

Research Article

Subcutaneous Administration of Histamine in Cluster Headache

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Abstract

Objective: To test whether limiting of excessive vascular inflammatory responses might preclude the presentation of autonomic and clockwise characteristic features of cluster headache.

Background: Dysfunction in the inferior hypothalamic gray matter has been proposed in the pathophysiology of cluster headache, rendering vascular flow changes as an epiphenomenon of the trigeminal activation. However further data is necessary to validate this last assumption.

Methods: Three male patients, with active episodic cluster headache, were subjected to a one year regimen of subcutaneous administration of histamine (1-10 µg) twice a week.

Results: After a four years follow-up period, two patients remained asymptomatic; whereas in the third case, after a five years follow-up, the time between episodes shifted from every two years to three, duration of episodes from 4 weeks to 1, and frequency of attacks from 8 per day to 2.

Discussion: Prophylactic treatment aimed at limiting excessive inflammatory responses, through the activation of H₃ receptors, disrupts the triggering of autonomic and clockwise characteristic features of cluster headache.

Keywords: Cluster headache; Pathophysiology; Histamine; H₃-receptors; Prophylaxis

Introduction

Cluster headache is clinically a well defined syndrome, involving autonomic features, that occurs in both episodic and chronic forms, in which patients several times a day suffer multiple excruciatingly severe one-sided pain attacks [1,2]. Incidence is rare when compared to other primary headache disorders [3]. Characteristic features of this syndrome include clockwise regularity, relapsing-remitting course, and seasonal variation. Observations using positron emission tomography (PET) have demonstrated that the rostral brainstem, is essential in migraine pathophysiology [4,5]. These findings suggest that brainstem regions play a pivotal role in either initiation or termination of the acute attack of migraine, such that migraine likely results from a dysfunction of the brainstem or diencephalic nuclei that are involved in the sensory modulation of craniovascular afferents [6,7]. Studies by May [8,9] and Goadsby [10], using (PET) lead to the proposition that dysfunction in pacemaker or circadian regions of the inferior hypothalamic gray matter constitutes the pathophysiology of this disorder [11]. All cluster headaches need to be treated with abortive, transitional, and preventive therapies [12-14]. In a randomized, placebo-controlled, double-blind study [15], we have recently shown subcutaneous administration of histamine as a novel and effective therapeutic approach in migraine prophylaxis, aimed to limit excessive inflammatory responses throughout the activation of H₃-receptors. Therefore we undertook an open clinical trial in order to test the efficacy of the subcutaneous administration of histamine in cluster headache.

Patients and Methods

The source of the patients was the department of neurology. Three male patients with active episodic cluster headache, according to the Headache Classification Committee of the International Headache Society [2], showing no additional neurological or cardiovascular pathologies after a complete clinical and laboratory examination, including computer-assisted tomography, were subjected to an open clinical trial. The diagnosis of cluster headache was validated. Treatment consisted of a regimen of subcutaneous (back region of the upper arm) administration of histamine phosphate (10 µg/mL of Evan's solution) twice a week. The regimen started with an administration volume of 0.1 mL of histamine (1 µg), which was consecutively increased (by 0.1 mL) until reaching 1 mL (10 µg); with continuous repetition of this scheme (beginning again with an administration volume of 0.1 mL) during one year. The present investigation was conducted under national and international guidelines for experimental research in humans.

Patient Histories

Patient 1: A 54-year-old man consulted for a 10 years history of episodic cluster headache. Episodes occurred every two years, lasting each one for a period of 4 weeks and did not have a particular month that a cycle would start. Severe left periorbital pain attacks of 30 min were present with a frequency of 8 per day, in association with ipsilateral blurry vision, conjunctival injection, lacrimation, palpebral ptosis, and rhinorrhea. Previous episodes of cluster headache showed

Table 1: Histamine in cluster headache.

Patient	Time since beginning of histamine treatment (y)	Time between episodes (y)		Duration of episodes (weeks)		Frequency of attacks (per day)	
		Histamine		Histamine		Histamine	
		Before	After	Before	After	Before	After
1	5	2	3	4	1	8	2
2	4	2-3	0	3	0	5	0
3	4	2-3	0	2	0	3	0

no improvement to sumatriptan, prednisone and ergotamine tartrate and prophylactic treatment with verapamil, divalproex sodium, topiramate, lithium carbonate and carbamazepine treatment, provided no significant relief for previous cluster headache episodes.

Patient 2: A 43-year-old man with a history of two previous episodes of cluster headache, which occurred 5 and 3 years before initiation of a third one. Each episode lasted for a period of 3 weeks and did not have a particular month that a cycle would start. Excruciating right-sided periorbital pain attacks of 1 hr were present with a frequency of 5 per day, in association with ipsilateral lacrimation and with photophobia, phonophobia, nausea, and rhinorrhea. Treatment with sumatriptan, lithium carbonate, and prednisone or sodium valproate provided no significant relief for previous cluster headache episodes.

Patient 3: A 50-year-old man with a history of two previous episodes of cluster headache, which occurred 5 and 3 years before initiation of a third one and did not have a particular month that a cycle would start. Each episode lasted for a period of 2 weeks. Excruciating right-sided periorbital pain attacks of 1 hr were present with a frequency of 3 per day, in association with ipsilateral lacrimation and with photophobia, phonophobia, nausea, and rhinorrhea. Cluster headache proved previously to be unresponsive to sumatriptan, lithium carbonate, and melatonin and sodium valproate treatment.

Results

Data obtained before and after histamine treatment is comparatively depicted in Table 1. In patient 1, cluster headache attacks disappeared 20 days after initiation of histamine treatment. After a 5-year follow-up, the patient has reported an episode of cluster headache; which occurred three years after histamine treatment and lasted for a week. Mild pain attacks were located at the left periorbital region, occurred twice a day, lasted for 20 to 30 min, and were relieved by sumatriptan. In addition, the patient presented mild conjunctival injection during pain attacks. Patients 2 and 3, respectively reported that cluster headache attacks disappeared 14 and 8 days after histamine administration began; remaining both asymptomatic after a 4-year follow up.

Discussion

Several drugs such as verapamil, lithium or corticosteroids are effective in CH prevention, but their mechanism of action is not understood [16]. Is necessary to demonstrate that limiting excessive vascular inflammatory responses fails to disrupt the triggering of autonomic and clockwise characteristic features of cluster headache. This study reveals that the subcutaneous administration of histamine, at considerable low doses (1-10 µg), seems to be effective and well tolerated for the prevention of cluster headache, disrupting the

triggering of autonomic and clockwise characteristic features of this syndrome. Dimitriadou [17] demonstrated that the control of mast cells by histamine acting at H₃-receptors involves neuropeptide-containing nerves and presumably reflects the operation of a local C fiber nerve ending-mast cell feedback loop, controlling processes such as neurogenic inflammation [18]. Furthermore, this loop still functions when mast cells proliferate in an inflammatory condition. Taken together, we hypothesized that these data suggest that vascular changes, taking place during active cluster headache, far from being an epiphenomenon of the trigeminal activation, represent a necessary condition for the triggering of autonomic and clockwise characteristic features of cluster headache.

Finally, in light of the prophylactic efficacy, ease, and economy of histamine treatment in cluster headache and migraine, low-dose histamine therapy appears to be a novel and valuable clinical tool in neurovascular headaches how an alternative to those who cannot take others agents. The outcome of this study provides hope for patients whose lives have been devastated [19] and an opportunity to understand the pathophysiology of primary headache. A limitation of this study is the absence of a control group. This is of particular concern as there is little doubt placebo effects are seen in cluster headache and the natural history of cluster headache is to fluctuate.

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