

Perioperative Anaphylaxis Including Kounis Syndrome due to Selective Cefazolin Allergy

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Keywords

Anaphylaxis · Drug Allergy · Drug-induced anaphylaxis · Kounis syndrome · Cefazolin · Diagnostic workup · Skin tests · Drug provocation tests

Abstract

Background: Perioperative use of cefazolin has been associated with severe allergic reactions, and patients are usually labelled as allergic to penicillin afterwards. The aim of our study was to describe a group of patients with immediate reactions to cefazolin, with proven selective hypersensitivity reactions. **Methods:** Systematic review of all patients followed at our drug centre with cefazolin-related reactions, between January 2012 and December 2016. All patients were investigated according to the European Network for Drug Allergy (ENDA) recommendations through skin testing (major and minor penicillin determinants, penicillin, amoxicillin, cefazolin, cefuroxime and ceftriaxone) and oral challenges tests. **Results:** We included 7 patients (median age 40 years) with perioperative anaphylactic reactions immediately after cefazolin injection, 4 with hypotension and 1 with Kounis syndrome (KS) type I. The presence of a selective IgE-mediated hypersensitivity through positive skin tests to cefazoline has been proven in all patients. Two patients experienced

systemic reactions during skin testing. All patients were successfully challenged with amoxicillin, and they tolerated cefuroxime. **Conclusions:** Cefazolin can be responsible for immediate severe allergic reactions in perioperative setting, including KS. Allergological workup is essential for an accurate diagnosis and to explore cross-reactivity between cefazolin and other beta-lactams. Our experience confirmed that patients with IgE-mediated hypersensitivity reactions to cefazolin can tolerate other beta-lactams. This selective pattern of clinical reactivity may be explained by its particular chemical structure, whose R1 side-chain is different from other beta-lactams.

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Introduction

Perioperative anaphylaxis is a life-threatening condition with an estimated incidence ranging from 1:1,250 to 1:20,000 procedures and a mortality rate up to 9%, although the incidence varies between studies from different countries [1–3].

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In the last decades, hypersensitivity to cephalosporins has been increasingly reported due to their growing use, with selective allergic responses to 1 specific cephalosporin and good tolerance to other beta-lactam antibiotics [4–6].

Cefazolin, a first-generation cephalosporin, is widely used in preoperative prophylaxis protocols [7]. Studies regarding perioperative anaphylaxis have shown that beta-lactam antibiotics are a leading cause of IgE-mediated hypersensitivity reactions, being cefazolin responsible for most of the reactions [8, 9]. Afterwards, patients are labelled as penicillin allergic, resulting in unnecessary antibiotic avoidance with economic and epidemiologic consequences [10, 11]. However, large series have clearly reported that cephalosporin hypersensitivity is not considered class hypersensitivity. The cross-reactivity patterns depend on side-chain determinants that are different, and often specific, between different cephalosporins [5, 6].

Since there is no reliable cefazolin-specific IgE antibody assay, clinical suspicion of cefazolin hypersensitivity is generally confirmed by skin tests [12]. Although skin tests with cephalosporins are not as well established as with those with penicillin, several studies have demonstrated their usefulness for the diagnosis of immediate reactions [5, 6, 13]. The European Network on Drug Allergy recommends a maximal non-irritating skin test concentration around 2 mg/mL for all cephalosporins [14]. Nevertheless, this group also emphasises that some studies have confirmed that an increased cefazolin concentration for skin tests up to 20 mg/mL is non-irritant and might improve sensitivity, without affecting specificity [15].

We aimed to describe a group of patients with immediate and severe reactions to cefazolin, with proven tolerance to other beta-lactams.

Methods

We performed a systematic evaluation of all patients referred to our allergy centre with cefazolin-related reactions between January 2012 and December 2016. All patients were investigated according to the European Network for Drug Allergy recommendations through skin testing to major and minor penicillin determinants, penicillin, amoxicillin, cefazolin, cefuroxime and ceftriaxone and finally oral challenges tests [16]. Serum-specific IgE antibodies and skin testing were performed with at least a 4-week interval after the clinical reaction to cefazolin. Skin prick tests (SPT) were the first step of *in vivo* investigation. Afterwards, intradermal tests (IDT) were carried out, only if SPT were negative. Skin tests were accomplished using solutions, daily prepared, of benzylpenicilloyl octa-L-lysine (5×10^{-5} mM) and sodium benzylpenicilloate – minor determinant (2×10^{-5} mM; DAP® Penicillin, Diater, Madrid, Spain), penicillin G (10,000 IU/mL), amoxicillin (DAP®-3 Amoxicillin,

Diater, Madrid, Spain; 20 mg/mL), cefazolin, cefuroxime and ceftriaxone (cephalosporins at 2.5 mg/mL) [14]. Histamine (10 mg/mL) was used as a positive control and 0.9% saline solution as a negative control. IDT was applied utilizing diluted solutions, according to the history of severe systemic allergic reactions. In our patients, we always began IDT with cefazolin at concentration of 0.25 mg/mL. If found negative, then we increased concentration to 2.5 mg/mL, and followed the same procedure till a value of 10 mg/mL was reached. We emphasize that concentrations of 2–20 mg/mL in IDT with cefazolin have been used as non-irritating in previous studies [5, 6, 8, 15]. First readings were taken after 15 and 20 min for SPT and IDT respectively. Both tests were performed on the volar forearm. In SPT, a mean wheal larger than 3 mm with negative response to negative control was considered positive. IDT were attained by the injection of 0.02–0.05 mL of the drug solution, producing a small wheal that is delimited initially. In IDT, an increase in the mean diameter greater than 3 mm of the original mark was considered positive.

Following skin tests, on different days, the patients underwent controlled oral challenges with alternative beta-lactam antibiotics (amoxicillin and cefuroxime) to assess cross-reactivity (with prior negative skin tests to these drugs).

Patients were fully informed about the procedures (risks and possible adverse reactions) and they signed an informed consent before participating in the allergological workup.

Results

We report data from 7 cases referred to our Drug Allergy Department with immediate and severe reactions due to cefazolin during the perioperative period. The median age was 40 years (ranging from 32 to 56 years), 4 of them were female and only 2 had history of other allergic diseases (one with cutaneous allergy and previous drug hypersensitivity and the other cutaneous and respiratory allergy). Cefazolin was administered by the intravenous route and was used as prophylaxis for surgical procedures at perioperative setting: 4 intraoperative (maxillofacial and orthopaedic surgeries, invasive biopsy and caesarean delivery), 1 woman during labour and 2 postoperative (orthopaedic surgeries). All patients presented anaphylactic reactions. Four patients had hypotension, 6 had cutaneous manifestations and 3 had respiratory symptoms. All reactions developed within 10 min after cefazolin infusion. Detailed information on each patient is presented in Table 1. One patient, a 56-year-old man without previous either allergic or cardiac diseases, developed a Kounis Syndrome (KS) type I. He presented anaphylactic shock with severe hypoxemia (peripheral oxygen saturation 62%), elevated troponin level (7 ng/mL) and ECG with diffuse ST segment depression, in a postoperative moment, immediately after intravenous administration of cefazolin. Ventricular

Table 1. Clinical and allergological characterization of our 7 patients with cefazolin allergy

Age, gender	Underlying disease	Allergic reaction		Positive skin testing (ST)	Systemic reaction during ST	Negative DPT
		setting; timing	description			
32, female	–	During labor; immediate	Facial angioedema and dyspnea	IDT cefazolin 0.25 mg/mL	Cough, oral pruritus, and facial angioedema	Amoxicillin Cefuroxime
40, female	CU, CD, HS NSAIDs/ macrolides	Intraoperative (caesarean); immediate	Generalized urticaria, swollen glottis and hypotension	IDT cefazolin 0.25 mg/mL	–	Amoxicillin Cefuroxime
34, female	–	Intraoperative (maxillofacial surgery); immediate	Tachycardia, lips swelling, swollen glottis, bronchospasm, and hypotension	IDT cefazolin 2.5 mg/mL	–	Amoxicillin Cefuroxime
42, male	–	Intraoperative (invasive biopsy); immediate	Generalized urticaria, dizziness and swollen glottis	IDT cefazolin 2.5 mg/mL	–	Amoxicillin Cefuroxime
56, male	–	Postoperative (knee arthroscopy); immediate	Kounis syndrome, anaphylactic shock and severe hypoxemia	IDT cefazolin 2.5 mg/mL	–	Amoxicillin*
39, female	AD, CD, AR, asthma	Intraoperative (orthopaedic surgery); immediate	Tongue and lips swelling, oral pruritus and dyspnea	IDT cefazolin 10 mg/mL	Oral pruritus and lip swelling	Amoxicillin*
41, male	–	Postoperative (cervical spine surgery); immediate	Generalized urticaria and hypotension	IDT cefazolin 10 mg/mL	–	Amoxicillin Cefuroxime

* Later the patient also tolerated cefuroxime during outpatient medical prescription.

AD, atopic dermatitis; AR, allergic rhinitis; CU, chronic urticaria; CD, contact dermatitis; DPT, drug oral challenge test in hospital setting; HS, hypersensitivity; IDT, intradermal test; NSAIDs, nonsteroidal anti-inflammatory drugs.

dysfunction and segmental alterations on echocardiographic evaluation led to cardiac catheterization, which showed a severe right coronary artery spasm. The coronary angiography excluded other abnormalities. He was admitted to the Intensive Care Unit and treated with epinephrine, hydrocortisone, clemastine, ranitidine, isosorbide dinitrate and norepinephrine infusion. He was discharged from the Intensive Care Unit 72 h after admission and after 7 days from the hospital, fully recovery, without either ECG or echocardiographic abnormalities.

Cefazolin skin tests were positive in all patients by IDT: 2 with cefazolin 0.25 mg/mL, 3 with cefazolin 2.5 mg/mL and 2 with cefazolin 10 mg/mL. Two patients experienced systemic reactions during IDT (oral pruritus and lip/facial angioedema) and were properly treated with oral antihistamines and corticosteroids. The time interval between the perioperative anaphylaxis and the performing of skin testing for the 7 patients ranged from 3 months to 2 years.

All patients had negative skin tests to the remaining extracts (major and minor penicillin determinants, penicillin, amoxicillin, cefuroxime and ceftriaxone). Accordingly, all patients, including the patient with KS, were successfully challenged in a hospital setting with amoxicillin and showed good tolerance to cefuroxime either by DPT or outpatient medical prescription.

Discussion

Skin testing is a crucial step to assess cross-reactivity within the beta-lactam antibiotics, including cephalosporins [5, 6]. Exploring the cross-reactivity between cefazolin and other beta-lactam antibiotics, we have confirmed that our 7 patients, with IgE-mediated hypersensitivity reactions to cefazolin, could tolerate other beta-lactams, representing a selective reactivity pattern. This may be explained by its chemical structure, with a different R1 side-chain from other beta-lactams [6]. The R1 side-chain of cefazolin consists of a heterocycle N-methylthio-diazole structure, which is different from other cephalosporin R1 side-chains [6, 13, 17]. There is no other cephalosporin commercially available in Portugal with this side chain. A selective avoidance of first-generation cephalosporins seems to be reasonable, although the cross-reactivity is mainly determined by a similar R1 side-chain structure [6, 13].

In a case series from our centre, cefazolin represented 16% of beta-lactam-induced anaphylaxis (7 in 43 patients) [18]. We speculate this higher incidence might be due to the frequent use of this first-generation cephalosporin, by parenteral route, in prophylactic surgical protocols. Considering all patients followed in our department over the same period, cefazolin was the most frequently cause of perioperative anaphylaxis. Cefazolin alone accounts for

39% of all cases (7 in 18 patients). There is a substantial geographical variability of drugs or substances involved. In our centre, perioperative anaphylaxis represents 14.4% of all cases of drug-induced anaphylaxis.

Our study is in line with previously published data reporting cefazolin as the most common cause of perioperative hypersensitivity reactions [8, 9, 19]. In a study performed by Kuhlen et al. [19], including patients referred due to perioperative hypersensitivity reactions, the culprit drug was identified in 36% (9 of 25) patients, cefazolin being the most common drug used (6 of 9).

We highlight that the occurrence of KS due to cefazolin is very rare. It was the type I variant, without predisposing factors for coronary artery disease. The concurrent presence of anaphylaxis and cardiac symptoms (KS) was recently described as “allergic angina syndrome” with coronary spasm, which represents a manifestation of endothelial dysfunction or microvascular angina and leads to allergic acute myocardial infarction [20, 21]. KS has increasingly been reported in the literature, it being associated to an endless list of specific triggers including multiple drugs, contrast media, skin disinfectants, foods, several environmental exposures as hymenoptera stings, exercise-induced anaphylaxis, and

even in a scenario of idiopathic anaphylaxis [21]. Recently, Renda et al. [22] published the largest overview of pharmacovigilance international data on KS for all drugs, which included 51 cases, antibiotics being the most common culprit. Additionally, another study from 2 pharmacovigilance databases identified a total of 16 cases of KS only associated to antibiotics use [23].

Cefazolin can be responsible for immediate severe allergic reactions in perioperative setting, including KS. Allergological workup is essential to perform accurate diagnosis and explore cross-reactivity between cefazolin and other beta-lactams. Cefazolin hypersensitivity appears to be a selective allergy with good tolerance for other beta-lactam antibiotics.

Statement of Ethics

Informed consent was obtained from patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

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