TOLERABILITY OF AZTREONAM IN PATIENTS WITH IGE-MEDIATED HYPERSENSITIVITY TO BETA-LACTAMS

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Cross-reactivity between aztreonam and penicillins is poor, but clinical tolerance of aztreonam has been assessed, by means of tolerance challenge tests, only in a few groups of penicillin-allergic patients. The aim of this study is to evaluate the tolerability of aztreonam in a large group of betalactam-allergic patients. We studied all patients (> 14 years of age), with a clinical history of immediate reactions to any betalactam and with positive immediate-type skin tests and/or positive specific IgE to any of the studied betalactam; they were studied by means of: skin prick and intradermal tests with penicilloyl polylysine, minor determinant mixture, semisynthetic penicillins, cephalosporins, aztreonam and imipenem; detection of specific IgE to penicillin G, penicillin V, ampicillin, amoxicillin, cefaclor and ceftriaxone. Patients with negative immediate-type skin tests with aztreonam then underwent a graded intramuscular challenge. Forty-five patients (mean age 46.1 ± 15.2 years), 27 females and 18 males, had positive skin tests and/or specific IgE to at least one of the studied betalactams. The most involved drugs were amoxicillin (23 cases), ampicillin (9 cases), penicillin G (8 cases) and other betalactams in the remaining cases. The most frequent reactions were anaphylaxis (27 cases) and urticaria (15 cases). All patients had negative intradermal tests with aztreonam and all patients tolerated the intramuscular graded challenge. Our data confirm the lack of cross-reactivity between betalactams and aztreonam. Immediate-type skin tests with aztreonam represent a simple and rapid diagnostic tool to establish tolerability in betalactam-allergic patients who urgently need this drug.

Aztreonam is a monocyclic β-lactam compound (a monobactam) which is resistant to many of the β-lactamases that are produced by most gram-negative bacteria. Gram-positive bacteria and anaerobic organisms are resistant. Activity against Enterobacteriaceae is good, as is that against *Pseudomonas aeruginosa* (1).

Cross-reactivity between aztreonam and penicillins in patients with IgE-mediated is poor. It has already been shown by means of skin tests that there is no cross-reactivity between penicillins and aztreonam in 41 penicillin-allergic patients (2). Moreover aztreonam has a very weak potential to elicit a drug-specific immunologic response: in fact, no IgE antibodies to aztreonam were detectable in serum specimens in 112 healthy subjects treated with aztreonam (3).

Even if it seems that there is no cross reactivity, as shown by *in vivo* or *in vitro* tests, between penicillins and aztreonam, clinical tolerability of aztreonam in penicillin-allergic patients has only been demonstrated in a small group (4 cases) of

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truly amoxicillin-allergic patients (4), in 21 patients with cystic fibrosis and severe adverse reactions to penicillins (5) and in 29 patients with dcocumented IgE-mediated allergy to betalactams (6).

The aim of this study is to evaluate aztreonam use in a larger group of patients with well demonstrated β-lactam allergy.

We evaluated a group of penicillin-allergic patients by using skin tests with aztreonam to assess cross-reactivity. Subjects with negative results were then challenged with aztreonam to establish if negative results could be considered an indicator of aztreonam tolerability.

MATERIALS AND METHODS

Patient selection

We studied all patients over 14 years of age who came to the Allergy Unit of the Policlinico Gemelli, Rome, Italy between 2001 and 2007 and who had clinical histories of immediate reactions to any β-lactam compound. The inclusion criteria were a positive skin test result to at least 1 β-lactam compound and/or the presence in serum of specific IgE to penicillin G, penicillin V, ampicillin, amoxicillin and/or cefaclor.

The exclusion criteria were: pregnancy; use of β-blockers; cardiovascular, renal or respiratory diseases.

Written informed consent was obtained from all the participants (from their parents, if younger than 18 years of age) and the study was approved by the local ethical committee.

Skin tests

Immediate-type skin tests were performed with a wide spectrum of β-lactam compounds, including penicilloyl-polylysine (PPL) (at a concentration of 3.5 and 35 μg/mL) and minor determinant mixture (MDM) (containing 500 μg/mL of benzilpenicillin and 600 μg/mL of benzipenicilloate, using 1:10 and 1:10000 solutions), penicillin G, penicillin V, semysinthetic penicillins (ampicillin, amoxicillin, bacampicillin, piperacillina, mezlocillin and ticarcicillin) imipenem, aztreonam and cephalosporins (cephalexin, cefaclor, cephalotin, cefadroxil, cephradin, acetoxyiethyl-cefuroxime, ceftriaxone, cefixima, ceftazidima and cefotaxime) as previously described (7-8). β-lactam concentrations are indicated in Table I.

Immediate-type skin tests were carried out with the preparation for parenteral route first by prick and, if negative, intradermally; for SPT of drugs unavailable on the market for parenteral use. The tablets were crushed in a mortar and the powder was dissolved in saline. Readings were performed as already described. Reactions at least 3 mm > than controls in diameter for prick tests and 5 mm > for intradermal tests were considered positive (9). Histamine (at a concentration of 10 mg/mL) as positive control and saline as negative control were employed.

Immediate-type skin tests with aztreonam were performed in 10 healthy subjects with no history of adverse drug reactions and who tolerated penicillins.

In vitro tests

Specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl, cefaclor and ceftriaxone were also detected (UniCAP, Pharmacia, Uppsala, Sweden). A value of 0.35 kU/L or greater was considered as positive. Blood samples were obtained at evaluation and sera were stored at –20°C until assayed.

Aztreonam test dosing

Challenges with intramuscular aztreonam were performed in patients who had negative immediate-type skin tests. One gram of aztreonam was diluted in 3 mL of sterile water for injections, and following doses of 0.1 mL, 0.8 mL and 2.1 mL were administered every half hour. Patients were obviously monitored during and for 3 hours after the end of the aztreonam challenges.

RESULTS

Forty-five patients, ranging in age from 15 to 74 years, with histories of immediate reactions to penicillin were studied. Table II shows the responsible beta-lactams and the clinical manifestations experienced by the patients. No patients had any exclusion criterion.

Anaphylaxis, as defined by the most recent EAACI position paper (10), was the most reported reaction.

All patients had a positive skin (prick or intradermal) test result to at least 1 penicillin reagent and/or a positive specific IgE assay result. All the participants and the control group had negative intradermal test results with aztreonam.

Of the 45 patients with negative skin test results to aztreonam, all accepted challenges with aztronam and they all tolerated it.

DISCUSSION

Aztreonam has very poor cross-reactivity with

Table I. β-*lactam concentrations used for skin tests.*

Drugs	Skin tests Concentrations
Penicillin G	0.2-2000 IU/mL
Penicillin V	100000 IU/mL
Ampicillin	1 mg/mL
Amoxicillin	1 mg/mL
Bacampicillin	90 mg/mL
Piperacillin	5 mg/mL
Mezlocillin	2.5 mg/mL
Ticarcillin	6 mg/mL
Imipenem	2.5 mg/mL
Aztreonam	3.3 mg/mL
Cephalotin	2.5 mg/mL
Cephalexin	90 mg/mL
Cefaclor	90 mg/mL
Cefadroxil	90 mg/mL
Cefuroxime	2.5 mg/mL
Acetoxyethyl-cefuroxime	90 mg/mL
Cefixime	90 mg/mL
Ceftibuten	90 mg/mL
Cefotaxime	2.5 mg/mL
Ceftazidime	2.5 mg/mL
Ceftriaxone	2.85 mg/mL

other beta-lactams in penicillin allergic patients, as already demonstrated by Saxon et al. by means of immediate-type skin tests (2). Aztreonam also has a very poor capability of eliciting an immunologic response in healthy subjects (3). For these reasons it has been stated that aztreonam and the monobactams can be safely given to penicillin-allergic patients (11).

Despite these findings, the tolerability of aztreonam has been assessed in small groups of penicillin-allergic-patients. Among patients with cystic fibrosis and penicillin allergy, Moss found a 5% cross-reactivity rate between aztreonam and penicillins and a sensitisation rate of 20% in patients who received a therapeutic course with aztreonam (5).

In our paper, we firstly assessed cross-reactivity (by means of immediate-type skin tests) and then tolerability (by means of intramuscular challenge tests) of aztreonam in a group of 45 patients with IgE-mediated allergy to beta-lactams: according to previous studies, we found no cross-reactivity between aztreonam and other betalactams and all patients could tolerate aztreonam (6).

The poor cross-reactivity of aztreonam with other beta-lactams may be explained by the different chemical structure between penicillins (which have a basic structure of a thiazolidine ring connected to a beta-lactam ring), cephalosporins (which contains a dihydrothiazine beta-lactam ring system) and aztreonam (which has a "simple" monocyclic structure) (12).

Immediate-type skin tests with aztreonam represent a simple, rapid diagnostic tool in patients with beta-lactam allergy who urgently need this drug. Usefulness of immediate-type skin tests have already been demonstrated for both imipenem (13) and meropenem (14) in patients with IgE-mediated allergy to penicillins.

Even if the risk of a reaction, after a negative immediate-type skin test, is very low, a graded challenge under medical control is advisable in penicillin-allergic patients who need aztreonam treatment, until studies in larger groups of patients can confirm our data.

Since aztreonam sensitisation may be elicited by the challenge, aztreonam testing should be repeated in order to exclude such a sensitisation before any

Table II. *Clinical characteristics of patients and results of allergy testing.*

Variable	Value	Variable	Value
All patients, *n*	45	Positive skin test results to penicillins, *n*	
Mean age (SD), *y*	46.1 (15.2)	Ampicillin	24
Women, *n*	27 (60%)	Amoxicillin	21
Median time since last penicillin reaction (range) [25th, 75th percentile], *mo*	53.3 (1 - 456) [2, 36]	PPL	10
Reactions, *n**	57	Bacampicillin	9
Culprit penicillins, *n*		Penicillin G	8
Amoxicillin	23 (40%)§	Piperacillin	6
Ampicillin	9 (16%)¶	Penicillin V	4
Penicillin G	8 (14%)	MDM	4
Piperacillin	3 (5%)	Cephalexin	4
Bacampicillin	3 (5%)	Mezlocillin	3
Ceftriaxone	3 (5%)	Ticarcillin	2
Cefaclor	3 (5%)	Cefaclor	2
Cephalexin	2 (3%)	Cephradine	1
Cefotaxime	1 (2%)	Cefadroxil	1
Cefixime	1 (2%)	Cefixime	1
Benzathine-penicillin	1 (2%)	Positive skin tests to aztreonam	0/45
Manifestations, *n*		Positive specific IgE assay results, *n*	
Anaphylaxis	27 (47%)	Penicilloyl G	15
Urticaria	15 (26%)	Penicilloyl V	14
Erythema	10 (17%)	Ampiclloyl	16
General itching	2 (3%)	Amoxicilloyl	11
Urticaria + angioedema	1 (2%)	Cefaclor	4
Erythema +Angioedema	1 (2%)	Ceftriaxone	1
Unknown	1 (2%)		

**Thirty-two of 45 patients had only 1 reaction, whereas 10 patients had distinct reactions to either the same betalactam (5 patients) and different betalactams (5 patients) in separate epsiodes*

§ Of these reactions, 15 were also with clavulanic acid and 1 with dicloxacillin

¶ Of these reactions, 3 were also with sulbactam

new therapeutic course.

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