

Usefulness of basophil activation test in the diagnosis of amiodarone hypersensitivity

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

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

We report herein the first two cases of immediate amiodarone hypersensitivity with positive basophil activation test (BAT), one of them with an anaphylactic reaction.

A 48-year-old male patient was referred to our allergy department after suffering an anaphylactic reaction in the operating theater. An immediate decreased blood pressure to 60/40 mm Hg, desaturation (<90%) and rash all over the body, had appeared after an intravenous injection of amiodarone 50mg used to treat an atrial fibrillation. The patient had also received treatment with etomidate, fentanyl and rocuronium as anesthesia induction for cholecystectomy.

He was treated with methylprednisolone 100mg, hydrocortisone 100mg and noradrenaline perfusion to 30ml/h. The symptoms of anaphylaxis resolved gradually. Tryptase levels were quantified with the following results 4.79 $\mu\text{g/L}$ when the anaphylaxis occurred, 4.6 $\mu\text{g/L}$ two hours later and 1.47 $\mu\text{g/L}$ on the following day.

We performed a complete medical history and we found dilated cardiomyopathy, hypothyroidism and permanent atrial fibrillation. Nevertheless, he did not have any allergy background. Skin prick test (SPT) results with anaphylaxis panel test (including latex, panallergens and the most allergenic food), and prick and intradermal tests with etomidate, fentanyl and rocuronium were negative.

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

BAT methodology is detailed elsewhere[6,7,8]. Briefly, 100µL of heparinized blood was incubated with 20µL of 0.2, 0.1, 0.01 µg/mL intravenous amiodarone for 15 minutes at 37°C. Negative and positive controls were included by incubating the blood without drug and 20 µL (10 mg/mL) anti-IgE (BD Bioscience, Erembodegem, Belgium), respectively. Basophil activation was determined by CD63 upregulation using flow cytometry (FACSCanto II from BD Bioscience) for the identification and quantification of alterations of specific activation markers on the surface-membrane of the basophils (through CD63/CD123/Anti-HLA-DR from BD Biosciences). At least 400 basophils were acquired. Results are expressed as the percentage of CD63-positive basophils and stimulation index (the ratio between the percentage of activated basophils after stimulation and percentage 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 stimulation index >3[7].

BAT was positive with intravenous amiodarone (37% of activation) (see figure 1), with stimulation indexes of 5.11 with an amiodarone concentration of 0.1mg/ml (stimulation index of 1 in our control) and 13.6 with 0.2mg/ml (and 0.8 in our control) and negative

with etomidate, fentanyl and rocuronium. He was diagnosed with amiodarone anaphylaxis.

An 84-year-old female patient, who had hypertension and hyperlipidemia and no allergy background was examined in the emergency room for palpitations. She had paroxysmal atrial fibrillation and was treated with intravenous amiodarone. 15 min after the amiodarone infusion she developed severe genital itching and redness with rash eruption. Antihistamine and steroid therapy were administered and the symptoms resolved.

She was referred to our allergy department. An appropriate clinical history and a complete physical examination were done. Total serum IgE level was 113 kU/L. BAT with amiodarone, with the same protocol as for case 1, was performed for safety reasons. It was positive with intravenous amiodarone (60% of activation) (see figure 1), with a stimulation index of 30 with an amiodarone concentration of 0.2mg/ml (stimulation index of 1.3 in our control), so the patient was diagnosed with amiodarone immediate allergic rash.

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

Hypersensitivity reactions to drugs account for 15% of all adverse drug reactions^[10] and represent an important health problem with significant morbidity and mortality. In the diagnosis of drug hypersensitivity, the measurement of specific IgE *in vitro* is available only for a limited number of drugs (as binding the molecules or their metabolites into a solid phase is often not possible), which generally display low sensitivity and are thus well complemented by BAT. Although rare, systemic reactions with skin tests have been described.

BAT seems to be a promising complementary *in vitro* technique in the allergological workup of drug anaphylactic reactions.

The sensitivity of BAT in the diagnosis of drug allergy is about 50% and the specificity up to 93%[7], although these data depend on the different drugs[10].

BAT is recommended for diagnosing penicillins and NMBA drug hypersensitivity reactions and can be complementary to other *in vitro* test. BAT can be recommended for diagnosing IgE-mediated allergy to pyrazolones, fluoroquinolones and RCM. In life-threatening reactions or in high-risk patients, BAT, when available, should be performed before *in vivo* test including skin test[10] according to the position paper of the ENDA/EAACI Drug Allergy Interest Group on *in vitro* test for drug hypersensitivity reactions[10]. Although with the limitations of only two cases, according to our results amiodarone BAT seems to be a useful diagnostic technique in hypersensitivity reactions to amiodarone.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Figure 1. Basophil activation with intravenous amiodarone. Bars represent the percentage of CD63-positive basophils after incubation with amiodarone (0.2, 0.1 and 0.01mg/ml).

