ORIGINAL ARTICLE

N^{α}-Methyl Histamine Safety and Efficacy in Migraine Prophylaxis: Phase III Study

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ABSTRACT: ***Background:*** The histamine catabolite, N^{α}-methylhistamine, possesses a selective affinity for H3 receptors. For this reason, we considered evaluating the efficacy of this histaminergic H3 agonist in migraine prophylactic treatment. ***Objective:*** To study the therapeutic potential of the subcutaneous administration of N^{α}-methylhistamine in migraine prophylaxis, in a Phase III clinical pharmacological study. ***Methods:*** Using a controlled double-blind, placebo controlled clinical trial for 12 weeks, 60 patients with migraine, who fit the criteria established by the International Headache Society, were selected. The efficacy of subcutaneous administration of N^{α}-methylhistamine 1 to 3 ng twice a week against placebo was studied, evaluating the outcome of headache intensity, frequency, duration, and analgesic intake. ***Results:*** Comparison between the groups treated with placebo (n=30) and N^{α}-methylhistamine (n=30), on data collected for the 4th, 8th and 12th weeks of treatment, revealed that N^{α}-methylhistamine exerted a significant ($p<0.0001$) reduction (compared to placebo) in intensity, frequency, and duration of migraine attacks, as well as on the use of analgesic intake. No significant ($p>0.05$) adverse experiences or side effects developed in either group. ***Conclusions:*** The present study provides evidence of the efficacy of N^{α}-methylhistamine, given subcutaneously at doses of 1 to 3 ng twice a week, offering a new therapeutic alternative and laying the clinical and pharmacological groundwork for the use of histaminergic H3-agonists in migraine prophylaxis, which may specifically inhibit the neurogenic edema response involved in migraine pathophysiology.

RÉSUMÉ: Sécurité et efficacité de la Nμ-méthyle histamine en prophylaxie de la migraine: étude de phase III. ***Contexte:*** La Nμ-méthyle histamine, un catabolite de l'histamine, possède une affinité sélective pour les récepteurs H3. C'est la raison pour laquelle nous avons décidé d'évaluer l'efficacité de cet agoniste histaminergique H3 en prophylaxie de la migraine. ***Objectif:*** Étudier le potentiel thérapeutique de l'administration sous-cutanée de Nμ-méthyle histamine en prophylaxie de la migraine dans un essai thérapeutique de phase III. ***Méthodes:*** Il s'agit d'une étude de 12 semaines à double insu, contrôlée par placebo, chez 60 patients migraineux selon les critères établis par l'International Headache Society. Nous avons évalué l'effet de 1 à 3 ng de Nμ-méthyle histamine par voie sous-cutanée deux fois par semaine sur l'intensité, la fréquence et la durée de la céphalée ainsi que sur la prise d'analgésiques et nous l'avons comparé à l'effet d'un placebo. ***Résultats:*** L'analyse des données recueillies chez le groupe recevant le placebo (n = 30) et la Nμ-méthyle histamine (n = 30) à la quatrième, huitième et douzième semaine de traitement a montré que la Nμ-méthyle histamine diminuait significativement l'intensité, la fréquence et la durée des accès de migraine ainsi que la prise d'analgésiques ($p < 0,0001$) par rapport au placebo. Aucun incident thérapeutique ou effet secondaire significatif n'a été observé dans l'un ou l'autre groupe ($p < 0,05$). ***Conclusions:*** Cette étude suggère que la Nμ-méthyle histamine à des doses de 1 à 3 ng par voie sous-cutanée deux fois par semaine serait efficace en prévention de la migraine, offrant ainsi une nouvelle alternative thérapeutique. Elle établit les bases cliniques et pharmacologiques de l'utilisation d'agonistes histaminergiques H3 en prophylaxie de la migraine. Ces substances pourraient inhiber spécifiquement la réponse d'œdème neurogénique impliquée dans la physiopathologie de la migraine.

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In recent years, there has been a proliferation of pharmacological agents used for migraine prophylaxis: β-blockers, calcium-channel blockers, antiepileptic drugs, some phenothiazines, tricyclic antidepressants, serotonin antagonists, non-steroidal anti-inflammatory drugs, etc.[1-4] As yet, none of the drugs employed in migraine prophylaxis acts on specific mechanisms related to the disease's pathophysiology, which continues to be poorly understood in spite of numerous studies directed at identifying the molecular mechanisms of primary headaches such as migraine and cluster headaches.[5] In 1991 we carried out an initial study[6] that provided evidence for the beneficial effects of histamine in migraine prophylaxis. Our data showed that subcutaneous administration of low doses (1 to 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-

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receptors which engage the nerves containing neuropeptides and probably reflects a local feedback circuit between C-fiber nerve endings and mast cells, which control neurogenic inflammation.[7-11] (Figure 1) Histamine could constitute a new therapeutic drug in migraine prophylaxis that acts by limiting the excessive inflammatory response involved in migraine pathophysiology, through H3-receptor activation. Two histaminergic H3-receptors have been identified, which differ in their sensitivity to guanidile-nucleotide inhibition and are differentially activated by R^{α}-methylhistamine (Kd=12 n*M*) and by N^{α}-methylhistamine (Kd=0.36 n*M*); the first crosses the blood-brain barrier easily, while the second does not.[12-13] The histamine catabolyte, N^{α}-methylhistamine, possesses a greater affinity for H3-receptors,[11-14] and we therefore considered it suitable to conduct a clinical pharmacological study to evaluate the efficacy of a selective histaminergic H3-agonist in migraine prophylactic treatment.

In order to test the hypothesis that subcutaneously injected N^{α}-methylhistamine is effective in migraine prophylaxis, pharmacological studies recommended[15] for "first-time use of a medication in migraine prophylaxis" were carried out in healthy volunteers (Phase I) and in migraine patients (Phase II).[16] After concluding Phase II, our objective was to study the therapeutic potential of the subcutaneous administration of N^{α}-methylhistamine in migraine prophylaxis, undertaking Phase III clinical pharmacological studies.

Methods

A double-blind study was designed for Phase III. Sixty patients diagnosed with recurrent migraine unresponsive to available abortive (acetaminophen, ergotamine, dexamethasone, sumatriptan) and/or prophylactic agents (propranolol, amitriptyline, verapamil) were selected using the criteria of the International Headache Society.[17-19] Participants were identified and recruited from the general population, patients came from multiple physicians and neurologists and their diagnoses were independently confirmed by a second member of the research team. The patients were male or female adults between the ages of 18 and 65, all having a history of migraine for several years, showing no additional neurological or cardiovascular pathologies after a complete clinical and laboratory examination, including computer-assisted tomography. We excluded from this study patients under 18 and above 65 years of age, pregnant women, those suffering daily headaches, and patients with vascular or heart diseases, biochemical or hematological alterations, as well as patients whose radiological tests revealed any pathology. Any subject having a secondary reaction to the drug or an alteration in any of the laboratory results or presenting with any acute problem such as gastroentiritis, viremias, etc. was excluded. Patients that abandoned the study were still considered in the final analysis. Participants were identified, the procedure was explained to them and they were invited to take part in the study. They all signed a letter of consent in accordance with the Helsinki statement.

Selected patients underwent a one month period of washout of prophylactic agents after which they were divided into two groups for treatment in randomized blocks of three, double blind fashion: the study group (n = 30) and the control group (n = 30). This randomization was done by a research collaborator who throughout the duration of the study had no contact with the patients (Table 1).

A research collaborator who had no contact with the patients prepared vials containing either 10 ng/ml of N^{α}-methylhistamine or placebo (Evan's solution= phenol 0.4%, isotonic sodium chloride). The vials were numbered and both the N^{α}–methylhistamine and the placebo looked the same, which allowed the blinding to be effective since neither the patients nor the physicians were able to identify vehicle or active drug. All other researchers who had contact with the patients were unaware of the vials' contents. The treatment consisted of a regimen of subcutaneous (back region of the upper arm) administration of placebo (Evan's solution) or of N^{α}-methylhistamine (10 ng/ml in Evan's solution) 1 to 3 ng, twice a week. The regimen started with an administration volume of 0.1 ml of either placebo or N^{α}-methyl histamine, which was consecutively increased (by 0.1 ml) until reaching 0.3 ml; with continuous repetition of this protocol (beginning again with an administration volume of 0.1 ml) for 12 weeks after which the study was concluded. During treatment, patients were allowed to take 500 mg acetaminophen tablets if they had a moderate or severe headache and if relative bed rest was needed for the patient in order to cope with headache intensity endured for more than 8 hr (a value of 2, on a scale of 1 to 3).
Patients were instructed to keep a daily record of events.

The variables studied[20] were: 1) headache frequency, measured by numbers of attacks per month; 2) intensity of pain (scale from 1 to 3); 3) duration of pain, measured by hours of headache per attack; and 4) intake of rescue analgesics, measured by the number of acetaminophen tablets (500 mg)

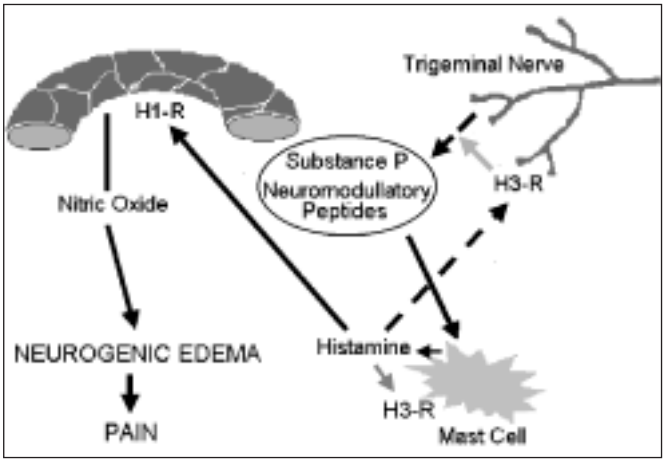

Figure 1: *Pathophysiology of Migraine. Antidromic stimulation of trigeminal nerve endings induces the release of substance P and other neuromodullatory peptides, which in turn stimulate the release of histamine from mast cells. In meningeal blood vessels, activation of H1-receptors (H1-R) by histamine, resulting in vasodilatation and plasma protein extravasation, causing neurogenic edema. However, degranulation of mast cells and neuropeptide release from C fiber endings are inhibited by the histamine interaction with H3-receptors (H3-R), representing a feed back loop controlling neurogenic inflammation.*

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

Feature	Nα-Methylhistamine (n=30)	Placebo (n=30)
Sex		
Female	24	23
Male	6	7
Age years (mean)	35 (± 12)	37 (± 12)
Years of migraine (mean)	12 (± 9)	15 (± 11)
Age at onset (mean)	10 (± 4)	8 (± 3)
Migraine Type		
with aura	4	6
without aura	26	24
Headache frequency (attacks per month)		
3	2	3
4	28	27
Duration of attacks (h)		
12-24	8	5
25-48	15	20
49-72	7	5
Headache intensity scale 1-3		
1 (minimum)	0	0
2 (moderate)	10	8
3 (severe)	20	22
Analgesic tablets/mo, mean (SEM)	13 (± 3)	12 (± 2)

* Values are number unless otherwise indicated

taken each month. Values for the parameters studied were collected during four weeks before initiation of treatment (baseline), and every four weeks thereafter.

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.[21]

The investigation was conducted under national and international guidelines for experimental research in humans. The study was approved by the Ethical and Scientific Committee of our hospital.

Results

For all variables studied, the statistical analysis of data collected showed no significant differences between baseline values obtained for the placebo and the N^{α}-methyl histamine treated groups (P>0.05). 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 protocol followed for the administration of placebo (P<0.001) or of N^{α}-methyl histamine (P<0.0001). For values found for the 4th, 8th, and 12th weeks of treatment, comparison between both groups revealed that N^{α}-methyl histamine treatment exerted a significant effect (P<0.0001) with a greater reduction (compared with placebo) on the frequency, intensity, and duration of migraine attacks, as well as on the use of rescue medication.

After four weeks, the group treated with placebo showed a reduction to 82% of frequency, intensity and duration of migraine attacks, and to 66% on the number of analgesic tablets ingested. The N^{α}-methylhistamine headache frequency decreased from 4.8 attacks per month in the baseline stage, to 1 attack per month (Table 2). Headache intensity was modified, from 3 (a level at which the patient is unable to work) to 0.6 (below the level at which the patient is able to work), with a reduction to 20% of baseline. The baseline value for headache duration was 26 hours and was reduced to 3 hours (11.5% of baseline). The number of tablets taken for rescue analgesics were reduced from 28 to 4 acetaminophen tablets per month, with a reduction to 14%of baseline. After eight weeks of treatment with placebo, we found (with respect to basal values) a reduction to 81% for frequency, intensity, duration of migraine attacks, and to 65% for the number of analgesic tablets ingested. N^{α}-

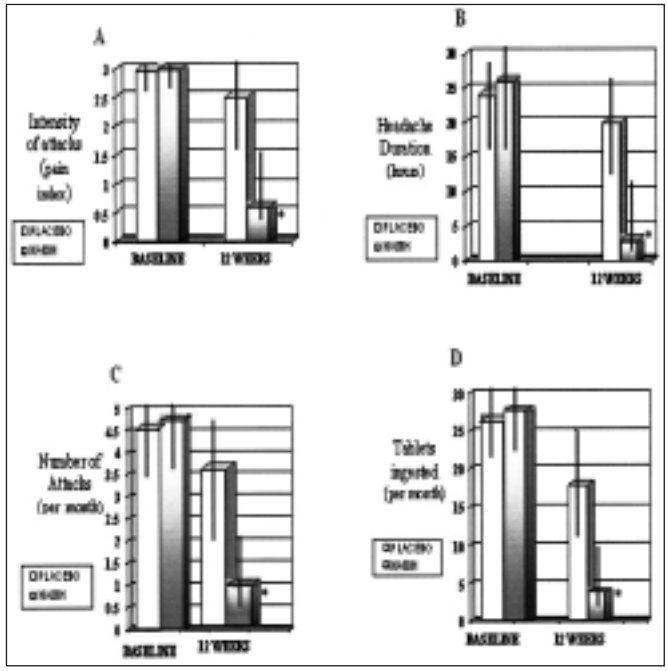

Figure 2: *Effects induced (in 60 patients with recurrent migraine) by the subcutaneous administration (twice a week, over a period of 12 weeks) of Na-methylhistamine (NAMH)(n=30) and placebo (n=30) on the intensity, duration, and frequency of migraine attacks; as well as on the consumption of 500 mg acetaminophen tablets used as rescue medication during headache. Data correspond to mean values (plus SEM) obtained during a 4-week period prior to initiation of treatment (BASAL), and to the last 4 weeks of treatment (NAMH). *P < 0.0001.*

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Table 2: Efficacy response measures. Comparison of treatment groups Phase III.

	Placebo (n=30) (%)				NαMethylhistamine (n=30) (%)			
Variable	**Pre**	**4w**	**8w**	**p**	**Pre**	**4w**	**8w**	**p**
Number of attacks	4.8(100)	3.9(82)	3.8(80)	<0.01	4.8(100)	1(20)	0.6(15)	<0.0001
Headache duration	24(100)	20(83)	20(83)	<0.01	26(100)	3(11.5)	0.6(10)	<0.0001
Intensity of attacks	3(100)	2.5(83)	2.4(82)	<0.02	3(100)	0.6(20)	0.1(18)	<0.0001
Tablets ingested	27(100)	18(66)	17(65)	<0.01	28(100)	4(14)	4(14)	<0.0001

*Values are percentage. w=weeks

Number of attacks (per month), Durations (hours), Intensity (1-3), Tablets (per month)

methylhistamine treatment resulted in a reduction to 14% for frequency, intensity, duration of migraine crisis, and number of tablets ingested. Although we found a slight decrease on the effects of placebo administration by the 12th week, compared with values obtained after eight weeks of treatment, such differences were not statistically significant (P>0.05). On the other hand, the effects of histamine after 12 weeks of treatment remained identical to values found at the 8th week. As can be observed in Figure 2, when comparing baseline values with those obtained during the last four weeks of N^{α}-methylhistamine treatment, a significant difference was obtained for all variables in relation to the baseline stage.

The treatment group reported transitory burning and itching at the injection site, but no significant differences (P>0.05) 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 blood pressure or cardiac rate 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. Two patients from the placebo group and three patients from the N-alpha group left the study because they were not satisfied with the efficacy of the results. There were no side effects reported.

Discussion

Based on results previously mentioned,[6] histamine has 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. We have had 80% efficacy, 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 contraindicated, or in patients who have developed secondary gastritis and cannot tolerate further oral drug therapy. To our knowledge, this is the first study providing evidence of the beneficial effects of low doses of histamine in the temporal course of migraine.

In the present study, N^{α}-methylhistamine, an H3-receptor agonist which acts directly upon migraine pathophysiology, is seen to have a probable greater therapeutic efficacy than histamine in migraine prophylaxis, based on the following data: 1) N^{α}-methyl histamine is a natural histamine metabolite in humans, which is eliminated through the urinary tract;[22] 2) this histaminergic H3-receptor selective agonist does not cross the blood-brain barrier,[13] therefore subcutaneous administration of this drug would not act at the central nervous level; and finally, 3) regarding histamine's therapeutic effectiveness in migraine prophylaxis, our previous results showed an effective dose range of 1 to 10 ng. Considering that N^{α}-methyl histamine's affinity for binding H3-receptors is greater than that of histamine, it would be expected that subcutaneous administration of this H3-agonist would have therapeutic efficacy in migraine prophylaxis at doses equal to or lower than 10 ng.

Now a Phase III clinical trial has been carried out, comparing the administration of N^{α}-methylhistamine with that of a placebo and following established guidelines of migraine research. The protocol used for the administration of N^{α}-methylhistamine in this study was in accordance with results of the Phase II trial and recommendations signaling that migraine prophylactic drugs should be administered in gradually increasing doses until a favorable effect is observed or secondary effects become unacceptable.[15,21] Our data reveal that the administration of N^{α}-methyl histamine, at considerably low doses (1-3 ng), induces significant relief from migraine symptoms without complications. After the clinical trial was over, some of the patients treated with N^{α}-methylhistamine remained asymptomatic, without headache crises, while others showed significant relief from migraine symptoms for a period ranging from six to twelve months. A cross-over study was not carried out, due to the fact that the use of drugs having a prolonged therapeutic effect does not lend itself well to such a study.

Altogether, the results obtained in this study show that N^{α}-methylhistamine is a safe drug with therapeutic potential in migraine prophylaxis, exercising specific mechanisms on pathophysiological processes involved in this disease.

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We consider the initial goals of our study were achieved, which were to bring about a new therapeutic alternative in migraine prophylaxis, to improve the quality of life for migraine patients who do not respond (30-40%) to the drugs being used today, to lay the clinical and pharmacological groundwork for the use of H3-agonists in migraine prophylaxis, and, finally, to obtain a drug which exerts specific mechanisms on pathophysiologic processes related to migraine.

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