

Brief communications

Independent anaphylaxis to cefazolin without allergy to other β -lactam antibiotics

Richard J. Warrington, MD, PhD, FRCPC,^a and Shawn McPhillips, RN^b

Winnipeg, Manitoba, Canada

Immediate hypersensitivity reactions to β -lactam antibiotics, such as penicillins, are relatively common and usually caused by IgE antibodies to the major and minor antigenic determinants of penicillin, although side-chain-specific reactions to semi-synthetic penicillins have been described.^{1,2} Although sensitivity to cephalosporins may occur because of cross-reactivity to β -lactam ring structures, immediate hypersensitivity to these medications can be side-chain-specific.³ Therefore in most patients who react to cephalosporins with immediate anaphylactic hypersensitivity, there should be either preexisting IgE-mediated allergy to penicillin or prior exposure to the specific cephalosporin that produced the reaction.

We report here the occurrence, over a 6-month period, of four cases of immediate anaphylaxis to cefazolin given before surgery, in patients lacking a history of penicillin allergy or documented cefazolin exposure. Skin testing for immediate hypersensitivity demonstrated positive reactions only to cefazolin, with no reactivity to other β -lactams, indicating preexisting unpredictable and unexplainable side-chain-specific immediate allergy to cefazolin.

CASE REPORTS

Patient 1 was a 19-year-old woman who received 1 gm of cefazolin intravenously in the operating room before kidney transplantation. She had taken 500 mg of amoxicillin by mouth three times daily for 10 days before surgery for treatment of a respiratory tract infection. She experienced anaphylactic shock after administration of the cefazolin, requiring 400 μ g of epinephrine and 5 L of normal saline solution to control her hypotension. She was intubated at the time of the administration of

Abbreviation used

MDM: Minor determinant mixture

cefazolin. Successful transplantation was carried out after resuscitation. She had never had surgery before.

Patient 2 was a 35-year-old woman who received a single dose of 1 gm of cefazolin intravenously before cholecystectomy, and within 5 minutes generalized hives developed, followed by angioedema of the throat. She was treated with diphenhydramine, and the subsequent operation was performed without problems. She could not recall receiving cefazolin previously. She had a history of hives induced by citrus fruits. Her only other surgery had been a tonsillectomy many years before.

Patient 3 was a 23-year-old woman who was given 1 gm of cefazolin before laparoscopic cholecystectomy and immediately experienced sneezing, generalized hives, and angioedema, followed by difficulty in breathing and swallowing and hypotension. She was treated with intravenous fluids, epinephrine, diphenhydramine, and corticosteroids. Her symptoms resolved over 24 hours. She had never reacted to penicillins previously and could not remember when she last received this type of antibiotic. She had never undergone surgery or received intravenous medications.

Patient 4 was a 29-year-old woman who experienced anaphylaxis with urticaria, wheezing, and hypotension during general anesthesia after 1 gm of cefazolin was given intravenously as prophylaxis before reduction of a compound tibial fracture. She was treated for anaphylaxis but continued to have respiratory symptoms, hives, and swelling for the next 24 to 48 hours. She had received amoxicillin without adverse effects during the previous year but had never, to her knowledge, received any cephalosporins. Her only other surgery had been a tonsillectomy 20 years before.

Skin testing was carried out approximately 2 months after the reactions (range, 1 to 4 months), and in two patients testing was repeated more than 6 months after the anaphylactic episode. Tests were carried out with benzylpenicilloyl polylysine (6×10^{-5} mol/L; Pre-Pen, Kremers-Urban Company, Milwaukee, Wis.), benzylpenicillin minor determinant mixture (MDM) (containing 1×10^{-2} mol/L benzylpenicillin, 1×10^{-2} mol/L

From ^aDepartments of Medicine & Immunology and ^bHealth Sciences Centre, Winnipeg, Manitoba, Canada.

Reprint requests: Richard J. Warrington, MD, PhD, Section of Allergy & Clinical Immunology, Health Sciences Centre, 820 Sherbrook Str., Winnipeg, Manitoba, Canada R3A 1R9.

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TABLE I. Intradermal skin test reactivity to penicillin and cephalosporin reagents in patients with cefazolin anaphylaxis

Patient No.	BPO-PL	BP-MDM	Cefazolin	Cefotaxime	Ceftazidime
1	Negative	Negative	8 millimeter	Negative	3 millimeter
2	Negative	Negative	6 millimeter	Negative	Negative
3	Negative	Negative	8 millimeter	Negative	ND
4	Negative	Negative	10 millimeter	Negative	ND

All skin test results are expressed as the size of the wheal at the skin test site minus the control wheal diameter.
BPO-PL, Benzylpenicilloyl polylysate; BP, benzylpenicillin; ND, not done.

benzylpenicilloate, and 1×10^{-2} mol/L benzylpenicilloate) and MDMs of cefazolin, cefotaxime, and ceftazidime (1×10^{-2} mol/L), prepared as described previously.² Phosphate-buffered saline and histamine phosphate, 1 mg/ml, were used as positive and negative controls, respectively.

Skin tests were carried out by the prick method and then intradermally. Test results were considered to be positive if a wheal of 3 mm or greater than that of the saline control was obtained and was also associated with a flare. The cefazolin skin test MDM did not produce a positive reaction in 30 patients tested but lacking skin test reactivity to benzylpenicilloyl polylysine, benzylpenicillin-MDM or a history of cefazolin allergy.

RESULTS

The results of intradermal skin testing are shown in Table I. In all four cases, no reactions occurred in response to epicutaneous prick and intradermal testing with the major and minor determinants of benzylpenicillin and cefotaxime. All four patients showed positive intradermal reactions to cefazolin with an average wheal diameter of 8 mm (range, 6 to 10 mm) with flare. In two patients tested with ceftazidime, one (patient 1) reacted with a small 3 mm response. Patients 2 and 3 were retested more than 6 months later and retained the same levels of skin test reactivity to cefazolin.

DISCUSSION

In these four patients, there was unpredictable anaphylaxis after the administration of cefazolin, associated with side-chain-specific IgE-mediated skin test reactivity to this drug, all of which occurred within a 6-month period. General anesthetics were not implicated in the reactions, because all patients subsequently had their surgery without untoward effects. It is unlikely that these patients had undetected penicillin MDM reactivity caused by a deficiency in this preparation because: (1) patient 1 received amoxicillin up to the time of surgery without adverse

reaction, (2) the relevant penicillin minor determinants would be unlikely to be only in the cefazolin reagent, (3) we have no clinical evidence of such a deficiency in our MDM preparation, (4) in the study by Thoburn et al.,⁴ of patients who reacted to penicillin and cephalothin, skin reactivity was to the major determinant benzylpenicilloyl polylysine. No potential previous exposure to cefazolin could be identified, including recent surgery, intravenous antibiotics, or occupational exposure. There does not appear to be any known cross-reactivity of cefazolin with non- β -lactam drugs, and the reactions occurred in three different hospitals in two different provinces.

Igea et al.⁵ reported two patients who reacted unexpectedly to cefazolin given before surgery, with anaphylaxis or with a rash. Results of skin tests were also positive in response to cefazolin but not in response to other penicillins or cephalosporins. Neither of these patients remembered receiving cephalosporins in the past, but there was opportunity, for one had received parenteral antibiotics for treatment of acute pyelonephritis, and the other had undergone two abdominal operations.

The four patients reported here show that cefazolin-specific and therefore side-chain-specific anaphylactic sensitivity can be present in patients with no history of β -lactam allergy and no obvious prior exposure to this drug. This allergic state would not have been demonstrable with β -lactams other than the implicated drug for skin testing. The source of original sensitization in these patients is of concern and is as yet undetermined.

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The multiple drug allergy syndrome: A matched-control retrospective study in patients allergic to penicillin

Ludwig Khoury, MD, and Richard Warrington, MB, BS, PhD, FRCP(C)
Winnipeg, Manitoba, Canada

Several studies have previously reported an increased rate of allergic reactions to drugs in patients with a history of drug allergy. The earliest such report by Smith et al.¹ showed that in patients with penicillin reactions, some of whom had positive skin test reactions to penicillin derivatives, a history of a drug reaction was present in 29.1%, compared with 11.5% in patients without a penicillin reaction. Sullivan et al.² found that 21% of patients with a history of immediate hypersensitivity to penicillin experienced immunopathologic reactions to non- β -lactam antibiotics. In children with a history of multiple antibiotic sensitivity, Kamada et al.³ reported that 35% had positive skin test reactions to penicillin reagents. Importantly, Moseley and Sullivan⁴ screened 37 patients with a history of allergic reactions to antimicrobial drugs and found that 13.2% subsequently reacted to a course of antimicrobial drug therapy, compared with only 1.4% of 74 matched control patients. The relative risk of developing an allergic drug reaction with a history of drug allergy in that study was 9.4. These results have been interpreted as indicating that some individuals are at increased risk of reacting to drug haptens that are quite different

immunochemically, although the mechanism for such hyperreactivity is unclear.

Because it was difficult in the above-mentioned studies to determine whether skin test-proven immediate hypersensitivity to penicillin was a risk factor for multiple drug allergies and because control groups were sometimes absent or not clearly defined, we compared retrospectively the frequency of multiple drug allergies in matched groups of: (1) patients with skin test-proven immediate hypersensitivity to penicillins, (2) patients allergic to penicillin with negative skin test results but a positive history, and (3) patients with vasomotor rhinitis.

METHODS

A total of 44 consecutive patients (41 of whom were female) who had a history of penicillin allergy characterized by (1) urticaria or angioedema, (2) maculopapular eruption, or (3) anaphylaxis and were documented as having positive immediate hypersensitivity skin test responses to the major and minor determinants of benzylpenicillin or semi-synthetic penicillins (group A), diagnosed as described previously,⁵ were matched in terms of sex and age with 44 patients who had a similar positive history of penicillin allergy but negative skin test responses to penicillin reagents (group B). A third group of patients with a diagnosis of vasomotor rhinitis and negative skin test responses to common inhalant allergens were matched in terms of age and sex with the groups A and B (group C). The clinical reactions to β -lactam antibiotics that occurred before skin testing for penicillin allergy in group A and group B are shown in Table I. No significant differences were seen in the types of clinical reactions reported in the two groups. The frequency and types of allergic reactions caused by

From Section of Allergy and Clinical Immunology, Department of Internal Medicine, University of Manitoba and the Health Sciences Centre.

Reprint requests: Richard J. Warrington, MB, BS, PhD, FRCP(C), Head, Section of Allergy and Clinical Immunology, 820 Sherbrook St., Winnipeg, Manitoba R3A 1R9, Canada.

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