; some transitory burning and itching at the injection site was reported, but it was not significant enough 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; neither were there any alterations in the laboratory analyses performed at the beginning and end of the study.

Discussion

During the study, headache symptoms improved in both the histamine and topiramate groups, and this was evident within the first month after the initiation of treatment. There were statistically significant reductions in headache frequency (50%), MIDAS (75%), intensity of pain (51%), duration of migraine attacks (45%) and use of rescue medication (52%). Taking into account that the efficacy of medications often becomes apparent while clinical practice is being carried out [30], the results obtained in this and in previous placebo-controlled studies [17] show that histamine is a safe drug with therapeutic potential in migraine prophylaxis, exercising specific mechanisms on pathophysiological processes involved in this disease. The degranulation of mast cells and neuromodulatory peptides released from C-fiber endings are inhibited by the histamine interaction with H3 receptors, representing local feedback circuit between C-fiber nerve endings and mast cells, controlling neurogenic inflammation [18–22, 31]. This equality was advantageous since we are dealing with an established treatment, and topiramate has received FDA approval for migraine prophylaxis. If histamine is determined to be at least as beneficial as topiramate, it will be considered to be an effective alternative without complications and with better tolerability.

Tolerability continues to be an issue for many patients, as reflected by the high discontinuation rates (13–21%), and may be one reason that prophylactic medications are vastly underutilized for those with migraine. Migraineurs want to be involved in the decision-making process of choosing a migraine preventive, and they want their physician to explain in depth the side effect profile of the particular preventive agent chosen [32]. Even though our data showed that the administration of histamine (1–10 ng) induced a significant relief of migraine symptoms, without complications, the prophylactic migraine treatment should be individualized [33]. Low concentrations of histamine (1–10 ng) have become a therapeutic alternative in our medical consultations in patients presenting with recurrent migraine who do not respond to β-adrenergic or calcium channel blockers, and it is our treatment of choice in migraine patients who have hypotension or cardiac rhythm alterations, and in whom the usual drugs are contraindicative. Subcutaneous histamine could constitute a new therapeutic drug in migraine prophylaxis in patients having developed secondary gastritis who cannot tolerate further oral drug therapy.

Treatment with histamine has minimal side effects such as insomnia and transitory pain at the injection site and an inconvenience is that it must be kept refrigerated at 5°C.

A limitation of this study is the sample size. A significant increase in sample size will be required in further studies.

References

1 Pearce JMS: Migraine. Eur Neurol 2005;53:109–110.
2 Patel NV, Bigal ME, Kolodner KB, Leotta C, Lafata JE, Lipton RB: Prevalence and impact of migraine and probable migraine in a health plan. Neurology 2004;63:1432–1438.
3 Bigal ME, Lipton RB: The preventive treatment of migraine. Neurologist 2006;12:204–213.
4 Silberstein SD: Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55:754–762.

5 Buchanan TM, Ramadan M: Prophylactic pharmacotherapy for migraine headaches. Semin Neurol 2006;26:188–198.
6 Silberstein SD, Hulihan J, Karim MR, Wu SC, Jordan D, Karvois D, Kamin M: Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. Clin Ther 2006;28:1002–1011.
7 Edwards KR, Potter DL, Wu SC, Kamin M, Hulihan J: Topiramate in the preventive treatment of episodic migraine: a combined analysis from pilot, double-blind, placebo-controlled trials. CNS Spectr 2003;8:428–432.
8 Mathew NT, Kailasam J, Meadors L: Prophylaxis of migraine, transformed migraine, and cluster headache with topiramate. Headache 2002;42:796–803.
9 Silberstein SD, Neto W, Schmitt J, Jacobs D, MIGR-001 Study Group: Topiramate in migraine prevention: results of a large controlled trial. Arch Neurol 2004;61:490–495.
10 Brandes JL, Kudrow DB, Rothrock JF, Rupnow MF, Fairclough DL, Greenberg SJ: Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clin Proc 2006;81:1311–1319.
11 Silberstein SD: Topiramate in migraine prevention: evidence-based medicine from clinical trials. Neurol Sci 2004;(suppl 3):S244–S245.
12 Lohman J, Van der Kuy-de Ree M: Patterns of specific antimigraine drug use – a study based on the records of 18 community pharmacies. Cephalalgia 2005;25:214–218.
13 Shields KG, Goadsby PJ: Propranolol modulates trigeminovascular responses in thalamic ventroposteromedial nucleus: a role in migraine? Brain 2005;128:86–97.
14 Sanchez-Del-Rio M, Reuter U, Moskowitz MA: New insights into migraine pathophysiology. Curr Opin Neurol 2006;19:294–298.
15 Buzzi MG, Moskowitz MA: The pathophysiology of migraine: year 2005. J Headache Pain 2005;6:105–111.
16 Waeber CH, Moskowitz MA: Migraine as an inflammatory disorder. Neurology 2005; 64(suppl 2):S9–S15.
17 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.
18 Thomsen LL, Olesen JB: Nitric oxide in primary headaches. Curr Opin Neurol 2001;14: 315–321.
19 Dimitriadou V, Rouleau A, Dam Trung Tuong M, Newlands GJF, Miller HRP, Luffau G, Schwartz J-C, and Garbarg M: Functional relationship between mast cells and C-sensitive nerve fibers evidenced by histamine H3-receptor modulation in rat lung and spleen. Clin Sci 1994;87:151–163.
20 Olesen J, Jansen-Olesen I: Nitric oxide mechanism in migraine. Pathol Biol (Paris) 2000; 48:648–657.
21 Arrang JM, Garbarg M, Schwartz JCH: Auto-inhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. Nature 1983;302:832–837.
22 West RE, Zweig A, Shih N-Y, Siegel MI, Egan RW: Identification of two H3-histamine receptor subtypes. Mol Pharmacol 1990;38: 610–613.
23 International Headache Society committee on clinical trials in migraine. Guidelines for controlled trials of drugs in migraine. Cephalalgia 1991;11:1–12.
24 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.
25 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.
26 International Classification of Headache Disorders, ed 2. Cephalalgia 2004;24:1–160.
27 Olesen J: International Classification of Headache Disorders, Second Edition (ICHD-2): current status and future revisions. Cephalalgia 2006;26:1409–1410.
28 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.
29 Hulley SB, Gove S, Cummings SR: Elección de los individuos que participarán en el estudio: especificación y muestreo; en Hulley SB, Cummings SR (eds): Diseño de la Investigación Clínica. Madrid, Harcourt Brace, 1997, pp 21–55.
30 Ljung O: Metoprolol in migraine. Cephalalgia 1981;1:142.
31 Akerman S, Williamson DJ, Kaube H, Goadsby PJ: The role of histamine in dural vessel dilation. Brain Res 2002;956:96–102.
32 Rozen TD: Migraine prevention: what patients want from medication and their physicians. A headache specialty clinic perspective. Headache 2006;46:750–753.
33 Silberstein SD: Preventive treatment of migraine. Rev Neurol Dis 2005;2:167–175.