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Case report

Betahistine-induced bronchospasm

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Betahistine is a cerebral vasodilator structurally related to histamine, which stimulates H_1 bronchial and vascular receptors. We report the case of a 28-year-old female patient who presented bronchospasm during treatment with betahistine hydrochloride. The prick test was negative. The oral challenge test showed bronchospasm and urticarial lesions. To the best of our knowledge, this is the first case of betahistine-induced bronchospasm reported in the literature. The study carried out failed to reveal the mechanism of the reaction.

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Betahistine (*N*-methyl-2-pyridylethylamine) is a cerebral vasodilator belonging to the beta-2-pyridylalkylamines. Due to its potent effect on cochlear blood flow, it is used to reduce episodes of dizziness associated with Ménière's disease (1–4). This drug has a chemical structure related to that of histamine: a heterocyclic ring containing nitrogen and a 2-aminoethylic lateral chain (Fig. 1). Betahistine shows affinity for H_1 histamine receptors in vascular and bronchial smooth muscle but, unlike histamine, is active when administered orally, has a more prolonged pharmacologic action, and produces little effect on gastric secretion.

Although the description included with commercial preparations of the drug advises caution in the administration of betahistine to patients with bronchial asthma, we have found no references in the literature to bronchospasm induced by this drug.

We report a patient who developed bronchospasm after administration of betahistine hydrochloride. The oral challenge test confirmed the clinical evidence, but the study failed to reveal the pathogenic mechanism of the reaction.

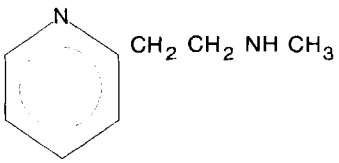

Fig. 1. Betahistine: *N*-methyl-2-pyridylethylamine.

Case report

A 28-year-old female patient, a nonsmoker, was referred to us for a study of bronchial asthma. She reported a history of frequent colds, and one bronchospasm attack in childhood. During the last year, she had had various outbreaks of pruriginous wheals on the chest and upper limbs after taking aspirin.

Eight months before our study, during treatment with Serc (betahistine hydrochloride, 8 mg) and Sermion (nicergoline, 5 mg), the patient presented from the first day dry cough, shortness of breath, and wheezing. These symptoms remitted 1 week later without bronchodilative treatment, a few hours after suspending treatment with both vasodilative drugs.

During the following months, she suffered several bronchospasm attacks with no known precipitating factors, requiring continuous treatment with theophylline, salbutamol, and inhaled corticosteroids.

Anterior rhinoscopy showed bilateral nasal polyps. Pulmonary auscultation revealed expiratory wheezing. The rest of the physical examination was unrevealing.

Hematimetry showed eosinophilia (1302 eosinophils/mm^3). Blood and urine biochemistry was normal. Sputum cytology showed eosinophilia, and bacterial and fungal cultures were negative. The chest radiograph was normal, while the sinus radiograph revealed thickening of the maxillary sinus

mucosa. Basal spirometry data were as follows: FVC 4290 (116%), FEV_1 3190 (113%), FEV_1/FVC 74%, MMEF 2750 (76%). The bronchial methacholine test showed raised bronchial hyperreactivity (PC_{20} FEV_1: 1.25 mg/ml). Total IgE was 82 IU/ml.

Material and methods

Skin tests

A standard prick-test was carried out with 30 common allergens, including mites, molds, pollens, animal dander, and foods.

Betahistine hydrochloride was prick-tested in saline solution at a maximum concentration of 8 mg/ml, and previously with three 10-fold dilutions. Histamine (10 mg/ml) and saline solution were used as positive and negative controls. All skin tests were read at 10 min. Betahistine was tested at equal concentrations in 10 control subjects (five atopic and five nonatopic). Nicergoline was not tested, being unavailable in soluble form.

Oral challenge test

Single-blind, placebo-controlled oral challenge tests were carried out with aspirin, nicergoline, and betahistine.

On the first day, only placebo was administered (opaque capsules with lactose) at 30-min intervals. If this was tolerated, on the second day, aspirin was administered at an initial dose of 15 mg, doubling the dose at 1-h intervals until a maximum of 500 mg was reached. On day 3, nicergoline was tested, at an initial dose of 0.30 mg and increasing every 20 min to a maximum of 5 mg. On the last day, betahistine was administered, starting at 0.08 mg and increasing every 20 min to a maximum of 8 mg.

At baseline and every 10 min, pulmonary spirometric recordings were performed, a positive response being defined as a greater than 20% fall from basal FEV_1. After the drug challenge, hourly peak expiratory flow rate (PEFR) measurements were recorded for 12 h. A response was considered to be positive if there was a greater than 25% fall in PEFR from baseline. The oral drug challenges were performed under medical observation, and full emergency therapy was available.

Specific IgE

Specific IgE (Phadezim RAST, Pharmacia Diagnostics, Uppsala, Sweden) was measured for the following allergens: *Dermatophagoides farinae, D. pteronyssinus,* and *Aspergillus fumigatus.*

Results

Skin tests

The standard prick test with common allergens and with betahistine in saline solution was negative. Betahistine did not produce cutaneous reaction in control subjects at any of the concentrations tested. The prick test with histamine was positive in the patient and in control subjects.

Oral challenge test

Aspirin. Ten minutes after administration of 62 mg aspirin (cumulative dose 107 mg), the patient presented pruriginous wheals on forearms. She was treated with antihistamines, and the reaction remitted over the next 2 h. Modification of FEV_1 and delayed response were not observed.

Nicergoline. The patient tolerated therapeutic doses of nicergoline (5 mg).

Betahistine. Fifteen minutes after administration of 0.64 mg betahistine (cumulative dose 1.20 mg), the patient presented a pruriginous wheal on the left wrist, erythematous plaques on the thorax and lower limbs, dyspnea, and wheezing. A 30% fall in FEV_1 was observed. These symptoms remitted after administration of inhaled salbutamol and orally administered antihistamine. There was no delayed response.

Fig. 2 shows the evolution of PEFR during challenge with placebo, aspirin, nicergoline, and betahistine.

Specific IgE

Significant levels of IgE for *D. farinae, D. pteronyssinus,* and *A. fumigatus* were not detected.

Discussion

Various drugs have been identified as precipitating or aggravating agents of bronchial asthma. Nonsteroidal anti-inflammatory drugs account for most drug-induced asthmatic reactions. Other pharmacologic agents such as beta-blocking agents, cholinergic agonists, antibiotics, and chemotherapeutic agents have also caused bronchospasm (5).

It has been shown experimentally that betahistine causes bronchoconstriction when inhaled by asthmatic and normal subjects, like histamine, by stimulating H_1-receptors of bronchial smooth muscle (6, 7). However, although this drug maintains its activity when administered orally, no publications mention bronchospasm in patients treated with betahistine at normal therapeutic doses. Using oral

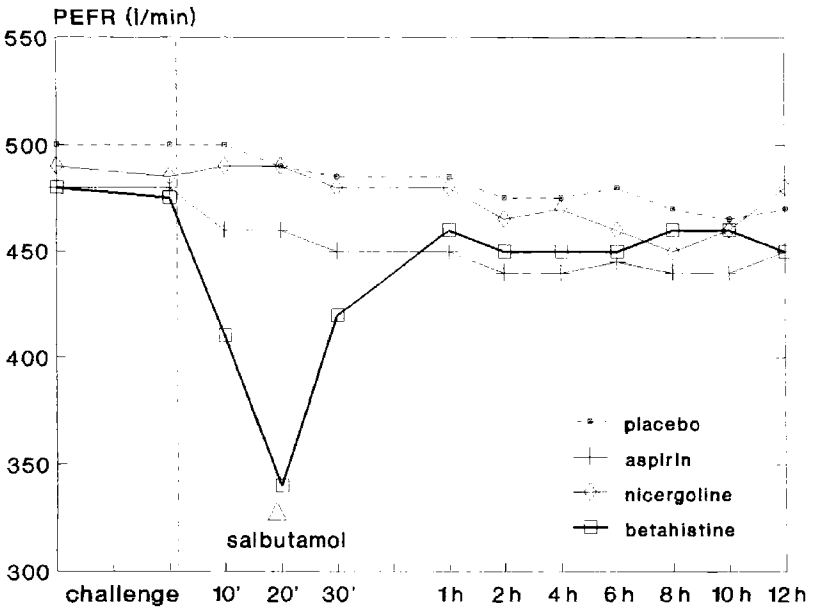

Fig. 2. PEFR recordings during challenge with placebo, aspirin, nicergoline, and betahistine.

challenge tests with therapeutic doses of betahistine, Senent et al. (8) studied 26 asthmatic patients and observed no spirometric alterations or signs and symptoms which could be attributed to the histaminic action of this drug.

In the patient we describe, the appearance of dyspnea and wheezing from the first day of treatment with betahistine, with no history of previous contact with the drug, leads us to suspect a mechanism related to its pharmacologic action as a stimulator of H_1-receptors. The low cumulative dose (1.20 mg) producing a positive response in the oral challenge test suggests that this patient was extremely sensitive to the drug.

The clinical course of the patient, who presented bronchospasm attacks after the initial episode related to betahistine, suggests a situation of clinical lability and might indicate a possible false-positive result in the oral challenge test. However, several facts support the validity of the test result. Firstly, the patient presented adequate clinical stability on the days before the oral provocation with betahistine, as reflected in the serial measurements of PEFR during the challenges with placebo, aspirin, and nicergoline. Moreover, the variation in basal FEV_1 during the 4 days of the provocation tests was less than 10%. Lastly, the appearance of urticaria simultaneously with bronchospasm during the challenge with betahistine also supports the validity of the test result.

The negative result of the prick test in our patient and in control subjects brings into question the affinity of betahistine to H_1 vascular receptors at the cutaneous level, although, strangely, the oral challenge test induced urticarial lesions simultaneously with bronchospasm. In accordance with our findings, Senent et al. (8) failed to obtain a response to betahistine with the prick test in 30 atopic and nonatopic subjects who presented normal cutaneous response to histamine.

It is unclear whether the sensitivity to aspirin shown by our patient may in some way have favored or increased the response to betahistine, and previous studies (8) do not specify whether patients undergoing oral challenge tests with betahistine had a history of aspirin-induced bronchospasm or urticaria.

Finally, we cannot exclude the involvement of an immediate hypersensitivity mechanism, since betahistine or its metabolites might act as immunogens after binding to proteins and elicit an IgE response, although the absence of previous contact with the drug does not support this hypothesis.

To summarize, to the best to our knowledge, we present the first case reported in the literature of betahistine-induced bronchospasm. Although the study carried out failed to reveal the mechanism involved, the pharmacologic action of this drug might explain the reaction presented by our patient.

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