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Prophylactic Activity of Increasing Doses of Intravenous Histamine in Refractory Migraine: Retrospective Observations of a Series of Patients With Migraine Without Aura

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ABSTRACT

Background: Histamine is thought to play a pivotal role in the modulation of peripheral and central pain. The administration of increasing doses of histamine may lead to desensitization of receptors of histamine types 1 and 2, causing meningeal vasodilation, and to depletion of neuropeptides in the trigeminal ganglion, thus inhibiting the initiation of migraine.

Objective: In this study, the efficacy and tolerability of increasing doses of IV histamine in migraine prophylaxis were investigated.

Methods: This single-center, open-label, retrospective, controlled study was conducted at the Headache Center (Department of Internal Medicine, University of Florence, Villa Monna Tessa, Italy). Patients included in the study had 3 to 6 migraines without aura per month that were refractory to common symptomatic and prophylactic agents in the 6 months preceding the study. Patients were treated with IV histamine hydrochloride for 21 days starting with a dosage of 0.5 mg/d and increasing to 4.0 mg/d. To assess the efficacy of the treatment, these patients were matched for age; sex; and frequency, duration, and severity of attacks with untreated migraineurs. *Clinical benefit* was defined as $\leq$1 migraine of mild intensity per month. Tolerability was assessed during the hospitalization period, and patients were instructed to contact the Headache Center to report any adverse effects after hospital discharge.

Results: The histamine group comprised 47 patients (40 women, 7 men; mean [SD] age, 42.0 [8.6] years) and the control group comprised 23 patients (20 women, 3 men; mean [SD] age, 38.8 [8.4] years). The histamine-treated patients showed a clinical benefit lasting for a mean of 10.4 (4.2) months, while the patients in the control group showed a clinical benefit of 3.8 (1.9) months.

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The difference in the duration of the clinical benefit between the 2 groups was 6.6 months (95% CI, 5.15–7.99). Adverse effects consisted of flushing, heat sensation during infusion, headache, and palpitations.

Conclusions: In this study, histamine showed lasting prophylactic efficacy in migraineurs. If further research confirms this preliminary finding, histamine could be considered when established prophylactic drugs, such as beta-blockers, calcium antagonists, antidepressants, and antiepileptics, have not been effective. (*Curr Ther Res Clin Exp.* 2004;65:70–78) Copyright © 2004 Excerpta Medica, Inc.

Key words: histamine, migraine, prophylaxis.

INTRODUCTION

Histamine is thought to play a pivotal role in the modulation of pain. Histamine is involved peripherally in the stimulation of nociceptive fibers, while it seems to have a centrally important role in antinociception.[1] Histamine seems to be involved in the pathophysiology of pain in migraine through different mechanisms. In migraine patients, the administration of histamine or the nitric oxide (NO) donor glyceryl trinitrate induces headache during infusion, followed by a typical migraine.[2,3] Histamine probably induces migraine by activating NO synthase, thereby promoting endogenous NO production.[4,5] NO causes immediate dilation of meningeal blood vessels, which provokes headache; this dilation is partially blocked by sumatriptan succinate and indomethacin.[6] Migraineurs experience a stronger headache than nonmigraineurs, possibly because of hypersensitivity in the NO–cyclic guanosine monophosphate pathway.[3] Also, some evidence shows that neurogenic inflammatory processes of the meninges cause the severe pain in migraine and cluster headaches.[7,8] Substance P (SP) and neurokinin A (NKA) are responsible for plasma extravasation in the dura mater, and calcitonin gene-related peptide (CGRP) seems to mediate the increase in meningeal blood flow. During migraine, an increase in CGRP levels has been described in venous flow from the head.[9] The release of neuropeptides leading to neurogenic inflammation in the vessels of the dura mater may be secondary to algesiogenic mediators (bradykinin, histamine, serotonin), which primarily activate the trigeminal nociceptive afferent nerves. These inflammatory mediators cause a massive release of CGRP and prostaglandin E_2 from the dura mater. The same effect can be obtained by electrical stimulation of the trigeminal ganglion.[10]

We hypothesized that administration of increasing doses of histamine would lead to desensitization of histamine types 1 and 2 (H_1 and H_2, respectively) receptors, causing meningeal vasodilation, and to depletion of neuropeptides in the trigeminal ganglion, thus inhibiting the initiation of migraine. Several classes of drugs (eg, beta-blockers, calcium antagonists, antidepressants, and antiepileptics) have shown prophylactic activity in migraine.[11–22] However, in our experience, these drugs are not always effective. At the Headache Center (Department of Internal Medicine, University of Florence, Villa Monna Tessa,

Italy) in the past, many patients with disabling migraines that were unresponsive or poorly responsive to the usual symptomatic treatments (nonsteroidal anti-inflammatory drugs [NSAIDs], dihydroergotamine mesylate) and prophylactic treatment with beta-blockers, calcium antagonists, and antidepressants (propranolol hydrochloride, flunarizine hydrochloride, and amitriptyline hydrochloride, respectively) who were given prophylactic treatment with increasing doses of IV histamine showed dramatic, long-lasting improvement in their symptoms. Various doses of histamine and durations of treatment have been used.

In this study, we compared the results obtained with the most frequently used dosing regimen in our clinic with those in untreated patients matched for age; sex; and frequency, duration, and severity of migraines. The clinical benefit of histamine prophylaxis was defined to endure as long as ≤1 mild attack per month was reported. Tolerability of the treatment was assessed during and after hospitalization.

PATIENTS AND METHODS

This open-label, retrospective, controlled study was conducted at the Headache Center (Department of Internal Medicine, University of Florence, Villa Monna Tessa, Italy) according to the principles of the Declaration of Helsinki.

We retrieved data from our files for all patients treated with the most frequently used dosing regimen of histamine from 1990 to 1995 who were followed up for ≤2 years. Patients were eligible for the study if they had had 3 to 6 migraines without aura per month in the 6 months preceding the study. Exclusion criteria were age <18 or >65 years, peptic ulcer, asthma, chronic obstructive pulmonary disease, or any other disorder requiring medical treatment. Pregnant, possibly pregnant, or breastfeeding women were excluded from the study. Treatment with oral contraceptives, if used, was continued during hospitalization. All patients provided verbal informed consent to histamine treatment and pharmacologic testing. Any prophylactic treatment for migraine was suspended in the 3 weeks preceding hospitalization, which lasted 23 to 30 days for both the histamine and control groups. The study was unblinded, as both physicians and patients were aware of treatments. Data extraction and matching with untreated patients were performed during 2003.

The treatment group (histamine group) comprised patients with migraine without aura diagnosed according to the International Headache Society criteria[23] totally or partially unresponsive to symptomatic (NSAIDs, dihydroergotamine) and prophylactic treatments (propranolol, flunarizine, amitriptyline). They were treated with a 21-day regimen of IV histamine hydrochloride (in 250 mg of saline 0.9%) in increasing doses, starting with 0.5 mg/d for 2 days, and increasing by 0.5 mg every 2 days until a 4.0-mg dose was reached; that dose was maintained for 1 week, and then was interrupted. The rate of infusion was self-controlled by the patients, who were instructed to reduce the rate of infusion at the onset of headache, palpitations, or flushing.

The control group comprised patients who were also poorly responsive to the usual symptomatic and pharmacologic treatments and who were matched to the histamine group by age; sex; and frequency, duration, and severity of migraines. Furthermore, patients included in the control group had been hospitalized during the same period but did not tolerate histamine infusion (these patients received only the first 0.5-mg dose) and underwent only diagnostic examinations. These examinations included pharmacologic tests (pupillometric tests with tyramine 2% eyedrops and phenylephrine hydrochloride 1% eyedrops) to assess pupillary adrenergic activity and venoconstriction tests to serotonin, dopamine, and norepinephrine administered in the dorsal vein of the hand at doses that elicited only local effects to assess reactivity to serotonin and monoamines. These tests were repeated every 2 or 3 days during days 0 to 21 for consistency. The pharmacologic tests were conducted to study a possible adrenergic peripheral impairment in migraine patients and are described elsewhere.[24–26] After the first dose, patients in the control group received only saline infusions for the treatment of migraine symptoms.

In both groups, clinical and laboratory examinations were performed every 2 or 3 days. The use of drugs for the relief of migraine symptoms was allowed in both groups except during histamine infusion in the treatment group, which usually lasted 30 minutes to 2 hours. At hospital discharge, patients were given symptomatic treatment and were instructed to maintain a daily record of their migraines, specifying the intensity (on a 4-point rating scale: 0 = none, 1 = mild, 2 = moderate, and 3 = severe) and duration of migraine (in hours). Control visits were scheduled at 6-month intervals for ≤2 years after treatment for each patient, and patients were instructed to contact the clinic if they had >3 migraines in a month. Clinical benefit was defined to last as long as ≤1 attack of mild intensity per month was reported.

Statistical Analysis

To assess the efficacy of the prophylactic treatment, the duration of clinical benefit in the 2 groups was compared using the Student *t* test. The 95% CI was calculated for the difference in the duration of clinical benefit between the 2 groups. Statistical analysis was performed using the Statistical Package for Social Sciences version 10.0 (SPSS Inc., Chicago, Illinois). Statistical significance was set at $P \leq 0.05$.

RESULTS

The histamine group comprised 47 patients (40 women, 7 men; mean [SD] age, 42.0 [8.6] years) and the control group comprised 23 patients (20 women, 3 men; mean [SD] age, 38.8 [8.4] years) (**Table I**). The mean (SD) history of migraine also was similar in the histamine and control groups (22.0 [8.5] years and 21.5 [13.8] years, respectively). The mean (SD) frequency of migraines per month was similar in the 2 groups (5.1 [1.2] and 5.0 [0.9], respectively), as was

Table I. Demographic and clinical characteristics of study patients (N = 70).*

Characteristic	Histamine Group (n = 47)	Control Group (n = 23)
Age, y		
Mean (SD)	42.0 (8.6)	38.8 (8.4)
Range	26–58	26–56
Sex, no. (%)		
Women	40 (85.1)	20 (87.0)
Men	7 (14.9)	3 (13.0)
Migraine characteristics		
History, mean (SD), y	22.0 (8.5)	21.5 (13.8)
No./mo, mean (SD)	5.1 (1.2)	5.0 (0.9)
Duration, mean (SD), h	43.9 (15.5)	46.4 (15.1)
Prophylaxis, no. (%)†		
Propranolol	40 (85.1)	18 (78.3)
Flunarizine	22 (46.8)	10 (43.5)
Amitriptyline	9 (19.1)	3 (13.0)

*No significant between-group differences were found.
†Some patients received >1 prophylactic drug, either in association or in sequence; that is, prophylaxis with propranolol was usually established at first, and then, in case of no clinical benefit within 2 months, propranolol was substituted with amitriptyline or flunarizine, or amitriptyline was added to the propranolol regimen.

the choice of prophylaxis, with most patients (85.1% and 90.0% of patients, respectively) having received propranolol. Some patients had been treated with >1 prophylactic agent, in association or in sequence; that is, prophylaxis with propranolol was usually established at first, and then, in case of no clinical benefit within 2 months, propranolol was substituted with amitriptyline or flunarizine, or amitriptyline was added to the propranolol regimen.

Analysis of the results showed a significant difference in the duration of clinical benefit in the 2 groups, with patients in the histamine group demonstrating a clinical benefit of 3 to 19 months (mean [SD], 10.4 [4.2] months [range, 3–19 months]) and patients in the control group demonstrating a clinical benefit of 1 to 7 months (mean [SD], 3.8 [1.9] months [range, 1–7 months]) ($P < 0.001$) (**Figure**). The difference between groups was large, with the mean duration being 6.6 months longer in the histamine group (95% CI, 5.15–7.99).

Histamine administration was fairly well tolerated. In the 47 patients receiving the full course, adverse effects (AEs) consisted of flushing (30 patients [63.8%]), heat sensation during infusion (27 patients [57.4%]), headache (pulsating and bilateral) (20 patients [42.6%]), and palpitations (15 patients [31.9%]) (**Table II**). None of the AEs were considered serious, and patients could limit them by controlling the rate of infusion. AEs resolved in 15 to 30 minutes after reducing the rate of infusion. No clinically significant alterations in laboratory findings were noted.

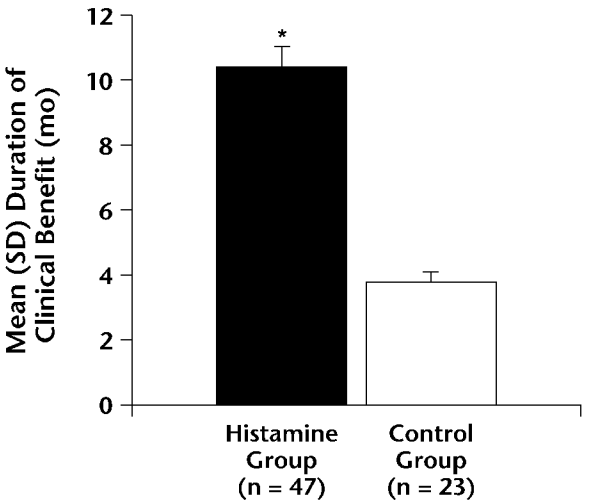

Figure. Duration of clinical benefit (defined as ≤1 migraine of mild intensity per month). *$P < 0.001$ versus the control group.

DISCUSSION

Histamine showed lasting clinical benefit (mean, 10.4 months) compared with 3.8 months in control patients. Control patients also showed clinical benefit, although this could have been due to prolonged hospitalization, with the likely reduction in stressful factors, which are certainly important in precipitating migraines. The clinical benefit shown by histamine in our trial was similar to that observed in the only 2 trials[27,28] of the efficacy of histamine and *N*-methylhistamine in migraine prophylaxis according to a MEDLINE search (key terms: *migraine, prophylaxis,* and *histamine*; years: 1970–2003). In those 2 studies, much lower doses were used (histamine 0.1–1.0 ng subcutaneously and *N*-methylhistamine 1–10 ng subcutaneously). Although the mechanism of action of histamine as a prophylactic agent in migraine remains to be elucidated, administering histamine in increasing doses might desensitize H_1 and H_2 recep-

Table II. No. (%) of patients experiencing ≥1 adverse effect (AE) with histamine administration in those receiving the full course of histamine therapy (N = 47).

AE	No. (%) of Patients
Flushing	30 (63.8)
Heat sensation during infusion	27 (57.4)
Headache (pulsating and bilateral)	20 (42.6)
Palpitations	15 (31.9)

tors, preventing the initiation of a migraine. Also, histamine, in the large doses used in our study, may have depleted SP, NKA, and CGRP in the trigeminal ganglion, thereby reducing the response to precipitating factors. Another possibility is that histamine directly evoked antinociceptive action[29]; it has been shown that injection of histamine into the periaqueductal gray has an antinociceptive effect in rats and that treatments that increase the levels of endogenous histamine in the brain relieve pain.[30,31] In fact, blocking the negative feedback mediated by histamine type 3 (H_3) autoreceptors and inhibiting histamine-*N*-methyltransferase (the primary histamine-degrading enzyme) both result in antinociception.[32,33] Furthermore, H_3-receptor agonists are currently being proposed for a variety of inflammatory diseases and pain disorders, including migraine.[34,35] Finally, the administration of histamine might normalize serum beta-endorphin concentrations.[36]

Our study suggests lasting efficacy of histamine administered intravenously in increasing doses from 0.5 to 4.0 mg for 21 days in migraine prophylaxis. Our study had some limitations in that it was not a prospective, randomized, double-blind trial; investigators selected the patients who were included in the histamine treatment group, and both investigators and patients were aware of the assigned treatment. Our preliminary findings deserve further investigation in prospective double-blind trials. However, the 2 treatment groups were homogeneous and were hospitalized in the same institution for the same time period under similar conditions, meaning that the 2 groups were comparable.

CONCLUSIONS

In this study, histamine showed lasting prophylactic efficacy in migraineurs. If further research confirms this preliminary finding, histamine could be considered when established prophylactic drugs, such as beta-blockers, calcium antagonists, antidepressants, and antiepileptics, have not been effective.

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