

Delayed allergic reaction to cefonicid

Jose A Martin, MD; Ma. Dolores Alonso, MD; Milagros Lázaro, MD; Fernando Parra, MD; Jose A Compaired, MD; and Emilio Alvarez-Cuesta, MD, PhD

We report a case of delayed cutaneous reaction to intramuscular treatment with cefonicid, a second generation cephalosporin. An isolated late skin test response was observed to cefonicid only and not to other betalactams. A patch test with cefonicid 1% was positive after 48 and 96 hours.

INTRODUCTION

Systemic administration of drugs may produce maculopapular or morbilliform skin rashes that resemble viral exanthems. The mechanism responsible for these eruptions is yet unclear.¹ Concerning these skin rashes, some authors have found isolated late skin test responses to several semisynthetic betalactams^{2,3} suggesting a role for cell-mediated immunity in the pathogenesis of such reactions.

We report a woman who presented with a morbilliform rash during treatment with cefonicid that could be caused by delayed hypersensitivity to this drug.

CASE REPORT

A 48-year-old woman presented with a buccal infection. She was treated with intramuscular Monocid (SK&F, Spain) that contains cefonicid, 500 mg, and lidocaine, 1%, as diluent. During the second day of therapy, six hours after the third dose of the drug, she developed a generalized rash consisting of mildly pruritic, erythematous papules that persisted for four days.

METHODS

One year after the adverse reaction and after obtaining informed consent from the patient, the following tests were performed:

- Skin prick and intradermal tests with benzylpenicillin (10,000

U/mL; Antibióticos A.A., Spain), benzylpenicilloyl polylysine (6×10^{-5} M; Kremers Urban, Milwaukee), a minor determinant mixture (composed of 0.6 mg/mL of benzylpenicillin and 0.5 mg/mL of benzylpenicilloate; Stallergens, France), and amoxicillin and ampicillin at 10 mg/mL (Beecham, Spain).

- Skin prick and intradermal tests and subcutaneous and intramuscular challenges with undiluted lidocaine.

Skin prick and intradermal tests with several cephalosporins at their therapeutic concentrations (cefonicid, 333 mg/mL; ceftazidime, 100 mg/mL, cefotaxime 250 mg/mL and cefazolin 125 mg/mL), using normal saline as diluent.

- Patch tests, using petrolatum as vehicle, with benzylpenicillin (5,000 and 10,000 U/g), cefonicid 1%, ceftazidime 1%, cefotaxime 1% to 5%, and cefazolin 1% to 5%.

• Open intramuscular challenges with benzylpenicillin (640,000 U), aztreonam (1 g), and cefonicid (50 mg). The patient was carefully monitored and full emergency cover was provided.

The concentrations used in intradermal and patch tests were shown to be nonirritating in a control population of 12 subjects, two of whom had been treated with cefonicid in the past. The concentrations used for patch tests with cephalosporins were in the range of those previously shown to elicit positive responses in hypersensitive patients.⁴

RESULTS

Skin tests to benzylpenicillin and its determinants, as well as to amoxi-

cillin and ampicillin were all negative and the patient tolerated challenges with benzylpenicillin and aztreonam. Skin and challenge tests with lidocaine were also negative.

All skin tests with cephalosporins were negative at the immediate (15 minutes) reading, but three hours later induration developed at the site of the intradermal cefonicid skin test. At six hours the induration was 22 mm in diameter, without surrounding erythema, and it was biopsied. Direct immunofluorescence was negative for deposition of immunoglobulins or complement. A Giemsa stain demonstrated a moderate interstitial and perivascular infiltrate with neutrophils and mononuclear cells; a mild intercellular edema was present. There was no increase numbers of basophils or mast cells or evidence of vasculitis.

Patch tests were only positive for cefonicid at 48 (++) and 96 (+++) hours and negative to the other drugs tested. The intramuscular challenge with an initial dose of 50 mg of cefonicid produced a mild morbilliform rash on the patient's trunk and forearms six hours after administration of the drug.

DISCUSSION

Four major types of late onset dermal reactions to injected antigens have been described⁵: a late phase reaction of an initial wheal and flare response, Arthus reactions, the so-called cutaneous basophil hypersensitivity, and classical tuberculin-type delayed hypersensitivity reactions. The pathogenesis of the reaction here reported is unclear. The isolated late intradermal test

From Allergy Department; Hospital Ramon y Cajal; Crt. Colmenar, Km 9,1; 28034 Madrid; Spain.

Received for publication January 2, 1992.
Accepted for publication in revised form May 29, 1993.

response as well as the positive patch test suggest the involvement of a type IV allergic mechanism, although the timing of the skin reaction is shorter than that of the classical delayed reaction to tuberculin.⁵

Systemic contact dermatitis due to drugs usually occurs in patients sensitized by topical treatment and later exposed to the drug orally or parenterally. The opposite situation occurred in our case, a phenomenon termed by Pirilä⁶ "primary endogenous contact eczema." In vitro studies have shown a T cell reaction to penicillin to occur in patients with exanthematous reactions to this drug.⁷ Delayed patch test responses have been observed in patients with late onset skin rashes after treatment with semisynthetic penicillins.⁸ Some authors support the use of patch tests in the routine investigation of systemic reactions to betalactams, regardless of the route of administration.⁹

Intradermal and patch test results with cephalosporins other than cefonicid were negative in our patient, who also showed good tolerance to other betalactam agents (benzylpenicillin and aztreonam). These findings suggest an immunologic mechanism with specificity for the side-chain structure in cefonicid. Stejskal et al¹⁰ have reported side chain-spe-

cific lymphocyte responses in workers with occupational allergy due to bacampicillin and good tolerance to benzylpenicillin. Cross-reactivity associated with delayed type hypersensitivity between cephalosporins with a tetrazoyl group in the C-3 side chain (eg, cefonicid) and those without it (eg, ceftazidime, cefotaxime, and cefazolin) has previously been shown to be very low.¹¹

Our study suggests a role for skin and patch tests in the diagnostic protocol of delayed systemic reactions to drugs. The mechanism underlying such reactions, though, remains to be clarified.

REFERENCES

1. Kaplan AP. Drug-induced skin disease. *J Allergy Clin Immunol* 1984; 74:573-9.
2. Dolovich J, Ruhno J, Sauder DN, et al. Isolated late cutaneous skin test response to ampicillin: a distinct entity. *J Allergy Clin Immunol* 1988;82:676-9.
3. Vega JM, Blanca M, Carmona MJ, et al. Delayed allergic reactions to betalactams. *Allergy* 1991;46: 154-7.
4. Conde-Salazar L, Guimaraens D, Romero LV, et al. Occupational dermatitis from cephalosporins. *Contact Dermatitis* 1986;14(1): 70-1.
5. Deshazo RD, Levinson AI, Dvorak HF. The late phase skin reaction: paradigm or epiphenomena? *Ann Allergy* 1983;51:166-72.
6. Pirilä V. Endogenic contact eczema. *Allergy Asthma* 1970;16: 15-9.
7. Koponen M, Pichler WJ, de Weck AL. T cell reactivity to penicillin: phenotypic analysis of in vitro activated cell subsets. *J Allergy Clin Immunol* 1986;78:645-52.
8. de Haan P, Bruynzeel DP, van Ketel WG. Onset of penicillin rashes: relation between type of penicillin administered and type of immune reactivity. *Allergy* 1986;41:75-8.
9. Patriarca G, Schiavino D, Romano A, et al. Status of patch and other skin tests in the diagnosis of systemic penicillin allergy. *Allergol Immunopathol* 1987;15(1):1-5.
10. Stejskal VDM, Forsbeck M, Olin R. Side chain-specific lymphocyte responses in workers with occupational allergy induced by penicillins. *Int Arch Allergy Appl Immunol* 1987;82:461-4.
11. Uno K, Yamasaku F. Structural correlations with cross-reactivity of betalactam antibiotics in delayed type hypersensitivity. *J Antimicrob Chemother* 1989;24:251-64.

Request for reprints should be addressed to:
Dr Jose A Martin
Servicio de Alergia
Hospital Ramon y Cajal
Carretera de Colmenar, KM 9,100
Madrid 28034
Spain