

Hypersensitivity to piperacillin

A 55-YEAR-OLD man was admitted to the hospital for acute gallbladder infection. During the postsurgery period, he had a high digestive hemorrhage and an intra-abdominal infection with much wound drainage, sepsis, and fever. He was treated with Tazocel® (piperacillin 4 g, tazobactam 0.5 g; Lederle, Madrid, Spain), Dattracin® (vancomycin), Nolotil® (metamizole), Zantac® (ranitidine), Losec® (omeprazole), and Maalox® (aluminum hydroxide with magnesium). On day 14 of treatment with these drugs, the patient suffered a generalized and diffuse maculopapular itchy skin eruption, and eosinophilia of 47% could be observed in his blood. His physicians replaced Tazocel with tobramycin and clindamycin and started treatment with oral antihistamines. Four days later, as the symptoms and fever remained, the patient was examined by a dermatologist, who diagnosed a toxic reaction. Vancomycin was stopped, but the cutaneous reaction persisted for another 11 days. Treatment with corticosteroids was then started, with progressive improvement of symptoms and development of itchy, scaling dermatitis. The patient was completely asymptomatic within 1 month and eosinophilia had disappeared from his blood by then.

Five months later, the patient was referred to our allergy clinic for study of a possible drug adverse reaction. Prick tests with all the drugs involved in the reaction, including Tazocel (commercial preparation) and piperacillin (100 mg/ml), as well as PPL (benzylpenicilloyl polylysine, 6×10^{-5} M), MDM (minor determinant mixture, 10^{-2} M) (Allergopen®; Allergopharma, Hamburg, Germany), penicillin G, amoxicillin, and ampicillin, were done before intradermal tests. The readings were all negative.

Epicutaneous tests were carried out with the standard battery of patch tests (TRUE Test) (ALK-ABELLÓ, Madrid, Spain), which includes the European standard series, and with all the drugs involved in the reaction. The patch test with Tazocel as is in petrolatum was positive at 72 and 96 h. In view of this result, we tried to isolate the two components of Tazocel in order to patch-test them. The pharmacy department in our hospital could not isolate tazobactam, but piperacillin sodium was prepared at 10 and 20%. Two months later, patch tests were performed again with Tazocel and piperacillin at two concentrations. Positives could be observed in all of them (Table 1). The piperacillin patch test at 20% remained positive for 196 h. At the 96-h reading of the patch test with piperacillin,

Table 1. Patch tests (in petrolatum)

Drugs	Readings		
	48 h	72 h	96 h
TRUE Test	—	—	—
Tazocel® as is	+	+++	+++
Piperacillin at 10%	++	++	+++
Piperacillin at 20%	++	++	+++
Penicillin G 10 000 U/l	—	—	—
Amoxicillin at 10%	—	—	—
Nolotil® as is	—	—	—
Dattracin® as is	—	—	—
Zantac® as is	—	—	—
Losec® as is	+	+	+

an erythematous, edematous, and itching lesion of 10×10 cm could be observed on the medial part of the patient's left thigh.

The Tazocel and piperacillin patch tests were negative in 20 healthy controls.

Biopsy of the positive patch test with piperacillin showed spongiosis with edema and cellular infiltrates of eosinophils and mast cells. In the biopsy of the thigh lesion, a lymphocytic infiltration appeared.

Total serum IgE was within the normal range (15 kU/l). Determination of specific IgE to piperacillin was not technically possible, and those by the CAP FEIA technique (Pharmacia Diagnostics, Uppsala, Sweden) to amoxicillin, ampicillin, and penicillins G and V gave a negative result.

Piperacillin is a semisynthetic penicillin with anti-*Pseudomonas* and anti-*Klebsiella* activity.

There have been few publications on immunologic reactions to piperacillin, probably because it is not a drug of common use.

In the study published by Moss (1), six patients had a history of generalized immediate hypersensitivity reaction to piperacillin. Two of them presented a positive intradermal test to PPL, MDM, and piperacillin, one was positive only to piperacillin, and another had a positive prick test to it.

Moscato et al. (2) have reported a case of occupational asthma, rhinitis, and urticaria due to piperacillin sodium. Prick-test and specific inhalation challenge with this drug were positive.

After cutaneous reaction to piperacillin, positive patch test and biopsy suggested the involvement of different immunologic mechanisms.

As far as we know, there have been only two reported cases of delayed hypersensitivity to piperacillin with positive patch test, as published in abstract form by Di Fonso et al. (3). Reactions of generalized erythema and pruritic maculopapular rash appeared after some days of treatment with piperacillin, resolving in a few days with corticosteroids in the one case, and spontaneously leaving generalized scaling in the other case. Both patients presented intradermal positivity to ampicillin, amoxicillin, and piperacillin at 48 h and positive patch tests with these same drugs at 48 and 72 h.

We present a case in which maculopapular eruption associated with fever and eosinophilia developed at day 14 of treatment with piperacillin. Prompt withdrawal of this drug was probably important in prevention of more severe symptoms; nevertheless, treatment with antihistamines was not enough to clear the dermal eruption, which required treatment with steroids and lasted for 1 month.

Immediate skin tests were negative; nevertheless, patch test with piperacillin showed strong positivity, and a satellite lesion appeared. In the cases reported by Di Fonso et al. (3), patch tests with ampicillin and amoxicillin were also positive, but this was not so in our case.

The findings of the biopsy of the piperacillin patch test were consistent with an immediate IgE reaction and even the initial stage of a late-phase cutaneous reaction, as described by DeShazo et al. (4), but these findings may also be observed in a type IV reaction, after the initial activation of lymphocytes and release of lymphokines (5). The biopsy of the satellite lesion with lymphocytic infiltration may suggest a type IV mechanism. There histology shows that a double mechanism may be involved in the reaction, a type I and a cell-

mediated type IV that may act simultaneously or in succession in β -lactam allergy, as suggested by de Weck et al. (5).

The role of the side chain in the specificity of immunologic reactions to β -lactams has been shown by several authors to be important in both immediate- and delayed-type allergy. The fact that patch tests with other β -lactams were all negative in our patient suggests that an antigenic determinant of the side chain may cause the reaction.

Key words: β -lactam drugs; epicutaneous tests; hypersensitivity reaction; piperacillin.

R. CABAÑAS*, L. MUÑOZ, C. LÓPEZ-SERRANO, J. CONTRERAS, A. PADIAL, T. CABALLERO, A. MORENO-ANCILLO, P. BARRANCO
*Avda. Europa, 4; P-2 1-C
28224 Madrid
Spain
Tel. 352 42 79
Fax: 695 20 03

Accepted for publication 20 April 1998
Copyright © Munksgaard 1998
ALLERGY 1998;53:819-820

REFERENCES

1. Moss RB. Sensitization to aztreonam and cross-reactivity with other beta-lactam antibiotics in high-risk patients in cystic fibrosis. *J Allergy Clin Immunol* 1991;87:78-88.
2. Moscato G, Galdi E, Scibilia J, et al. Occupational asthma, rhinitis and urticaria due to piperacillin sodium in a pharmaceutical worker. *Eur Respir J* 1995;8:467-9.
3. Di Fonso M, Romano A, Quarantino D, Giuffreda F, Venuti A. Delayed hypersensitivity to piperacillin: two case reports [Abstract]. *Allergy* 1996;51 Suppl 31:98.
4. DeShazo RD, Boehm TM, Kumar D, Galloway JA, Dvorak HF. Dermal hypersensitivity reactions to insulin: correlations of three patterns to their histopathology. *J Allergy Clin Immunol* 1982;69:229-37.
5. de Weck AL. Immunopathological mechanisms and clinical aspects of allergic reactions to drugs. In: de Weck AL, Bundgaard H, editors. *Allergic reactions to drugs (Handbook of experimental pharmacology, vol 63)*. Berlin: Springer-Verlag, 1983:76-133.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.