

Case report

Hypersensitivity to cefuroxime with good tolerance to other betalactams

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C. Marcos Bravo, I. Luna Ortiz,
R. González Vázquez

Servicio Alergología, Hospital Xeral-Cies, Vigo
(Pontevedra), Spain

A 60-year-old man developed an anaphylactic reaction immediately after administration of intramuscular sodium cefuroxime. By means of oral controlled challenge, the reaction was reproduced with a smaller dose of cefuroxime axetil. Cross-reactivity with other betalactam antibiotics was ruled out by *in vivo* tests. This case supports once again the relevance of the side-chain in betalactam allergy.

Key words: anaphylaxis; cefuroxime; cephalosporins; cross-reactions; drug hypersensitivity.

Dra. Carmen Marcos
Servicio Alergología
Hospital Xeral-Cies
C/ Pizarro 22
36204 Vigo (Pontevedra)
Spain

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Cefuroxime is a semisynthetic cephalosporin antibiotic which is widely used mainly in treatment of respiratory infections. Allergic reactions to cephalosporins are uncommon (8), and in such cases clinicians usually have doubts about the tolerance of other betalactam antibiotics.

We present a case of immediate systemic reaction after administration of sodium cefuroxime, in which cross-reactivity with other betalactam antibiotics was ruled out.

Case history

A 60-year-old man was treated with cefuroxime 750 mg t.i.d. i.m. for tonsillitis. He experienced a systemic reaction within 5 min of the injection of the first dose of 750 mg. His symptoms were general discomfort, generalized urticaria, shortness of breath, sweating, and palpitations. He was treated in an emergency room with 6-methyl-prednisolone 40 mg and dextroclorphenhydramine 5 mg, after which the symptoms largely disappeared within 1 h and had completely disappeared after 24 h.

The patient had previously tolerated this drug. He had no previous history of atopy or drug allergy and no family history of allergic disease.

The patient was referred to our department in order to study the drug reaction and to determine safe alternative antibiotics for the future.

He subsequently underwent the following tests. Determination of serologic specific IgE antibodies to benzylpenicilloyl-polylysine (BPO-PLL) by RAST (Pharmacia Diagnostics AB, Uppsala, Sweden) was performed and proved to be negative. Total IgE was 273 kU/l. Skin tests were performed with various betalactam antibiotics (reagents PPL and MDM (minor determinant mixture), penicillin G, semisynthetic penicillins, and cephalosporins) by prick and afterwards by intradermal technique (Table 1), producing negative results. The concentrations used were shown to be specific and nonirritant by testing in a negative control group of five subjects. Skin prick test and intradermal test with cefuroxime were also negative.

In order to confirm cefuroxime as the cause of patient reaction, the patient underwent a single-blind, placebo-controlled oral challenge with progressively increasing doses of cefuroxime axetil. Within 10 min of receiving the second dose of cefuroxime axetil 250 mg (cumulative dose 281.2 mg), he began to experience palmar pruritus, facial flush, and shortness of breath, and urticarial rash appeared

Table 1. Cutaneous tests performed in patient: drugs and highest concentrations used

Reagent	Concentration
PPL (Allergopen, Allergopharma)	6×10^{-5} M
MDM (Allergopen, Allergopharma)	0.5 mg/ml
Penicillin G (Uniclin, Antib. Farma)	10 000 U/ml
Amoxicillin (Clamoxyl, Beecham)	25 mg/ml
Ampicillin (Gobemicron, Normon)	25 mg/ml
Cefuroxime axetil (Zinnat, Glaxo)	0.5 mg/ml
Cefotaxime (Primalen, Hoechst)	25 mg/ml
Cefazolin (Kefol, Lilly)	25 mg/ml
Ceftriaxone (Rocephin Roche, Roche)	100 mg/ml

MDM: minor determinant mixture; PPL: BPO-PLL.

on his trunk and arms. Blood pressure and heart rate remained normal during the reaction. He was treated immediately with subcutaneous epinephrine 0.3 ml of a 1:1000 dilution, dextrochlorphenhydramine 5 mg, 6-methylprednisolone 40 mg, and intravenous fluids, with favorable outcome.

Single-blind, placebo-controlled challenges with progressively increasing doses of penicillin G, amoxicillin, and cefixime were negative.

Discussion

Cefuroxime (Fig. 1) is a second-generation cephalosporin that is commercially available for parenteral administration as the sodium salt and for oral administration as cefuroxime axetil, an acetoxyethyl ester prodrug of cefuroxime. The most frequently reported adverse effects were diarrhea (5%) with cefuroxime axetil, and cutaneous rash (0.6%), liver alterations (<4%), eosinophilia (7%), and phlebitis (2%), with sodium cefuroxime (7).

The problem of cross-reactivity between penicillins and cephalosporins is complex. Different de-

grees of cross-reactivity have been reported, mainly depending on the stringency of the criteria applied to define the penicillin-allergic group. Classically, it was widely accepted that the cross-reactivity was related to the betalactam ring. More recently, other authors think that variations in the acyl side-chain structure play the dominant role in determining the specificity of the immunologic reactions in betalactam allergy (1-3).

There has been little experience of penicillin tolerance in primary cephalosporin-allergic patients, because allergic reactions to cephalosporins are uncommon. In the last few years, some immediate reactions to cephalosporins have been reported. In some of these cases, selective sensitization to the cephalosporin and good tolerance of other betalactams have been demonstrated (4-6, 9).

Only two cases of reactions to cefuroxime have been reported in the literature (8, 10), to the best of our knowledge. One case was a reaction with cefuroxime axetil, presenting severe pruritus, angioedema, abdominal pain, and diarrhea. No study of betalactam sensitivity was performed (8). The other was a case of severe refractory anaphylaxis with intravenous cefuroxime (10). In this patient, betalactam allergy was confirmed by positive skin testing to penicillin G. Therefore, this is the first reported case in which there has been demonstrated a sensitivity to cefuroxime with good tolerance to other betalactam antibiotics. The lack of cross-reactivity with other betalactam antibiotics, including other cephalosporins, leads us to believe that the side-chain of the cefuroxime was probably the antigenic determinant in our patient.

The exact mechanism of the reaction remains unclear, although a type I hypersensitivity reaction to cefuroxime is probable because of the clinical features of the reaction, because of the prior exposure to the drug that was tolerated without adverse effect, and finally because the reaction was reproduced by administering small doses of the drug. Negative results obtained in the skin tests, as with most drug allergies, should be carefully considered and they do not exclude type I hypersensitivity. Most drugs and their metabolites have too small a molecule to be immunogenic in themselves; usually, they must be conjugated to a macromolecular complex to be immunogenic.

More experience is needed about tolerance of betalactam antibiotics in primary cephalosporin-hypersensitive patients.

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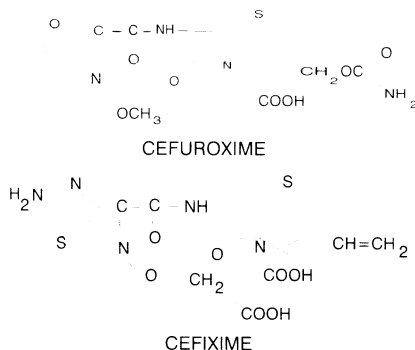


Fig. 1. Chemical formulas of cefuroxime and cefixime.

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