

Immunoglobulin E–Mediated Severe Allergy to Hyoscine Butylbromide

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Hyoscine butylbromide is an antispasmodic cholinergic agent with a quaternary ammonium structure [1]. Kounis syndrome (KS) is an acute coronary syndrome during an allergic anaphylactic reaction. It is classified into 3 variants [2]:

- Type I, without coronary heart disease, in which the allergic reaction leads to coronary vasospasm.
- Type II, with coronary disease, in which the acute release of mediators leads to the rupture of a preexisting atheromatous plaque
- Type III, in which the allergic event leads to pharmacoactive stent thrombosis.

A 51-year-old man received 20 mg of hyoscine butylbromide, 2 g of metamizole, 10 mg of metoclopramide, and 40 mg of pantoprazole for biliary colic. Ten minutes after endovenous administration of the drugs, the patient complained of epigastric pain, sweating, sickness, and vomiting and presented loss of consciousness, hypotension (58/30 mmHg), ST-segment elevation on the inferior heart wall, and cardiorespiratory arrest. No skin symptoms were observed. After being stabilized, the patient was admitted to the intensive care unit (ICU) for orotracheal intubation and mechanical ventilation. Owing to the persistence of abdominal pain a further dose of 20 mg of hyoscine butylbromide was administered; macular exanthema appeared immediately on the face and trunk.

The ECG performed in the emergency room showed a 5-mm ST-segment elevation on the inferior heart wall and a decreased ST-segment in V2-V3, I, and aVL. Serum troponin was elevated (0.54 ng/mL).

Twenty-four hours after admission, ECG abnormalities had resolved and troponin levels returned to normal values.

All the cardiological tests performed showed normal results. Contractility alterations were not found in echocardiography, the thoracic CT angiogram ruled out acute aortic syndrome, and coronary angiography showed normal coronary arteries.

The allergology study revealed the following results: positive skin prick test (SPT) to hyoscine butylbromide at 20 mg/mL (5×3-mm papule diameter) and negative at 0.4 g/mL to metamizole. SPT with hyoscine butylbromide was performed in 3 atopic and nonatopic patients, with negative results. Histamine phosphate (10 mg/mL) (5×7 mm) was used as a positive control and saline (0.9%) as a negative control.

Intradermal tests (ID) with 1/100 metamizole and 1/10 metamizole were negative.

The patient refused to undergo challenge with metamizole. The results of challenge tests (CT) with pantoprazole and metoclopramide were negative.

The eosinophil count in peripheral blood was normal (110 eosinophils/μL), as was basal serum tryptase (4.5 μg/L). Specific IgE to hyoscine butylbromide could not be determined, because the test is not commercially available.

The basophil activation tests (BAT) with hyoscine butylbromide at 1/100, 1/10, and undiluted were negative.

Passive sensitization with hyoscine butylbromide 20 mg/mL in the histamine release test was positive (10 ng/mL of histamine released 10%) (Figure).

KS can manifest as coronary spasms, acute myocardial infarction, or stent thrombosis. Although this clinical entity is well-documented, there are many unanswered questions regarding its etiology, pathophysiology, and treatment [3]. In addition, while not rare, KS is infrequently diagnosed [4].

Diagnosis is based on symptoms and suggestive signs of an acute allergic reaction simultaneously with acute coronary syndrome (angina, vegetative symptoms) related to previous contact with a possible allergen [4,5]. The patient we report, who had no coronary risk factors, had presented 2 episodes of epigastric pain with bilious vomiting during the previous 6 months. On those occasions, ECG did not reveal myocardial ischemia, and serum troponin was within the normal range. The diagnosis was uncomplicated biliary colic. At the last visit for abdominal pain, empirical analgesic treatment was started after an ECG performed to rule out cardiac angina in the emergency department before drug infusion.

Therefore, the sudden onset of symptoms of acute coronary syndrome and ST-segment elevation associated with increased troponins after treatment with various drugs, together with an echocardiogram with no contractility alterations, led us to suspect type I KS.

In the absence of a commercial test to determine specific IgE to hyoscine butylbromide, a dot-blot was performed with the patient's serum against hyoscine butylbromide and metamizole, although the results were negative. In the release of histamine via passive immunization, specific IgE binds to the IgE receptor of the healthy donor basophil. After stimulation with the reagents, histamine release was significant and probably IgE-mediated [6]. Given these results, the positive skin test with hyoscine butylbromide, the positive reexposure with hyoscine butylbromide in the intensive care unit, and the histamine release test result, we considered that hyoscine butylbromide was the most probable culprit drug, with a high probability of an IgE-mediated mechanism. The normal basal tryptase levels ruled out mast cell activation syndrome [7].

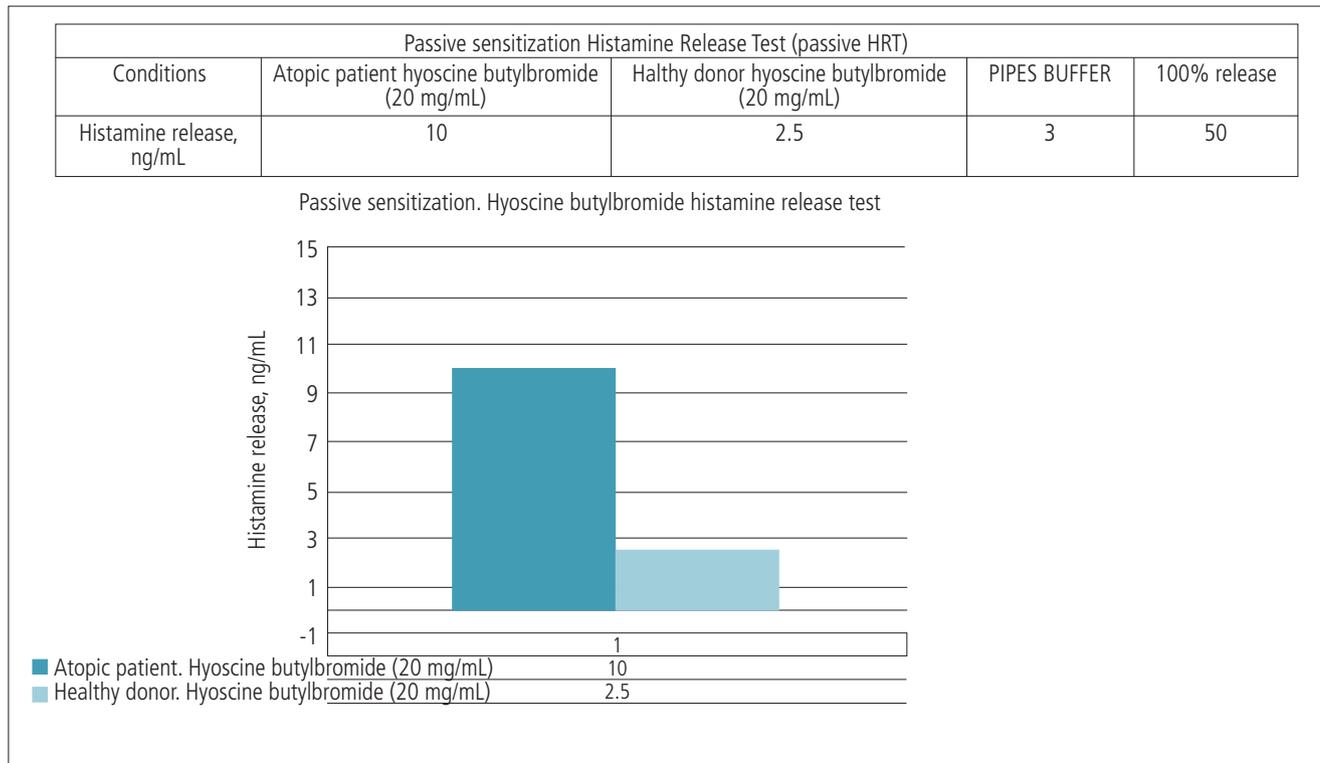


Figure. Histamine release test (hyoscine butylbromide).

Reexposure to hyoscine butylbromide in the intensive care unit was performed 24 hours after onset of the clinical picture, when the patient was receiving vasoactive drugs. The infusion of hyoscine butylbromide was not completed because of cutaneous exanthema. Therefore, it does not seem likely that a new episode of anaphylaxis and acute coronary syndrome was triggered.

We cannot exclude hypersensitivity to metamizole as the main etiology of KS owing to the absence of a CT scan (gold standard test). Similarly, we cannot exclude the possibility of further exanthema due to sensitization to hyoscine butylbromide (double sensitization).

Although hyoscine butylbromide is widely used, very few associated hypersensitivity reactions have been reported. González-Mendiola et al [8] reported a case of urticaria with positive skin and challenge tests to hyoscine butylbromide. Thirty years ago, another possible reaction manifesting only with bronchospasm was attributed to hyoscine butylbromide, although the patient did not undergo allergy testing. Angioedema and urticaria have been reported in a patient treated with hyoscine butylbromide; the authors suggested an IgE-mediated mechanism based on the patient's symptoms, although they did not perform an allergy study [9]. A case of sudden death due to intramuscular hyoscine butylbromide was reported in a patient with significant elevated serum tryptase (100 mg/L), thus indicating that death was due to type I allergy to this drug [10].

We report the first case of severe type I KS probably caused by an IgE-mediated hypersensitivity reaction to hyoscine butylbromide.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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