Evaluation of Immediate Allergic Reactions to Cephalosporins in Non-Penicillin-Allergic Patients

Raz Somech^{a, c} Elizabeth A. Weber^b Sasson Lavi^a

^aDivision of Immunology and Allergy, The Hospital for Sick Children, and ^bDrug Safety Clinic, Division of Clinical Pharmacology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ont., Canada;

^cPediatric Immunology Service, Safra Children's Hospital, Chaim Sheba Medical Center, Tel Hashomer, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Key Words

Cephalosporin • Penicillin • Drug allergy • Anaphylaxis • Immunoglobulin E • Skin test • Oral challenge

Abstract

Background: Cephalosporins can induce severe or life-threatening IgE-mediated reactions in some individuals. In this study, we wish to describe a group of non-penicillin-allergic patients who were evaluated for immediate allergic reactions to cephalosporins. **Methods:** The patients were assessed by skin tests with the culprit cephalosporin as well as with other cephalosporins and penicillins. If indicated, oral challenge testing was performed. **Results:** Six patients were assessed. A total of 42 skin tests and 20 oral challenges were performed. In 4 patients, skin tests included the causative drug; in 2 patients, the diagnosis of a cephalosporin allergy was made by skin test; in 4 patients, the diagnosis of a cephalosporin hypersensitivity was made by oral challenge. In 96.9% of the oral challenges, which were done using medications with no structural side chain similarities to the culprit drug, no adverse reaction occurred. **Conclusion:** A positive skin test to cephalosporin implies the presence of drug-specific IgE antibodies. Cephalosporins without side chain similarities are suggested to patients with cephalosporin reactions and no β -lactam reactivity.

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Introduction

Cephalosporin antibiotics are widely used for the treatment of common pediatric and adult infections. After the penicillins, they are the most common antibiotics to induce severe or life-threatening IgE-mediated reactions [1]. The estimated risk of developing an allergic reaction with cephalosporins ranges from 1 to 3% and is even higher in patients with documented penicillin allergy, because of the known crossreactivity related to the β -lactam ring, which is shared by both the penicillins and cephalosporins [2, 3]. Since the degradation of penicillin into the major and minor determinants is well described, skin testing that includes these degradation products is considered the most reliable tool for diagnosing IgE-mediated penicillin allergy [4]. Consequently, penicillin skin testing is also recommended in the evaluation of cephalosporin allergy to identify those patients that are allergic to the common β -lactam ring [5]. However, allergic reactions to cephalosporin antibiotics may occur in non-penicillin-allergic patients and are then related to determinants unique to the structure of the specific cephalosporin [5, 6]. In this particular group of patients, the diagnosis of the allergy to cephalosporin is first suggested by the clinical history. Skin testing or in vitro IgE antibody tests using cephalosporin preparations have only limited clinical value [7, 8]. Unlike penicillins, cep-

alosporin skin tests are performed with the native molecule, as the degradation products of the cephalosporins are not available for testing [9]. This may result in a false-negative skin test and a subsequently high-risk oral challenge test. In addition, since the available cephalosporin skin tests are not standardized, there is the potential for false-positive tests from non-specific irritant reactions in non-allergic patients [10]. Since we do not have well-defined skin test concentrations regarding characteristics such as specificity and sensitivity, oral challenges would be helpful, especially in those patients that reacted positively in the skin test in order to prove a correct positive skin test. A position paper by the European Network for Drug Allergy, the European Academy of Allergology and Clinical Immunology interest group on drug hypersensitivity, suggests considering drug provocation tests as the 'gold standard' to establish or exclude the diagnosis of hypersensitivity to a certain substance. The 2 main indications for drug provocation tests with the suspected compounds are to exclude hypersensitivity in non-suggestive histories of drug hypersensitivity or to establish a firm diagnosis in suggestive histories of drug hypersensitivity with negative, non-conclusive or non-available allergologic tests [11, 12].

In this report, we describe a group of non-penicillin-allergic patients who had suspected IgE-mediated allergic reactions to cephalosporins. These patients were assessed by skin tests with the culprit cephalosporin as well as with other cephalosporins and penicillins, including the penicillin determinants. If indicated, oral challenge testing was also performed.

Material and Methods

Patients

Six patients were investigated for suspected IgE-mediated allergy to cephalosporin. None of the patients had a documented penicillin allergy. An immediate reaction was defined as any reaction which occurred within 1 h after receiving the drug. The reaction was diagnosed based on information obtained from medical records or the patients' descriptions. Anaphylaxis was defined if cardiovascular symptoms plus 1 of the following symptoms had been present during the allergic episode: systemic pruritus, generalized erythema, breathing difficulties or dysphonia. Patients consented to be investigated before any evaluation commenced.

Clinical Investigations

Intradermal skin tests were performed on the outer aspect of the upper arm with 0.02 ml of penicillin G 1,000 U/ml, penicillin G 10,000 U/ml, minor determinant mixture 10 mM, ampicillin 15 mg/ml, cloxacillin 3 mg/ml, cefazolin 1 mg/ml, cefuroxime 3 mg/

Table 1. Clinical data of patients

Patient No.	Sex	Age years	Drug	Clinical reaction
1	F	15	cefaclor	urticaria
2	M	53	cephalexin	urticaria, angioedema
3	F	56	cefuroxime	urticaria
4	M	12	cefazolin	anaphylaxis
5	F	40	cefuroxime	anaphylaxis
6	F	43	cefuroxime	urticaria

ml, ceftriaxone 1 mg/ml, cefotetan 1 mg/ml, ceftazidime 1 mg/ml. The dilutions used in this study were similar to those found by others to be non-irritating [10]. Positive and negative control skin prick tests were carried out on the volar aspect of the forearm with histamine hydrochloride and 0.9% sodium chloride, respectively. Skin tests were considered positive if the wheal increased to >3 mm in diameter as compared with the negative control.

When in vivo skin tests were negative, oral challenges were performed using a full-strength dose of the putative cephalosporin as well as additional cephalosporins. One challenge per patient was done per clinic visit. The patient was carefully monitored during test dosing, and complete equipment for cardiopulmonary resuscitation was immediately available. Any symptoms occurring within 24 h after an oral challenge were documented, and a positive challenge was defined if the following had been present: urticaria, angioedema, pruritus, breathing difficulties, dysphonia or cardiovascular symptoms.

Results

Clinical Presentation

Six patients (4 females, 2 males), ranging in age from 12 to 56 years, with clinical histories of immediate reactions to cephalosporins were investigated and form the basis of this report. The responsible compounds were cefuroxime (3 patients), cefaclor (1 patient), cefazolin (1 patient) and cephalexin (1 patient). The reported adverse reactions to cephalosporins included: isolated urticaria (3 patients), anaphylaxis (2 patients), urticaria and angioedema (1 patient). The responsible compounds in the 2 anaphylactic cases were cefuroxime and cefazolin (table 1).

Skin Testing and Oral Challenging

A total of 42 skin tests and 20 oral challenges were performed with the culprit drug, other cephalosporins and penicillins, including the penicillin determinants (table 2). Two patients (No. 4 and 5) with histories of reactions to cefazolin and cefuroxime had positive skin tests

Table 2. Results of skin test and challenge test

Patient No.	Skin test		Oral challenge test		
	drug tested	positive results	drug tested	positive results	clinical reaction
1	penicillin G ¹ , cloxacillin, ampicillin, cefazolin, cefuroxime	none	penicillin VK, cefaclor	cefaclor	anaphylaxis
2	penicillin G ¹ , cloxacillin, ampicillin, cefazolin, cefuroxime, ceftriaxone, cefotaxime, ceftazidime	none	penicillin VK, amoxicillin ² , cloxacillin, cefuroxime, cephalixin ² , cefaclor ²	cephalexin ² , cefaclor ²	anaphylaxis urticaria
3	penicillin G ¹ , cloxacillin, ampicillin, cefazolin, cefuroxime, ceftriaxone, cefotaxime, ceftazidime	none	penicillin VK, cefaclor, cefuroxime ³ , cephalixin ³	cefuroxime ³ , cephalixin ³	urticaria urticaria
4	penicillin G ¹ , cloxacillin, ampicillin, cefazolin, cefuroxime, ceftriaxone, cefotaxime, ceftazidime	cefazolin ¹	penicillin VK ² , amoxicillin, cefaclor	none	
5	penicillin G ¹ , cloxacillin, ampicillin, cefazolin, cefuroxime,	cefuroxime	none	none	
6	penicillin G ¹ , cloxacillin, ampicillin, cefazolin, cefuroxime, ceftriaxone, cefotaxime, ceftazidime	none	penicillin VK, cloxacillin, cefaclor, cephalixin, cefuroxime	cefuroxime	urticaria, angioedema

¹ Penicillin skin test including penicillin G and minor determinants.

² Medication with similar structure of 7-position side chain.

³ No similarities in structure of 3- or 7-position side chains.

with the culprit drug (wheal = 30 and 28 mm, respectively) but not with other drugs. These patients were not orally challenged with the culprit drug. Four patients (No. 1, 2, 3 and 6) displayed negative results to all the allergy skin tests. Two of them (No. 3, 6) displayed negative results to the culprit cephalosporin; the other 2 patients (No. 1, 2) were not tested with the culprit cephalosporin but were negative to a panel of different cephalosporins. Oral challenge tests with the culprit and other cephalosporins were offered to these patients. The chemical structure of drugs used for oral challenge is given in figure 1. All 4 patients reacted during oral challenge tests with the culprit drug, including cefuroxime (No. 3 and 6), cefaclor (No. 1) and cephalixin (No. 2). In addition, patient No. 2 who had a positive challenge test to cephalixin also had a positive challenge test to cefaclor but not to amoxicillin, which shares structural similarities in the 7-position side chain. Patient No. 3, who was challenge positive to cefuroxime, was also challenge positive to cephalixin, which is from a different cephalosporin generation with no structural similarities to cefuroxime in the 3- or 7-position side chains. Patient No. 4, who had a positive skin test to cefazolin, was able to tolerate penicil-

lin VK despite the 7-position side chain similarities of the 2 drugs. Thirteen oral challenge tests performed using medications different from the culprit drug in the 3- or 7-position side chains were negative. A total of 9 oral challenge tests were performed with different penicillins and were all negative.

At the completion of the testing, all patients were considered to have evidence of IgE allergy to the culprit drug. However, 4 patients (No. 2, 3, 4 and 6) were able to tolerate other cephalosporins, which differed from the culprit drug in the 3- or 7-position side chains.

Discussion

The increased therapeutic use of cephalosporins brings about the risk of developing allergic reactions in susceptible patients. Yet, the evaluation of patients with primary cephalosporin allergy has many difficulties and controversies, including the accuracy of cephalosporin skin testing and the incidence and specificity of side chain-specific antibodies in the immune response to cephalosporins [1].

Fig. 1. Structure of the β -lactam ring and 3- and 7-position side chains of several cephalosporins shows the 3- and 7-position side chain similarities between cefaclor and cephalexin which are different from those of cefuroxime. Amoxicillin has a 7-position side chain similarity to both cefaclor and cephalexin.

We described 6 patients with histories suggestive of IgE-mediated reactions to cephalosporins. Their symptoms ranged from urticaria to anaphylaxis, and the diagnosis was confirmed by skin testing (2 patients) or oral challenge testing (4 patients). Skin testing with the native

drug was helpful in establishing the diagnosis in only 2 out of 4 patients tested with the culprit drug. The allergy in the 2 patients who displayed a negative skin test with the culprit drug was confirmed by the oral challenge test. We must assume that for these skin test-negative/oral challenge-positive patients, unidentified drug metabolites or degradation products were clinically relevant and were missed by the currently available skin tests. Therefore, in the face of strong clinical history suggestive of an IgE-mediated reaction to a cephalosporin, negative skin testing should be considered a false negative, until an oral challenge can be carried out.

Penicillin skin testing should always be done first in patients with cephalosporin reaction, even if there is no history of a previous penicillin allergy, to exclude general β -lactam sensitivity. Then, skin testing with the culprit cephalosporin is worthwhile in all patients. A positive confirms the history, while a negative leads to an oral challenge for final confirmation. In addition, skin and challenge testing using non-culprit cephalosporins is valuable to allow the use of other cephalosporins in the future. The latter is possible because of the known lack of cross-sensitivity between most cephalosporins [6]. Since the side chain-specific antibodies predominate in the immune response to cephalosporins [13], classification based on side chain structures, which does not necessarily correlate with the antimicrobial classification of the cephalosporin generations, is considered a valuable tool when choosing an alternative cephalosporin [14]. For example, when 21 patients allergic to amoxicillin [14] were tested for allergenic crossreactivity to cefadroxil and cefamandole, 38% had a positive response to cefadroxil (same side chain) and none to cefamandole (different side chain). Similarly, only 10.5–12% of patients with known penicillin allergy have reacted to a cephalosporin with an identical side chain [16, 17]. We performed a side chain comparison of all the cephalosporins used by us for oral challenge tests. A total of 20 oral challenges were performed on 5 patients (excluding patient No. 5). Of them, 14 challenges were done using medications with no structural side chain similarities to the culprit drug. These medications are unlikely to cross-react. Indeed, 13 of the 14 oral challenges were negative, suggesting that crossreactivity between medications with no structural side chain similarities in our cohort of patients was only 7.1%. In addition, 1 patient had a positive challenge test to 2 medications with a similar 7-position side chain (cefaclor and cephalexin, patient No. 2), further suggesting the significance of that specific side chain to the immune response to cephalosporins in

that patient. Interestingly, this patient tolerated amoxicillin, which has a similar but not identical 7-position side chain, suggesting that the minor variation in the 7-position side chain was accountable for the original cephalosporin reaction. Similarly, patient No. 4, who had a positive skin test to cefazolin, was able to tolerate penicillin VK despite the 7-position side chain similarities of the 2 drugs. In addition, 1 patient had positive challenge tests to 2 medications without 3- or 7-position side chain similarities (cefuroxime and cephalexin, patient No. 3). This is of interest since challenging with a medication with no side chain similarities to the culprit is considered highly unlikely to produce an allergic reaction [6]. In fact, rabbit antibodies against cephalosporins with a different side chain do not crossreact [18]. Finding a patient who reacted to different medications with no side chain similarities can be explained by either additional selective response to unique determinants or crossreactivity [19].

In summary, we have shown that in non-penicillin-allergic patients with a suspected IgE-mediated reaction to a cephalosporin, a positive skin test to that cephalosporin implies the presence of drug-specific IgE antibodies and the patient should receive an alternate drug or undergo desensitization. In the face of clinical history suggestive of IgE-mediated reaction, negative skin test results to the culprit cephalosporin should be considered falsely negative, until an oral challenge can be carried out. Cephalosporins without side chain similarities are suggested for oral challenging to patients with cephalosporin reactions and no β -lactam reactivity; however, the procedure should be carried out cautiously in a hospital setting. More extensive structural analysis of cephalosporins and their metabolic byproducts, as well as better skin testing materials including these metabolic byproducts will help our understanding of the specificity of the immune response to cephalosporins and our ability to test for side chain specificity and potential crossreactivity.

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