

Allergy to cefazolin: study of *in vivo* cross reactivity with other betalactams

Juan Manuel Igea, MD; Juan Fraj, MD; Ignacio Davila, MD; Manuela Cuevas, MD; Javier Cuesta, MD, PhD; and Miguel Hinojosa, MD

We present two cases of hypersensitivity to cefazolin (one anaphylaxis). The skin prick tests with cefazolin at therapeutic concentration were positive. For the in vitro study we used conjugates of cefazolin with human serum albumin, obtaining a positive result in the histamine release test in both patients. In one case, we demonstrated anticefazolin-specific IgE antibodies by RAST. The controls did not react to any of these tests.

Finally, we carried out skin tests and challenge tests with other betalactam antibiotics, including benzylpenicillin, amoxicillin, aztreonam, cefuroxime and cefotaxime, showing in both patients good tolerance to all these drugs.

INTRODUCTION

Cephalosporins are betalactam antibiotics widely used, mainly for their efficacy in gram(+) and gram(-) infections, and their few side effects; nevertheless, they rarely are first choice drugs because there are other less expensive drugs of similar effectiveness.

Hypersensitivity reactions are the most important side effects of these drugs because of their potential seriousness although life-threatening reactions have been reported only rarely.¹⁻⁴

The exact haptenic determinants of the cephalosporin molecule that cause allergic reactions are not known, making questions about the incidence of immunologic cross-reactivity with penicillins and other betalactam drugs difficult to answer. Although some retrospective surveys support a high incidence of cross-reactivity between penicillins and cephalosporins,⁵⁻⁷ more recent studies do not confirm this.⁸⁻¹⁰

In this study, we present two cefazolin-allergic patients with good tolerance of other betalactams. In both cases, cefazolin was employed

as prophylaxis against surgical infection. Cefazolin (in a single dose) provides a high degree of prophylaxis against infection in patients undergoing surgery because of its effectiveness in nosocomial infection by gram(-) organisms;¹¹ furthermore, cost considerations favor the use of this antibiotic.¹²

CASE REPORTS

Case 1

A nonatopic 21-year-old woman without any history of adverse reaction to drugs was admitted to the hospital to undergo a third molar extraction. During surgery, while she was hemodynamically stable, 1 g of cefazolin was administered intravenously as surgical prophylaxis, and in a few seconds she developed a generalized urticarial rash, hypotension and tachycardia (Fig 1). There was no sign of bronchospasm. These symptoms disappeared 20 minutes after appropriate treatment. She did not remember having taken any cephalosporin before, although, in the past, she had been treated with parenteral antibiotics because of acute pyelonephritis and penetrating and blunt injury of her left leg.

Case 2

A nonatopic 45-year-old woman without any history of adverse reactions to drugs was admitted to the hospital to undergo cholecystec-

tomy. Before surgery 1 g of cefazolin was administered by intramuscular injection as prophylaxis against surgical infection. In a few seconds she developed a generalized pruriginous urticarial rash without any other symptoms. This resolved after appropriate treatment. She did not remember having taken any cephalosporin before, although she had undergone two abdominal operations in the past.

MATERIAL AND METHODS

Skin Tests

We performed skin prick tests with cefazolin at different concentrations: 1, 2, 5, 10, 100, and 250 mg/mL in normal saline.

Furthermore, we performed skin prick tests with a battery of six cephalosporins frequently used in our hospital, at their normal therapeutic concentrations, including ceftazidime (100 mg/mL), ceftriaxone (100 mg/mL), cefotaxime (250 mg/mL), cefoxitin (100 mg/mL), cefuroxime (125 mg/mL), and cefamandole (333 mg/mL). If these were negative, we performed intradermal tests with the same cephalosporins at the same concentrations.

We also carried out prick and intradermal tests with other betalactam antibiotics, including:

- benzylpenicillin at 10,000 U/ml (Antibioticos SA, Spain); we also used the major determinant penicilloylpolylysine 0.000006 M (Kre-

From the *Servicios de Alergología e Inmunología; Hospital Ramón y Cajal; Cra. Colmenar Viejo, Km 9.1; 28034 Madrid; Spain.

Received for publication December 26, 1990.

Accepted for publication July 18, 1991.

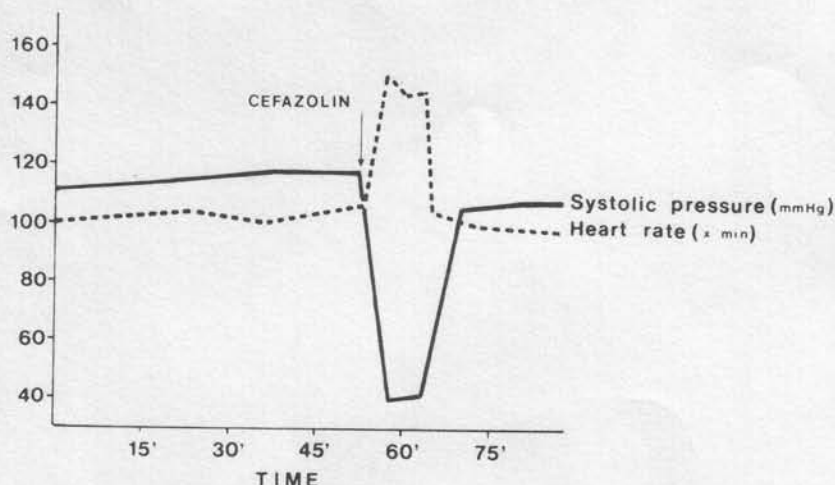


Figure 1. Hemodynamic changes in patient no 1 after the administration of 1 g of cefazolin IV during surgery.

mers Urban Co, EEUU) and a minor determinant mixture composed of 0.6 mg/mL of benzylpenicillin and 0.5 mg/mL of benzylpenicilloate (Stallergens Lab, France).

- amoxicillin at 20 mg/mL (Beecham, Spain)

- aztreonam, at normal therapeutic concentration (250 mg/mL) (Squibb SA, Spain).

All the skin test solutions were prepared and used immediately. All these tests were applied in duplicate.

Normal saline was used as a negative control. Clorhydrate histamine at 10 mg/mL and 0.1 mg/mL was used as positive control for prick and intradermal tests, respectively. The injected volume for intradermal tests was 0.02 mL for controls and drug solutions. All skin tests were examined after 15 minutes and six hours.

For skin prick tests, we considered a reaction as positive if the wheal size induced by the allergen was 3 mm larger than the one obtained in the negative control; for intradermal test, a reaction was considered positive if the wheal size was similar to the one obtained with the positive control or if, regardless the size, the wheal had pseudopods.

The nonspecific irritant capacity of each skin test solution was investigated in a control population of

ten subjects with no history of adverse drug reactions.

Total IgE

Total IgE was measured by IgE EIA technique according to the manufacturer's instructions (Pharmacia, Sweden).

Cefazolin Protein Conjugate

Protein conjugates of cefazolin with human serum albumin were prepared according to the method of Levine and Ovary.¹³

Histamine Release Test

This test was performed using an automated fluorometric method according to Siraganian¹⁴ with the modifications described previously,¹⁵ with six different concentrations (1:5, 1:25, 1:125, 1:625, 1:3125, 1:15625) of cefazolin conjugated with human serum albumin. A result higher than 10% release was considered positive.

Before allergen challenge, blood samples were tested with four dilutions of goat antihuman IgE (Tago, Burlingame, USA).

The total basophil histamine content was measured in the patients by adding perchloric acid (Merck, Darmstadt, Germany) at a concentration of 10% vol/vol to the sample blood.

The same test was performed on

five sera from subjects without histories of adverse drug reactions.

Specific IgE Determination

Specific IgE was determined by RAST. Nitrocellulose paper discs (Hoeffer Scientific Instrument, US) were coupled with cefazolin conjugates by a 24-hour incubation at room temperature. Thereafter, the discs were washed three times in PBS 0.1% Tween 20 (PBS-Tw). To facilitate the desorption, 1% bovine serum albumin in PBS was added and the discs were incubated for one hour at room temperature. After washing again three times with PBS-Tw, discs were ready for use; then they were stored in PBS at 4 °C.

The RAST assay was carried out incubating our cefazolin conjugate nitrocellulose discs with 50 µL of serum for 18 hours at room temperature. Then the discs were washed three times with PBS-Tw to remove unreacted serum. Afterwards, 50 µL of ¹²⁵I labeled anti-IgE (Pharmacia Diagnostics, Sweden) were added and incubated 18 hours at room temperature. Then, the washing steps were repeated and discs were read on a gamma counter. The RAST was performed in duplicate.

The control group consisted of a pool of sera from five normal individuals and a pool of sera from five penicillin-allergic patients with positive RAST to penicillin. A value in the RAST higher than the mean plus 2 SD was considered positive.

Challenge Tests

If skin tests to benzylpenicillin and its determinants were negative, the patient was challenged by administering benzylpenicillin. We started with 10,000 U administered subcutaneously. After one hour, if no reaction was observed, we continued with 10,000 U intramuscularly, and then double doses were administered at 1-hour intervals until a therapeutic dose was reached (600,000 U).

If skin tests to amoxicillin were negative, the patient was challenged by the oral route with this drug,

administering 5, 50, and 500 mg, at 2-hour intervals.

If skin tests to aztreonam were negative, the patient was challenged with this drug. Aztreonam (1 mL of 25 mg/mL) was administered subcutaneously, and if this dose was tolerated, further injections of 250, 500, and 1,000 mg intramuscularly were administered at 2-hour intervals.

If skin tests to cephalosporins other than cefazolin were negative, we carried out the following challenges:

- cefuroxime (Glaxo, Spain) by the oral route: 5, 25, 100, and 500 mg with 2-hour intervals.

- cefotaxime (Roussel Ibérica, Spain) by the parenteral route: 0.2 mL of 250 mg/mL was administered subcutaneously, and if this was tolerated, further injections of 100, 500, and 1,000 mg intramuscularly were administered every two hours.

These challenges were carried out as open procedures. Written informed consent of the patients was obtained before challenges. The patients were carefully monitored and full emergency therapy was available.

All the studies were performed in our hospital.

RESULTS

Skin prick tests with cefazolin were positive in the two patients at normal therapeutic concentration; smaller concentrations did not elicit responses (Table 1). The same test was negative in the control subjects.

Total serum IgE was less than 100 IU/mL in the two patients.

Both patients had positive leukocyte histamine release tests, with maximum releases of 50% in patient 1 and 29% in patient 2 (Fig. 2). Both patients had positive histamine release with the goat anti-human IgE. The control subjects had negative results with the same test.

Specific anti-cefazolin IgE was found only in patient number 1. We obtained by RAST 1,095 cpm which was ten times greater than the

Table 1. Results of Skin Prick and Intradermal Tests with the Different Betalactam Antibiotics and their Concentrations in Both Patients

	Patient 1		Patient 2	
	Prick	ID	Prick	ID
Benzylpenicillin (10,000 U/mL)	neg	neg	neg	neg
MDM*	neg	neg	neg	neg
PPL*	neg	neg	neg	neg
Amoxicillin (20 mg/mL)	neg	neg	neg	neg
Aztreonam (250 mg/mL)	neg	neg	neg	neg
Cefazolin				
1 mg/mL	neg	—	neg	—
2 mg/mL	neg	—	neg	—
5 mg/mL	neg	—	neg	—
10 mg/mL	neg	—	neg	—
100 mg/mL	neg	—	neg	—
250 mg/mL	7 mm	—	6 mm	—
Ceftazidime (100 mg/mL)	neg	neg	neg	neg
Ceftriaxone (100 mg/mL)	neg	neg	neg	neg
Cefotaxime (250 mg/mL)	neg	neg	neg	neg
Cefoxitin (100 mg/mL)	neg	neg	neg	neg
Cefuroxime (125 mg/mL)	neg	neg	neg	neg
Cefamandole (333 mg/mL)	neg	neg	neg	neg
Controls				
Histamine	7 mm	7 mm	5 mm	6 mm
Saline	neg	neg	neg	neg

* MDM = minor determinant mixture and PPL = penicilloylpolyllysine.

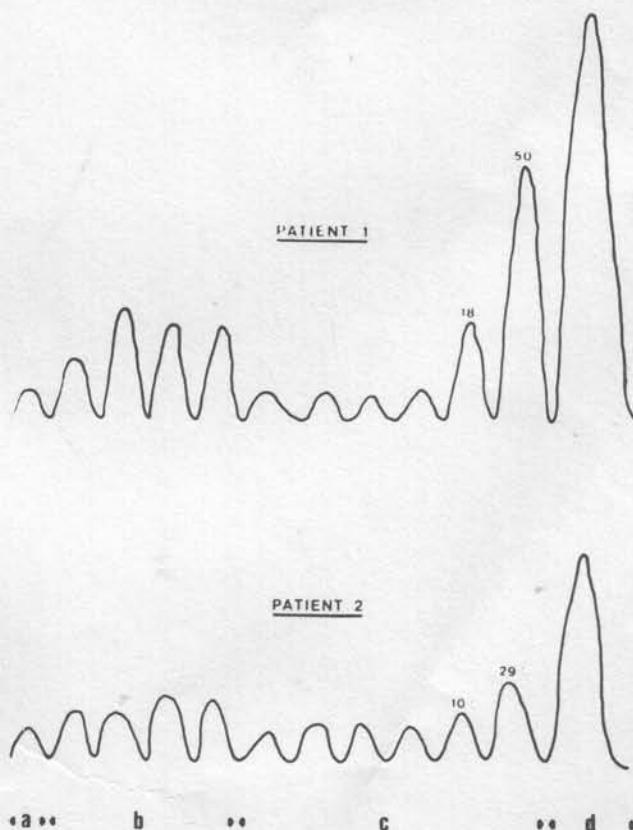


Figure 2. Histamine release tests in both patients (a = basal; b = antihuman IgE; c = cefazolin-human serum albumin; and d = total histamine).

mean of the control group (including penicillin-allergic patients with positive RAST to penicillin). The count obtained in patient number 2 was similar to the control group (Table 2).

The skin and challenge tests with the other antibiotics (benzylpenicillin, amoxicillin, aztreonam, and the other cephalosporins) were all negative in both patients, showing a perfect tolerance to all these betalactam antibiotics (Tables 1 and 3).

DISCUSSION

We present two cases of hypersensitivity reactions to cefazolin, one of which is anaphylaxis. Although we have demonstrated anticefazolin-specific IgE antibodies in only one case, the symptomatology described, the positive skin prick tests, and the histamine release tests with cefazolin in both patients strongly suggest a type I hypersensitivity reaction to this cephalosporin.

Skin (prick) tests with cefazolin at therapeutic concentration seem a reliable and effective method for identifying patients allergic to this drug, although more studies are required with a more extensive number of patients. The negative results in the control subjects support the specificity of this test. There is no previous report about skin tests with

cephalosporins and concentrations to be used; only one study¹⁶ suggests that cephalotin concentrations greater than 1 mg/mL in intradermal testing tend to give many false positive reactions.

Because cefazolin is probably an incomplete antigen due to its low molecular weight, we have combined this drug with an autologous protein to produce a complete antigen to be used in *in vitro* tests. The histamine release test and RAST with conjugates of cefazolin have helped us diagnose cefazolin-allergy. We think they could be a helpful diagnostic procedure in cefazolin-allergy, at least in some cases.

The study of *in vivo* cross-reactivity with other betalactams showed good tolerance to penicillin, amoxicillin, and aztreonam in both patients. These results are consistent with low clinically relevant cross-reactivity between the betalactam antibiotics (penicillin, cephalosporins, and aztreonam), as indicated by recent reports.^{8-10, 17} In some of these, penicillin-skin test-positive patients were challenged with cephalosporins without adverse reactions. Saxon et al established a reaction rate of 3% to 7% for cephalosporins in patients with a positive history of penicillin allergy.⁸

All these investigators have studied tolerance to cephalosporins in penicillin-allergic patients, but none has studied tolerance to other betalactam antibiotics in patients with primary cephalosporin allergy; in fact, cases of primary cephalosporin allergy have been reported only rarely.^{4, 18, 19}

On the other hand, both of our patients tolerated administration of

other cephalosporins. Others have suggested low cross-reactivity among cephalosporins.^{8, 20} In fact, antibodies to cephalosporins with different side-chains prepared in rabbits fail to cross-react.²¹

All these works, including the present one, strongly suggest that side-chain specific antibodies predominate in the immune response to cephalosporins. This would explain the low cross-reactivity among different cephalosporins, which share the same nucleus but different side-chains. Furthermore, it would explain the low cross-reactivity among cephalosporins and other betalactam antibiotics, which share the same betalactam ring in the nucleus but different side-chains. Probably, the few cases of penicillin-allergic patients who react to cephalosporins (fewer than 7%⁸) are due to antibodies to the betalactam ring or to similar side-chains of the two antibiotics.

In the group of penicillins, although betalactam-specific antibodies predominate in the immune response, recent works indicate the importance of side-chain specific antibodies.^{22, 23}

Cross-reactivity between a cephalosporin and other betalactams, or the lack of it, could be rationalized in part, in terms of side-chain structure considerations. It is useful to remember that cephmandole, cephaloram, cephalotin, and cephaloridine have side-chains very similar to that of benzylpenicillin^{21, 24, 25}; that cephalexin has a side-chain identical to that of ampicillin; that cephadroxil has the same side-chain as amoxicillin; and that ceftazidime has the same one as aztreonam.

It seems that the cephalosporin nucleus is less immunogenic than the penicillin nucleus, perhaps because of greater lability of the cephalosporin nucleus following aminolysis of the betalactam ring.²¹ This would explain, at least in part, the lesser incidence of cephalosporin allergy when compared with penicillin allergy.²⁶ It is of interest that

Table 2. RAST Results in the Two Patients and the Mean and Standard Deviation in the Control Group (5 Normal Individuals and 5 Penicillin-Allergic Patients), Expressed in c.p.m.

Patients	CPM
Patient no. 1	1095
Patient no. 2	93
Control group (mean + 2 SD)	74.8 + 19.2

Table 3. Challenge Test Results in Both Patients with the Route and Maximum Dose Administered

Drugs	Doses	Route	Patient 1	Patient 2
Benzylpenicillin	600,000 U	IM	neg	neg
Amoxicillin	500 mg	Oral	neg	neg
Aztreonam	1,000 mg	IM	neg	neg
Cefuroxime	500 mg	Oral	neg	neg
Cefotaxime	1,000 mg	IM	neg	neg

some cephalosporins can reduce IgE levels *in vivo*²⁷ and other immunogenic responses *in vitro*,²⁸ which could contribute to this.

In conclusion, patients primarily sensitized to cefazolin can tolerate penicillins, aztreonam, and even other cephalosporins. Although more studies are required, soon we may be able to advise physicians about the use of one of these drugs in the cephalosporin-allergic patient, when the right indication has been established and always under medical supervision during and after therapy. For the present it is reasonable to avoid the use of any betalactam antibiotic in the cephalosporin-allergic patient.

ACKNOWLEDGMENTS

The authors thank Teresa Sanchez, Francisca Jaime, and Dolores Esteban for laboratory assistance and Pablo Mugüerza, MD for his advice in translating.

REFERENCES

1. Spruill FG, Minette LJ, Sturmer WQ. Two surgical deaths associated with cephalotin. *JAMA* 1974;229:440-3.
2. Saleh Y, Tischler E. Severe anaphylactic reaction to intravenous cephaloridine in a pregnant patient. *Med J Australia* 1974;1:490-3.
3. Barnett AS, Hirshman CA. Anaphylactic reaction to cephalirin during spinal anesthesia. *Anesthesia Analgesia* 1979;58:337-9.
4. Hoffman DR, Hudson P, Carlyle SJ, et al. Three cases of fatal anaphylaxis to antibiotics in patients with prior histories of allergy to the drug. *Ann Allergy* 1989;62:91-3.
5. Petz LD. Immunologic reactions of humans to cephalosporins. *Postgrad Med J* 1971;47(Suppl):64-9.
6. Petz LD. Immunologic cross-reactivity of penicillins and cephalosporins. *J Infect Dis* 1978;137:S74-9.
7. Grieco MH. Cross-allergenicity of the penicillins and cephalosporins. *Arch Intern Med* 1967;119:141-6.
8. Saxon A, Heall GN, Rohr AS. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med* 1987;107:204-15.
9. Solley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: clinical experience with a battery of skin-test reagents. *J Allergy Clin Immunol* 1982;69:238-44.
10. Blanca M, Fernandez J, Miranda A, et al. Cross-reactivity between penicillins and cephalosporins: clinical and immunological studies. *J Allergy Clin Immunol* 1989;83:381-5.
11. Nichols RL. Surgical infections and choice of antibiotics. In: Sabiston DC. *Essentials of surgery*. Philadelphia: WB Saunders Company, 1987:141-68.
12. Duff P, Robertson AW, Read JA. Single-dose cefazolin versus cefonicid for antibiotic prophylaxis in cesarean delivery. *Obstet Gynecol* 1987;70:718-21.
13. Levine BB, Ovary Z. Studies on the mechanism of formation of the penicillin antigen III. The N-(D-benzylpenicilloyl) group as an antigen determinant responsible for hypersensitivity to penicillin G. *J Exp Med* 1961;114:875-884.
14. Siraganian RP. An automated continuous flow system for the extraction and fluorometric analysis of histamine. *Anal Biochem* 1974;57:383-94.
15. Moneo I, Botello A, Hinojosa M, Alcover R. Nuevos avances en la determinación de histamina automatizada. *Allergol Immunopathol* 1980;Suppl VIII:311-15.
16. Pedersen-Bjergaard J. Cephalotin in the treatment of penicillin sensitive patients. *Acta Allergy* 1967;22:299-306.
17. Saxon A. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Rev Infect Dis* 1983;5:S368-76.
18. Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy* 1988;18:515-40.
19. Petz LD. Immunologic reactions of humans to cephalosporins. *Postgrad Med J* 1971;47(Suppl):64-73.
20. Levine BB. Antigenicity and cross-reactivity of penicillins and cephalosporins. *J Infect Dis* 1973;128:S364-6.
21. Hamilton-Miller JMT, Abraham EP. Specificities of haemagglutinating antibodies evoked by members of the cephalosporin C family and benzylpenicillin family. *Biochem J* 1971;123:183-90.
22. Blanca M, Perez E, Garcia J, et al. Anaphylaxis to amoxicillin with good tolerance for benzylpenicillin. *Allergy* 1988;43:508-10.
23. Blanca M, Vega JM, Garcia J, et al. Allergy to penicillin with good tolerance to other penicillins; study of the incidence in subjects allergic to betalactams. *Clin Exp Allergy* 1990;20:475-81.
24. Batchelor FR, Dewdney JM, Weston RD, et al. The immunogenicity of cephalosporin derivatives and their cross-reaction with penicillin. *Immunology* 1966;10:21-30.
25. Shibata K, Atsumy T, Horiuchi Y, et al. Immunological cross-reactivities of cephalotin and its related compounds with benzylpenicillin (penicillin G). *Nature* 1966;212:419-27.
26. Ragnar S. Side effects of cephalosporins. *Drugs* 34 (Suppl 2). ADIS Press Limited, 1987;105-20.
27. Robert J. Eczema and hyper-IgE. Effect of cephalosporins. *Allerg Immunol* 1988;20(3):87-90.
28. Rouveix B, Chau F. Action of cephalosporin on T lymphocytes: the role of mediators. *Pathol Biol* 1987;35(10 PEL):1450-3.

Request for reprints should be addressed to:
 Juan Manuel Igea, MD
 Servicio de Alergia, Hospital Ramón y Cajal
 Cra. Colmenar Viejo, Km 9.1
 28034 Madrid
 Spain