Usefulness of the Basophil Activation Test in the Diagnosis of Hypersensitivity to Amiodarone

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Amiodarone is a class III antiarrhythmic agent that inhibits outward potassium channels. It also has class I sodium channel–blocking effects, class II antiadrenergic effects, and class IV calcium channel–blocking effects and is widely prescribed owing to its efficacy in the management of ventricular and supraventricular arrhythmia [1].

Although prolonged use of amiodarone may cause numerous adverse effects (affecting the thyroid gland, liver, lungs, eyes, and skin), hypersensitivity reactions to amiodarone are rare. Moreover, few case reports include a thorough allergy work-up (anaphylaxis confirmed with determination of mast cell tryptase levels and skin testing [2], angioedema confirmed with positive oral challenge results [3,4], and amiodarone-induced hypersensitivity pneumonitis confirmed with positive results in skin testing and basophil degranulation tests [5]).

We report the first 2 cases of immediate amiodarone hypersensitivity reaction with a positive basophil activation test (BAT) result. An anaphylactic reaction was recorded in 1 of the cases.

A 48-year-old man was referred to our allergy department after experiencing an anaphylactic reaction in the operating room. An intravenous injection of amiodarone (50 mg) to treat atrial fibrillation was followed immediately by a decrease in blood pressure (60/40 mmHg), oxygen desaturation (<90%), and rash all over his body. The patient had also received treatment with etomidate, fentanyl, and rocuronium to induce anesthesia for cholecystectomy.

He was treated with methylprednisolone 100 mg, hydrocortisone 100 mg, and infusion of noradrenaline at 30 mL/h. The symptoms of anaphylaxis resolved gradually. Tryptase levels were as follows: 4.79 µg/L when the anaphylaxis occurred, 4.6 µg/L 2 hours later, and 1.47 µg/L on the following day.

The medical history revealed dilated cardiomyopathy, hypothyroidism, and permanent atrial fibrillation. Nevertheless, the patient had no history of allergy. Negative results were recorded in the skin prick test with an anaphylaxis panel (including latex, panallergens, and the most allergenic food) and prick and intradermal tests with etomidate, fentanyl, and rocuronium.

In an attempt to clarify the underlying mechanism and the culprit agent, BAT was performed with etomidate (1-100 µg/mL), fentanyl (1-100 µg/mL), rocuronium (5-500 µg/mL), and amiodarone before skin tests for safety reasons owing to the severity of the initial reaction.

The BAT methodology is detailed elsewhere [6-8]. Briefly, 100 µL of heparinized blood was incubated with 20 µL of intravenous amiodarone (0.2, 0.1, and 0.01 µg/mL) for 15 minutes at 37ºC. Negative and positive controls were included by incubating the blood without the drug and with 20 µL (10 mg/mL) of anti-IgE (BD Bioscience), respectively. Basophil activation was determined by CD63 upregulation using flow cytometry (FACSCanto II, BD Bioscience) for the identification and quantification of alterations in specific activation markers on the basophil surface membrane (using CD63/CD123/Anti-HLA-DR, BD Bioscience). At least 400 basophils were acquired. The results are expressed as the percentage of CD63-positive basophils and the stimulation index (SI, that is, the ratio of the percentage of activated basophils after stimulation to the percentage of activated basophils in negative controls). The result is considered positive when the percentage of basophils activated after stimulation with the drugs was 5% or more and the SI >3 [7].

BAT was positive with intravenous amiodarone (37% activation) (Figure), with an SI of 5.11 at an amiodarone concentration of 0.1 mg/mL (SI of 1 in the control) and 13.6

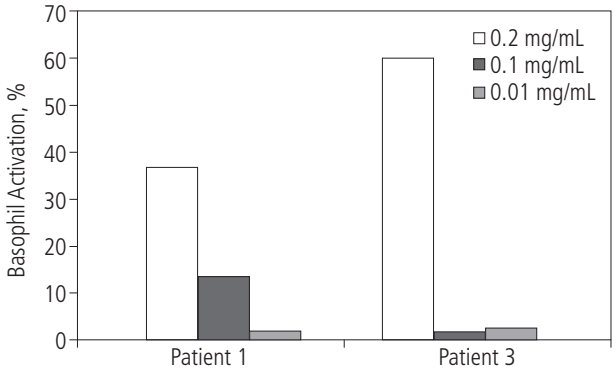

Figure. Basophil activation with intravenous amiodarone. Bars represent the percentage of CD63-positive basophils after incubation with amiodarone (0.2, 0.1, and 0.01 mg/mL).

at 0.2 mg/mL (0.8 in the control), and negative with etomidate, fentanyl, and rocuronium. The patient was diagnosed with anaphylaxis to amiodarone.

An 84-year-old woman with hypertension and hyperlipidemia and no history of allergy was examined in the emergency room for palpitations. She had paroxysmal atrial fibrillation and was treated with intravenous amiodarone. Fifteen minutes after the amiodarone infusion she developed severe genital itching and redness with rash. The symptoms resolved with antihistamines and corticosteroids.

The patient was referred to our allergy department. An appropriate clinical history was taken, and a complete physical examination was performed. The total serum IgE level was 113 kU/L. BAT with amiodarone based on the protocol described above was performed for safety reasons. The result was positive with intravenous amiodarone (60% activation) (Figure), with an SI of 30 and an amiodarone concentration of 0.2 mg/mL (SI of 1.3 in the control); therefore, the patient was diagnosed with immediate allergic rash induced by amiodarone.

We present the first 2 cases of immediate hypersensitivity to amiodarone with a positive BAT result.

Hypersensitivity reactions to drugs account for 15% of all adverse drug reactions [10] and represent a major health problem with significant morbidity and mortality. In the diagnosis of drug hypersensitivity, in vitro measurement of specific IgE is available for a limited number of drugs (it is often impossible to bind the molecules or their metabolites into a solid phase), which generally display low sensitivity and for which BAT is a very suitable complementary approach. Although rare, systemic reactions with skin tests have been described.

BAT seems to be a promising complementary in vitro technique in the allergological work-up of anaphylactic reactions to drugs.

The sensitivity of BAT in the diagnosis of drug allergy is about 50%, and the specificity can reach 93% [7], although these data depend on the drug in question [10].

BAT is recommended for diagnosing hypersensitivity reactions to penicillins and neuromuscular blocking agents and can complement other in vitro tests. In addition, BAT can be recommended for diagnosing IgE-mediated allergy to pyrazolones, fluoroquinolones, and radiocontrast media. In life-threatening reactions or in high-risk patients, BAT, when available, should be performed before in vivo approaches, including skin testing, according to the position paper of the ENDA/EAACI Drug Allergy Interest Group on in vitro testing for drug hypersensitivity reactions [10]. Despite the fact that we report only 2 cases, our results indicate that BAT is a useful diagnostic technique in hypersensitivity reactions to amiodarone.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

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