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Selective hypersensitivity to cefazolin and contribution of the basophil activation test

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KEY WORDS

basophil activation test; cefazolin; R1 side chain; selective hypersensitivity.

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Summary

The authors present 2 case reports of selective cefazolin hypersensitivity: a 49 year-old woman with a history of two perioperative reactions (urticaria and severe anaphylaxis) after the use of rocuronium, propofol and cefazolin; a 36 year-old pregnant woman who developed facial erythema, lips angioedema and hypotension immediately after administration of ropivacain, sufentanil, cefazolin, oxytocin and ephedrine. In both cases, intradermal skin tests were positive for cefazolin. A basophil activation test was performed for cefazolin, which was positive in one patient. Oral challenge tests with penicillin, amoxicillin and other cephalosporins were negative. This selective hypersensitivity to cefazolin may be associated with a R1-side chain different from other beta-lactams.

Introduction

The prevalence of hypersensitivity to cephalosporins is increasing due to the rising number of prescriptions (1,2). Several studies suggest that the R side chain of cephalosporins is the preferential way of hypersensitivity, thereby explaining the cross-reactivity between cephalosporins and other β -lactams; however, the chemical structure of the antigenic determinants is not yet fully understood. In particular, the aminopenicillins have the same R-group side chains as well as some of the first- and second-generation cephalosporins. The highest cross-reactivity rate documented is around 27%, with cefadroxil, which has also the same R-group side chain as amoxicillin (3,4). Concerning cefazolin, the selective hypersensitivity seems to be the preferential presentation because the R1 side chain is different from the other cephalosporins; also, due to its parenteral use, hypersensitivity reactions are often immediate and severe (5-8).

It is well documented that approximately 40% of perioperative anaphylaxis related to drugs is due to cephalosporins prophylactic administration, thereby being extremely important to hold a high level of suspicion and notify all cases (9).

The drug allergy diagnosis workup for β -lactam hypersensitivity includes skin testing and drug challenge tests. Two main in vitro methods are used to confirm this type of immediate allergy: evaluation of specific IgE antibodies by immunoassay, in the serum, and the basophil activation test (BAT) upon incubating the blood sample with different concentrations of the drug. All these techniques are accepted to be complementary, although in those cases with severe reaction the in vitro tests may be the alternative for the diagnostic evaluation. The specificity of these methods is acceptable, but the sensitivity needs to be improved, especially in those patients with a clinical history of anaphylaxis and negative skin tests. Since several cases with negative skin tests and positive specific IgE have been reported, it is advisable

to perform this assay in addition to skin testing, in order to improve the sensitivity of the overall workup.

The basophil activation test (BAT) may add an additional contribution in those cases of immediate and severe allergy and negative skin tests, since it could avoid a risky drug challenge.

The authors describe two patients with immediate drug reactions, whose drug allergy workup including basophil activation test, confirmed as being selective cefazolin hypersensitivity reactions.

Case Report 1

The first patient is a forty-nine year-old woman with a past history of morbid obesity and several hospitalizations due to surgery in this setting. In 2008, three hours following a gastric banding procedure she developed an acute generalized urticaria. In 2009, she undergone revision gastric banding surgery, with no reaction documented during entire procedure. In 2012, approximately 15 minutes after the anesthetic induction for sleeve gastrectomy, she developed a IV-grade anaphylaxis which required immediate treatment with epinephrine, hydrocortisone, fluids, and subsequent mechanical ventilation was necessary in intensive care unit. The common drugs used in both interventions with documented reaction were rocuronium, propofol and cefazolin. She had no previous history of any drug allergies and was referred to our Immunoallergology clinic for evaluation.

The drug allergy diagnosis workup was performed after obtaining informed consent. Specific IgEs were negative for beta-lactams. Skin prick tests with all the drugs involved were negative, and the intradermal test with cefazolin was immediate positive at the concentration of 0.1 mg/mL. In order to test tolerance to other β -lactams, open drug challenges for penicillin, amoxicillin and other cephalosporins (cefuroxime and ceftriaxone) were performed, and the immediate and delayed responses negative. The basophil activation test was positive with cefazolin in the two concentrations used, with a percentage of activated basophils of 15.86% and 9.79% and a stimulation index of 10 and 6 respectively (**figure 1**).

Case Report 2

A thirty-six year-old woman, 38 weeks pregnant and otherwise healthy, was submitted to epidural block with ropivacain and sufentanil for cesarean section in March 2010. Immediately after the administration of cefazolin, oxytocin and ephedrine intravenous bolus, she developed a facial rash, lips angioedema and hypotension. She was given intravenous fluids, hydrocortisone and clemastine, with reversal of symptoms. No previous history of drug allergy had been documented, and the patient was referred to our Immunoallergology clinic for evaluation.

The drug allergy diagnosis workup was performed after obtaining informed consent. Specific IgEs were negative for beta-lact-

ams. Skin prick and intradermal tests were negative for all drugs used, except the intradermal for cefazolin which was positive at 1 mg/mL (immediate response). Open oral challenge tests with penicillin, amoxicillin and other cephalosporins (cefuroxime and ceftriaxone) were performed and the immediate and delayed results were negative. The basophil activation test was negative with cefazolin. This patient has tolerated several treatments with cefuroxime after this evaluation.

Discussion

The drug allergy diagnosis workup performed in these two cases confirmed a selective hypersensitivity to cefazolin with tolerance to other beta-lactam antibiotics, thereby cross-reactivity was ruled out. This reactivity pattern is most probably associated with the R1 side chain, which is different in cefazolin when compared to other cephalosporins.

A study by Pipet et al. (10) assessed patients with suspected hypersensitivity to cefazolin during the perioperative period. Patients were selected from the "Drug Allergy and Hypersensitivity Database" (DAHD). Among 4200 notifications, cefazolin was the suspected culprit drug in 25 cases. Allergy diagnosis to cefazolin was confirmed in ten patients, and reactions were classified as severe and immediate: anaphylactic shock in 6 patients, anaphylaxis in 2 patients, urticaria and angioedema in 2. Only one patient with hypersensitivity to cefazolin had positive skin tests for other beta-lactams. In this series, the prevalence of allergy was approximately 0.2%, which was lower when compared with other studies (6,11). Reactions are generally documented as immediate and severe mainly due to its administration in bolus. Although there may be false negatives, the skin tests seem to have a high predictive value. On the other hand, a study of Weber (11) documents that the hypersensitivity to cefazolin is extremely rare and the majority of patients were also sensitized to other beta-lactams. The basophil activation test performed in this study was validated with a healthy control under the same conditions. It is well documented that, the shorter the time interval between the reaction and the allergy diagnosis workup, the more likely will be to get a positive BAT. This may have a major role in our study since the positive BAT corresponded to the most recent reaction (2 years before) as opposed the patient who had reacted five years before (12). Although there is no fully established cutoff for BAT positivity, we followed the published criteria for positivity in drug allergy: percentage of activated basophils > 5% and a stimulation index > 2 (13).

Concerning the reactions to betalactams, several studies have shown the sensitivity of the technique to be around 50%, with a specificity of 93%. Interestingly, in patients with negative skin tests the sensitivity of BAT can be as high as 60% when the immunoassay is also positive, and 14% when it is negative and the drug challenge test is positive (14).

Figure 1 - Basophil activation test: Patient 1 vs Healthy control

The BAT was performed using FLOW2 CAST® kit, modified (Bühlmann Laboratories AG) according to the manufacturer's instructions. Testing for each patient was done by using separate tubes as follows:

Patient 1

A - patient background (negative control)

B - positive control (stimulation with formyl-Met-Leu-Phe (FMLP))

C - cefazolin 1/40 of initial concentration (100 mg/mL), and

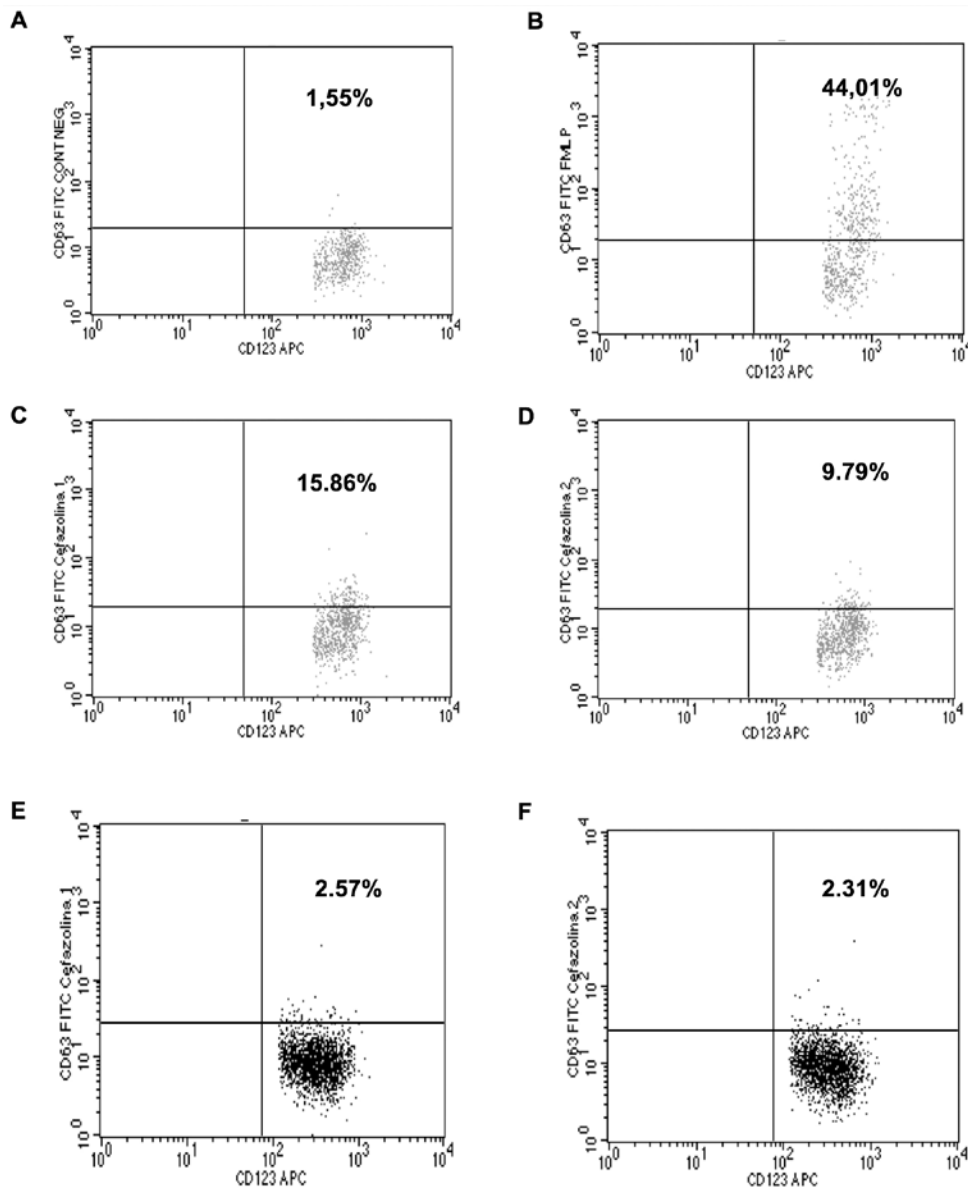
D - cefazolin 1/160 of initial concentration (100 mg/mL);

Healthy Control

E - cefazolin 1/40 of initial concentration (100 mg/mL)

F - cefazolin 1/160 of initial concentration (100 mg/mL).

Basophils were identified by CD123bright / side scatter and activation presented according to % of CD63 expression.



We might overall speculate that hypersensitivity to this cephalosporin is rare. Although the hapten determinants of cephalosporins are still unclear, we may presume that R1 is the major side chain involved, being on the basis of cross-reactivity. Cefazolin has a particular R1 side chain consisting of a heterocycle linked to an amide function by a methylene group (CH₂).

The notified cases are scarce and insufficient to draw concrete conclusions or predict the existence of cross-reactivity, however it is generally possible to define three different patterns of sensitivity. In descending order of frequency, we may find: patients with selective allergy to cefazolin; patients with allergy to cephalosporins, but who tolerate amoxicillin; patients with allergy to several beta-lactams, due to hypersensitivity to the beta-lactam ring. A study of Romano et al. (2015) that involved one hundred patients with suspected cephalosporin allergy suggested that cephalosporin hypersensitivity doesn't seem to be a transversal class hypersensitivity. Oral challenges were performed with cephalosporins with different side-chains from the culprit drug, and were well tolerated. Therefore, it is important that patients who need alternative treatment should be prescribed with cephalosporins with different side-chain determinants different from those of the culprit drugs (15,16).

According to the literature not all studies are concordant, and this is mainly due to the different sensitivity pattern which varies according to the studied population and time of data collection. It is important to alert possible non-notified cases and refer them to Allergy Units, since the complete workup of beta-lactam is essential due to the relative predominance of selective hypersensitivity, and these patients might tolerate other beta-lactams.

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