

Repeated anaphylaxis to cefuroxime in teenager and cross-reactivity to cephalosporins due to R2 side chain



Cephalosporins are one of the most prescribed classes of antibiotics,¹ and 1% to 3% of the population report a cephalosporin allergy.² Cephalosporins are β -lactam antibiotics, and their chemistry, mechanism of action, and toxicity are similar to those of penicillins. The most common classification of cephalosporins is by generation, and there are 5 generations of cephalosporins.

Immediate and late hypersensitivity to cephalosporins can occur. Most allergic reactions to cephalosporins consist of cutaneous rashes. Anaphylactic reactions are rare, with relative risks ranging from 1:1000 to 1:1,000,000 and different rates based on the R1 side chain.² Drug hypersensitivity reactions can occur to a specific cephalosporin, to multiple cephalosporins that have identical or similar side chains (R1 and R2), or as a cross-reactivity to other β -lactam antibiotics.¹ Cross-reactivity among cephalosporins appears to be attributable to the similarity of the side chains as presented by Romano et al.³ A classification of cephalosporins into 4 groups based on skin test positivity to 1 or more cephalosporins was proposed: group A includes ceftriaxone, cefuroxime, cefotaxime, cefepime, cefodizime, and ceftazidime; group B contains aminocephalosporins (eg, cefadroxil, cephalixin, and cefaclor); group C involves cephalosporins other than those in group A and group B (eg, cefazolin, cefamandole, cefoperazone, and ceftibuten); and group D includes patients with positive skin test results to cephalosporins belonging to 2 different groups. This classification is mainly based on similarity of the R1 chain. Cephalosporin hypersensitivity is not a hypersensitivity to all generations of cephalosporins, and patients with cephalosporin allergy might be treated with compounds that have different side chains from those of the culprit cephalosporin and have negative allergy workup results. Cross-reactivity between penicillins and cephalosporins stems mainly from whether the R1 side chains are structurally similar. Therefore, various cephalosporins are safe to treat patients who are allergic to penicillins.⁴

We report a rare case of hypersensitivity to cephalosporins in which the R2 chain is involved. A 17-year-old patient who had experienced anaphylaxis to cefuroxime twice was referred to our clinic. The first instance of anaphylaxis (generalized urticaria, vomiting, and hypotension) occurred 30 minutes after oral administration of cefuroxime 3 years ago, with the patient being treated in an intensive care unit. The patient had taken cefuroxime once before without any adverse effects. The second instance of anaphylaxis occurred 2 months before allergy diagnostic workup 20 minutes after oral cefuroxime intake, when generalized urticaria, abdominal pain, diarrhea, and hypotension appeared. After this episode, an allergist's consultation was recommended.

The patient had celiac disease, which was being treated with a gluten-free diet, and gastroesophageal reflux disease and *Helicobacter pylori* infection, which were treated by proton pump inhibitors. *H pylori* eradication was not performed because of the possibility of adverse effects of antibiotics.

The results of the tests for specific IgE antibodies to penicilloyl G, penicilloyl V, ampicillin, and amoxicillin were negative. In addition, IgE antibodies to cephalosporins were not administered because they were not available in our country. The patient's basal tryptase level was normal (3.09 μ g/L; reference range, <11.4 μ g/L). Skin testing was performed according to the European Academy of Allergy and Clinical Immunology/European Network on Drug Allergy

guidelines^{5,6} with β -lactams and cephalosporins available in our country. Skin prick test results were negative to all antibiotics. Intradermal test results were positive to cefuroxime and cefotaxime (intradermal tests at 2 mg/mL) but negative for benzylpenicillin, ampicillin, amoxicillin–clavulanic acid, ceftriaxone, and cefazolin. Searching for a safe alternative, broad-spectrum antibiotic provocation tests were performed. Because of the patient's and her parents' intention to find more alternative medications, 2 oral provocation tests were performed: the test with amoxicillin (cumulative dose, 1500 mg) was performed to rule out cross-reactivity with penicillins, and the test with cefadroxil (cumulative dose, 1000 mg) was performed to rule out cross-reactivity with aminocephalosporins. The results of these provocation tests were negative.

Cefuroxime and cefotaxime possess an identical methoxymino group in the R1 side chain and are cross-reactive. In addition, the R1 side chain is identical in ceftriaxone and cefepime. All these cephalosporins belong to group A.³ The results of intradermal tests for our patient were positive for cefuroxime and cefotaxime but not ceftriaxone. Skin testing with cefepime was not performed. Cefuroxime and cefotaxime contain identical R2 side chains, but ceftriaxone possesses a different R2 side chain.³ A provocation test with intramuscular ceftriaxone (cumulative dose, 1000 mg) was performed to evaluate R2 side chain cross-reactivity, the results of which were negative. In conclusion, hypersensitivity to cefuroxime and cefotaxime due to an identical R2 side chain was confirmed.

A similar case report was published in 2016⁷ in which hypersensitivity to the R2 side chain was confirmed in a woman who experienced anaphylaxis to cefuroxime and had positive skin test results for cefuroxime and cefotaxime. A provocation test was performed with ceftriaxone, the results of which were negative. In another case report, a selective systemic anaphylaxis attributable to cefuroxime was described.⁸ Cross-reactivity between specific IgEs to cefuroxime and cefotaxime was demonstrated in this case.

Our case and the cases reported previously confirm that hypersensitivity due to the R2 side chain should be evaluated in patients who experience type I hypersensitivity to cephalosporins. In the evaluation of a patient with a suspected cephalosporin allergy, a detailed history should be obtained, and skin tests should be performed with native cephalosporins that can predict hypersensitivity to the cephalosporin skin test reagent or cephalosporins with similar side chains. If the skin test result is negative, it is necessary to perform a provocation test with a culprit or an alternative drug. Cross-reactivity to R1 and R2 side chains should also be evaluated.

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Mixed drug reaction to amiodarone characterized by sequential immediate, immune complex, and delayed hypersensitivity



Amiodarone is a class III antiarrhythmic agent indicated for the treatment of tachyarrhythmias and frequently used in the management of atrial fibrillation. Pulmonary, cardiac, thyroid, hepatic, ocular, and neurologic toxic effects caused by the accumulation of the drug in the tissue from long-term therapy attributable to its long half-life and lipid solubility have been previously described.¹ Phototoxic effects resulting from the accumulation of free oxygen radicals from radiation is a common complication of long-term therapy.¹ Hypersensitivity reactions, however, account for less than 1% of adverse effects.^{2–4} We describe a patient with an unusual hypersensitivity reaction to amiodarone that involved 3 sequential phases: acute anaphylaxis, followed by a type 3 serum sickness–like reaction, and finally, a delayed type 4 reaction that manifested as exfoliative dermatitis with eosinophilia.

An 81-year-old man was administered amiodarone for atrial fibrillation associated with atrial thrombosis for which rivaroxaban was administered more than 4 weeks ago. The patient has ischemic heart disease and received a coronary artery bypass graft 35 years ago with percutaneous angioplasty performed 10 years ago, which was complicated by stent occlusion. His cardiovascular disease was treated for several years with a regimen of isosorbide mononitrate, ramipril, atorvastatin, and ezetimibe. He had no history of type B (idiosyncratic responses that cannot be predicted from the known pharmacologic mechanisms of a drug) allergic reactions, iodine, or contrast reactions.

After 6 days of amiodarone therapy, anaphylaxis characterized by generalized urticaria, facial angioedema, wheezing, and chest pain developed in the patient. He was successfully treated with adrenaline and fexofenadine in the hospital, and his amiodarone therapy was ceased. His electrocardiogram revealed atrial fibrillation with no ischemic change. His chest radiograph revealed minor atelectasis of his left lung base. There was a short-term increase in his tryptase level to 6.8 $\mu\text{g/L}$ against a baseline of 2.8 $\mu\text{g/L}$.

Seven days after the administration of amiodarone, fever, polyarthralgia, and a diffuse purpuric rash accompanied by an elevated C-reactive protein level (280 mg/L) and hypocomplementemia (C3: 0.26 g/L; C4: 0.06 g/L) developed in the patient. Skin biopsy revealed leukocytoclasia and a perivascular eosinophilic infiltrate in the absence of other changes of vasculitis, such as fibrinoid necrosis or thrombosis. There was no detectable antinuclear antibody, antineutrophil cytoplasmic antibody, or cryoglobulin. IgG, IgA, and IgM levels were normal. Furthermore, HIV, hepatitis B, and hepatitis C serologic test results were negative, and the antistreptolysin titer was normal. Blood cultures, urinalysis, and respiratory viral swabs did not isolate a pathogen.

A tapering course of prednisone was commenced at 1 mg/kg daily. His fever, purpuric rash, and arthralgia resolved after 10 days of therapy. However, with a dose of prednisone at 0.7 mg/kg daily,

the following symptoms developed in the patient: a desquamating rash (Fig 1), mild erythroderma accompanied by eosinophilia (eosinophil count, $2.9 \times 10^9/\text{L}$), cervical lymphadenopathy, and mild transaminitis (alanine aminotransferase, 82 U/L [reference range, <55 U/L]; aspartate aminotransferase, 54 U/L [reference range, 12–34 U/L]). There was no recurrence of fever or arthralgia. His C-reactive protein and complement levels were normal, and human herpesvirus 6 DNA was not detected. Prednisone therapy was increased to 1 mg/kg daily and tapered during 6 weeks without recurrence of hypersensitivity. His atrial fibrillation was subsequently treated with diltiazem. The patient did not experience pulmonary or thyroid toxic effects during follow-up.

Basophil activation testing (BAT) was performed to amiodarone and the excipient povidone per our previously published protocol.⁵ Interferon gamma release assays and bromide uridine enzyme-linked immunosorbent assays were performed to determine in vitro stimulation and proliferation of the patient's lymphocytes to amiodarone, but the results of these studies were negative.⁶

Hypersensitivity reactions to short-term use of amiodarone are rare and have been sparsely described in the literature. Our case is unique because our patient's reaction comprised multiple immunologic mechanisms (types 1, 3, and 4 Gell and Coombs reactions), which may be termed a *mixed drug reaction* according to the Joint Task Force on Practice Parameters.⁷ This type of reaction is not described in any other practice parameter. We did not find another case report of a mixed drug reaction in the literature.

Our patient had a type 1 hypersensitivity reaction demonstrated by urticaria, angioedema, and wheezing with significant dynamic change in serum mast cell tryptase. In addition, BAT supported an immediate hypersensitivity reaction to amiodarone (Fig 1), and this is the first report, to the best of our knowledge, of a positive BAT result to the drug in a case of anaphylaxis after the administration of the oral formulation.⁸ Excipients within the oral amiodarone formulation include iodine (povidone), maize starch, lactose, magnesium stearate, and anhydrous colloidal silica. Moreover, BAT was performed to iodine (povidone) because it is an excipient and has been reported rarely (<1%) to be an allergen in patients with amiodarone hypersensitivity.⁹ No CD63 up-regulation was observed with povidone in our patient (Fig 1).

The patient's type 3 reaction was characterized by fever, arthralgia, and purpuric rash. Amiodarone-induced vasculitis and type 3 reactions have been rarely reported, with approximately 10 cases cited in the literature.³

Many cutaneous adverse reactions of amiodarone are described, the most common being photodermatitis. Amiodarone may rarely cause life-threatening reactions, such as toxic epidermal necrolysis.⁴ Our patient's type 4 reaction is characterized by desquamating rash, erythroderma, lymphadenopathy, and transaminitis, which did not satisfy the criteria for a drug reaction with eosinophilia and systemic syndrome reaction. Our in vitro studies did not find lymphocyte proliferation, but it has been reported that