

Tolerability of Aztreonam in Patients with Cell-Mediated Allergy to β -Lactams

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Key Words

Adverse reactions to drugs · Delayed-type hypersensitivity · Drug allergy · Penicillin allergy

Abstract

Background: Cross-reactivity between aztreonam and β -lactams is poor, but tolerability of aztreonam has been assessed in a few groups of patients suffering from IgE-mediated allergy to β -lactams. The aim of this study was to assess the cross-reactivity of aztreonam with other β -lactams and its tolerability in patients with cell-mediated allergy to these drugs. **Methods:** We studied 78 patients with cell-mediated allergy to β -lactams who underwent skin prick, immediate and delayed-reading intradermal tests as well as patch tests with penicilloyl-polylysine, minor determinant mixture, semi-synthetic penicillins, cephalosporins, aztreonam and imipenem. Patients with negative allergy testing with aztreonam underwent an intramuscular test dosing and were observed for 3 h. **Results:** Our patients experienced 94 non-immediate reactions; delayed-onset urticaria (34 cases), maculopapular exanthema (13 cases), urticaria/angioedema (15 cases) and itching erythema (13 cases) were the most reported symptoms. Amoxicillin (35 cases), ampicillin (28 cases) and bacampicillin (18 cases) were the most involved drugs. All patients had a positive patch test and/or a positive delayed-reading intradermal test to at least 1 β -lactam anti-

biotic and none had a positive patch or delayed-reading intradermal test to aztreonam. Then, 65 patients underwent intramuscular test dosing with aztreonam, and none of them had a clinical reaction. **Conclusions:** Our data confirm the lack of cross-reactivity between β -lactams and aztreonam in patients with cell-mediated allergy to these drugs. Delayed-reading intradermal tests and patch tests with aztreonam represent a simple and rapid diagnostic tool to establish tolerability in β -lactam-allergic patients.

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Introduction

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 activity against *Pseudomonas aeruginosa* [1].

Cross-reactivity between aztreonam and penicillins in patients with IgE-mediated allergy is poor. Saxon et al. [2] investigated cross-reactivity between aztreonam and penicillins: 41 subjects with IgE-mediated allergy to 1 or more penicillin moieties were tested with the aztreonam reagents and none of them showed reactivity. Moreover, aztreonam has a very weak potential to elicit a drug-spe-

cific immunologic response: in fact, no IgE antibodies to aztreonam were detectable in serum specimens in 112 healthy subjects treated with aztreonam [3].

Clinical tolerability of aztreonam in penicillin-allergic patients has been demonstrated in a small group (4 cases) of truly amoxicillin-allergic patients [4] and in 29 patients with documented IgE-mediated allergy to β -lactams [5]. On the contrary, Moss [6] found a 5% rate of cross-reactivity and a 20% rate of sensitization in 21 patients with cystic fibrosis and IgE-mediated allergy to penicillins.

Our group recently highlighted the lack of cross-reactivity and the tolerability of aztreonam in a group of 45 subjects with well-demonstrated IgE-mediated allergy to β -lactams [7].

In the last decades, the role of cell-mediated allergy in the pathogenesis of allergic reactions to β -lactams has risen in importance [8], but cross-reactivity between aztreonam and other β -lactams has not been extensively tested in patients with delayed-type cell-mediated hypersensitivity to β -lactams.

For these reasons, we decided to investigate the cross-reactivity between aztreonam and other β -lactam moieties in patients with well-documented cell-mediated allergy to β -lactams and to assess the clinical tolerability of aztreonam in this group of subjects.

Material and Methods

Patient Selection

From our database, we selected patients >14 years of age who had clinical histories of non-immediate reactions to any β -lactam compound. Non-immediate reactions encompass both accelerated reactions that occur 1–72 h after drug intake and delayed reactions that take more than 72 h to appear. The inclusion criteria were a positive patch test result to at least 1 β -lactam compound and a compatible clinical history of delayed β -lactam hypersensitivity.

The exclusion criteria were: pregnancy; use of β -blockers; cardiovascular, renal or respiratory diseases; and a concomitant IgE-mediated hypersensitivity to any β -lactam compound.

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

Skin Tests

Immediate-type skin tests were performed with a wide spectrum of β -lactam compounds, including penicilloyl-polylysine (PPL) and minor determinant mixture (MDM), penicillin G, penicillin V, semi-synthetic penicillins (ampicillin, amoxicillin, bacampicillin, piperacillin, mezlocillin and ticarcillin), imipenem-cilastatin, aztreonam and cephalosporins (cephalexin, cefaclor, cephalotin, cefadroxil, cephadrine, cefuroxime, ceftriaxone, cefixime, ceftazidime, cefamandole, cefoperazone, cefotaxime and cefepime) as previously described [9].

Table 1. Concentrations of β -lactams for parenteral use for intradermal tests

Drugs	Concentrations
Penicillin G, U/ml	100–10,000
Ampicillin, mg/ml	2–20
Amoxicillin, mg/ml	2–20
Ticarcillin, mg/ml	2–20
Piperacillin, mg/ml	2–20
Mezlocillin, mg/ml	2–20
Imipenem-cilastatin, mg/ml	0.1–1
Aztreonam, mg/ml	0.2–2
Cephalotin, mg/ml	0.2–2
Cefamandole, mg/ml	0.2–2
Cefoperazone, mg/ml	0.2–2
Ceftriaxone, mg/ml	0.2–2
Ceftazidime, mg/ml	0.2–2
Cefotaxime, mg/ml	0.2–2
Cefuroxime, mg/ml	0.2–2
Cefepime, mg/ml	0.2–2

In 2004, Allergopharma (Allergopen, Hamburg, Germany) decided to stop the production of PPL and MDM (containing 0.5 mg of benzylpenicillin and 0.6 mg of benzylpenicilloate) reagents; for this reason, from 2004, we started using PPL and MDM (containing 0.5 mg of sodium benzylpenicillin, 0.5 mg of benzylpenicilloic acid and 0.5 mg of sodium benzylpenicilloate) reagents from Diater Laboratorios (Madrid, Spain). Skin testing with Diater Laboratorios reagents showed to be a reliable alternative to Allergopen ones, with a high concordance: 100% for MDM and 97.4% for PPL [10].

Immediate-type skin tests were carried out with the preparation for parenteral route first by prick and, if negative, intradermally (table 1); for the skin prick test of drugs unavailable on the market for parenteral use, the tablets were ground in a mortar and the powder was dissolved in saline. Intradermal tests were performed only with parenteral forms of β -lactams. Reactions at least 3 mm in diameter for prick tests and >3 mm than the initial injection bleb for intradermal tests were considered positive [11]. Histamine (at a concentration of 10 mg/ml) as positive control and saline as negative control were employed. Immediate-type skin tests were read after 20 min and also after 48 h should any delayed reaction occur. An infiltrated erythema with a diameter >5 mm has been considered a positive reaction [12].

Patch Tests

Patch tests were carried out using the same drugs as for skin tests, as previously described [9, 13]. Patches were applied on the interscapular region, removed after 48 h and evaluated after 72 h. Patch results were scored according to ENDA indications [12]: faint erythema was considered as a doubtful reaction; erythema, induration and discrete papules a weak positive reaction (+); erythema, induration, papules and vesicles a strong positive reaction (++); intense erythema, induration and coalescing vesicles an extremely positive reaction (+++). Negative controls were performed with petrolatum.

Table 2. Clinical data of the patients

Variable	Value
All patients	78
Age, years	
Mean $\pm$ SD	43.9 $\pm$ 16.9
25th, 75th percentile	29.5, 59
Men	23 (31.5)
Time since last penicillin reaction and allergy testing, months	
Median	96.3
25th, 75th percentile	12, 150
Range	1–360
Reactions ¹	101
Culprit β -lactams	
Amoxicillin	35 (34.6) ²
Ampicillin	28 (27.7) ³
Bacampicillin	18 (17.8)
Penicillin G	9 (8.9)
Unknown β -lactam	5 (4.9)
Benzathine penicillin	2 (2)
Topical penicillin	2 (2)
Ceftriaxone	1 (1)
Cephalexin	1 (1)
Manifestations	
Urticaria	34 (33.7)
Urticaria + angioedema	15 (14.8)
Maculopapular exanthema	13 (12.9)
Erythema	13 (12.9)
Maculopapular exanthema + angioedema	12 (11.9)
Angioedema	9 (8.9)
Erythema + angioedema	3 (3)
Contact dermatitis	1 (1)
Stevens-Johnson syndrome	1 (1)

Figures in parentheses are percentages.

¹ Fifty-six of 78 patients had only 1 reaction, whereas 20 patients had distinct reactions to either the same β -lactam (5 patients) or different β -lactams (15 patients) in separate episodes.

² Of these reactions, 12 were with amoxicillin + clavulanic acid.

³ Of these reactions, 3 were also with cloxacillin and 1 also with sulbactam.

We also performed patch tests with aztreonam in 20 healthy control participants who tolerated penicillins.

In vitro Tests

Specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, amox-icilloyl and cefaclor was also detected (UniCAP, Pharmacia, Uppsala, Sweden). A value of ≥ 0.35 kU/l was considered positive. Blood samples were obtained at evaluation and sera were stored at -20°C until assayed.

Aztreonam Test Dosing

Aztreonam test dosing was performed on 2 days, with 1 week interval: on the first day, patients received increasing doses of 20,

Table 3. Allergy testing results

Positive patch test results to penicillins	
Bacampicillin	71
Amoxicillin	70
Ampicillin	70
Penicillin V	36
Penicillin G	33
Ticarcillin	18
Piperacillin	15
Mezlocillin	11
Cefaclor	7
MDM	5
Cephalexin	5
Cefuroxime axetil	4
PPL	2
Cefadroxil	2
Cefixime	2
Cephradine	2
Cefoperazone	1
Cephalotin	1
Cefamandole	1
Cefuroxime	1
Positive patch tests to aztreonam	0/78
Positive specific IgE assay results	0
Positive delayed-reading immediate-type skin tests	
Amoxicillin	71
Ampicillin	70
Penicillin G	33
Ticarcillin	18
Piperacillin	15
Mezlocillin	11

40 and 80 mg every half hour; on the second day, they received increasing doses of 160, 320 and 520 mg every half hour. Patients undergoing the intramuscular challenge tests were monitored during and for 3 h after the end of the aztreonam test dosing and again after 24 and 72 h, in case any delayed reaction should occur.

Results

We studied 78 patients ranging in age from 15 to 74 years, with histories of non-immediate reactions to β -lactams. We performed the allergy testing with intervals ranging from 1 to 360 months after the most recent reaction. These patients had experienced a total of 101 reactive episodes to β -lactams. The responsible drugs and clinical manifestations are shown in table 2.

All participants had a positive patch test to at least 1 β -lactam antibiotic (table 2) and none of them had a positive patch test to aztreonam (table 3).

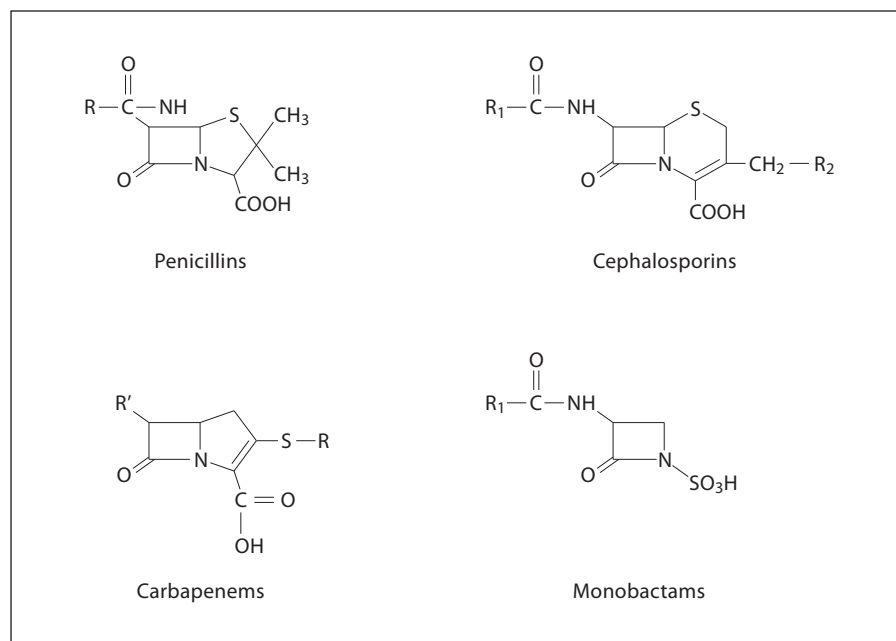


Fig. 1. Chemical structure of β -lactam molecules.

Thirty-three patients had a selective delayed-type allergy to aminopenicillins (positive patch tests with amoxicillin, ampicillin and bacampicillin) and 2 had a delayed-type allergy to aminopenicillins and an aminocephalosporin (cefaclor and cephadrine).

Immediate-type skin tests were all negative at the 20-min reading.

Thirteen patients with negative patch tests with aztreonam refused to undergo the intramuscular test dosing; the remaining 65 patients underwent the aztreonam test dosing and none of them experienced any adverse reaction. The negative predictive value of patch tests with aztreonam was 100%.

Discussion

Aztreonam has got very poor cross-reactivity with other β -lactams in penicillin-allergic patients, as already demonstrated by Saxon et al. [2] by means of immediate-type skin tests. Aztreonam has also got a very poor capability to elicit 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 [14].

Despite these findings, clinical tolerability of aztreonam has been assessed in small groups of truly penicillin-allergic patients. Among patients with cystic fibrosis and

penicillin allergy, Moss [6] found a 5% cross-reactivity rate between aztreonam and penicillins and a sensitization rate of 20% in patients who received a therapeutic course with aztreonam.

There are no data in the literature about the tolerability of aztreonam in patients with delayed-type, cell-mediated allergy to β -lactams, and for this reason, we first assessed cross-reactivity (by means of delayed-reading immediate-type skin tests and patch tests) and then tolerability (by means of intramuscular challenge tests) of aztreonam in these patients.

First of all, our results show a lack of cross-reactivity between aztreonam and other β -lactams in patients with delayed, cell-mediated allergy to at least 1 β -lactam compound.

The lack of cross-reactivity of aztreonam with other β -lactams may be explained by the different chemical structure between penicillins (which have a basic structure of a thiazolidine ring connected to a β -lactam ring), cephalosporins (containing a dihydrothiazine β -lactam ring system) and aztreonam (with a 'simple' monocyclic structure) [15] (fig. 1). Ceftazidime is the only drug that shares the same side chain with aztreonam, and there is evidence of clinical cross-reactivity between these drugs in a single patient [16]. None of our patients had positive patch and/or delayed-reading intradermal tests with ceftazidime, and thus, we could not assess cross-reactivity between these drugs.

Delayed-reading intradermal tests and patch tests showed the same sensitivity in our work, while other investigators found different results. Positive patch tests and delayed-reading intradermal tests share the same immunological mechanism, as demonstrated by skin biopsies, and thus, in our opinion, they should both be considered as valuable instruments for the diagnosis of non-immediate reactions to β -lactams [9, 13, 17].

In our study, the most reported symptom was delayed-onset urticaria. However, in these cases, the skin is infiltrated by activated CD8 and CD4 T cells, which are responsible of skin damage. In these cases, maculopapular exanthema and delayed-appearing urticaria share the same pathogenic mechanism.

Patch tests represent a simple and reliable diagnostic tool, as already demonstrated in our previous papers in

patients with delayed-type allergy to aminopenicillins and other β -lactams [9, 18]. However, in patients with cell-mediated allergy to β -lactams and a negative patch test with aztreonam, we suggest performing a graded challenge test until the predictive value of such tests will be confirmed by larger studies.

Challenges were not followed by full therapeutic courses, and this is the main limitation of our study; however, the poor capability of aztreonam to elicit an immunological response let us affirm that aztreonam can be safely used in β -lactam-allergic patient who urgently need this drug, except in patients with previous hypersensitivity reactions to ceftazidime.

In conclusion, our study confirms the lack of cross-reactivity between β -lactams and aztreonam also in patients with cell-mediated allergy to β -lactams.

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