

Original article

Cross-reactivity and tolerability of imipenem in patients with delayed-type, cell-mediated hypersensitivity to β -lactams

Background: Administration of imipenem-cilastatin to patients with IgE-mediated hypersensitivity to β -lactams has always been considered potentially harmful. Recent studies have demonstrated the tolerability of carbapenems (imipenem-cilastatin and meropenem) in patients with IgE-mediated hypersensitivity to β -lactams; there are no studies on this topic regarding patients with cell-mediated allergy to β -lactams. The aim of this study is to assess cross-reactivity and tolerability of imipenem in patients with cell-mediated allergy to β -lactams.

Methods: From our database we selected 73 patients with cell-mediated allergy to β -lactams, diagnosed by means of immediate-type skin tests, delayed reading intradermal tests, patch tests and detection of specific IgE. Patients with negative patch tests with imipenem-cilastatin underwent an intramuscular test dosing.

Results: Our patients had a total of 94 nonimmediate reactions to penicillins. All patients had positive patch tests and/or delayed reading intradermal tests for at least one of the penicillin reagent tested and negative immediate-type skin tests and specific IgE. Four patients out of 73 had a positive patch tests to at least one penicillin reagent and imipenem-cilastatin showing cross-reactivity. Sixty-four patients underwent the imipenem-cilastatin intramuscular test dosing and none of them had a clinical reaction.

Conclusions: Our rate of cross-reactivity between imipenem-cilastatin and other β -lactams was 5.5%. This result is different from previous findings and this may be explained by the fact that we investigated patients with cell-mediated allergy to β -lactams. Patients with cell-mediated allergy to β -lactams should undergo patch tests and a tolerance challenge test before treatment with imipenem-cilastatin.

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Key words: β -lactams; cell-mediated hypersensitivity; cross-reactivity; tolerability of imipenem-cilastatin.

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Accepted for publication 18 February 2009

Imipenem-cilastatin is a β -lactam antibiotic with a wide-spectrum antibacterial activity against many Gram+ and Gram- bacteria. It has a bicyclic structure and it shares with penicillins and cephalosporins the characteristic β -lactam ring (BLR).

Cross-reactivity between imipenem-cilastatin and other β -lactams has not been tested in patients with delayed-type cell-mediated allergy to β -lactams. Administration of imipenem-cilastatin to patients with IgE-mediated hypersensitivity to β -lactams is considered potentially harmful because of a 47% rate of cross-reactivity between imipenem and penicillin (1). For this reason it has been stated that imipenem-cilastatin should not be given to patients with proven penicillin hypersensitivity (2). Some retrospective studies (3–5) reported a lower rate of cross-reactivity (from 7% to 11%) between penicillins and carbapenems in patients with reported penicillin allergic-like reactions, but these patients did not undergo allergy testing. However, it has been recently demonstrated that

cross-reactivity between penicillins, imipenem-cilastatin and meropenem is very low (0.9% for imipenem and meropenem) in patients with proven IgE-mediated allergy to β -lactams and that negative skin tests with both imipenem-cilastatin and meropenem have a high negative predictive value (6–8).

In a guinea pig model of delayed-type hypersensitivity to penicillins, it has been shown that there is very low cross-reactivity between imipenem-cilastatin and other β -lactams (9). No data are available regarding a large group of patients with proven cell-mediated allergy to β -lactams. Cell-mediated allergy to β -lactams have risen in importance in the last years and its prevalence is now higher than IgE-mediated allergy to β -lactams (10). For this reason we evaluated a large group of patients with cell-mediated allergy to β -lactams by means of patch test with imipenem-cilastatin to assess cross-reactivity. Patients with negative results were then challenged to assess clinical tolerability.

Methods

Patient selection

From our database we selected patients older than 14 years of age who had clinical histories of nonimmediate reactions to any β -lactam compound. Nonimmediate 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 one β -lactam compound.

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

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 ethics committee.

Skin tests

Immediate-type skin (prick and intradermal) tests were performed with a wide spectrum of β -lactam compounds, including penicilloyl-polylysine (PPL), minor determinant mixture (MDM), penicillin G, penicillin V, semisynthetic penicillins (ampicillin, amoxicillin, bacampicillin, piperacillin, mezlocillin and ticarcillin) imipenem-cilastatin, aztreonam and cephalosporins (cephalexin, cefaclor, cephalotin, cefadroxil, cephadrin, cefuroxime, ceftriaxone, cefixima, cefoperazone, cefamandole, ceftazidime and cefotaxime) according to the indications of the European Academy of Allergology and Clinical Immunology (11).

In 2004 Allergopharma (Allergopen, Hamburg, Germany) decided to stop production of PPL and MDM (containing 0.5 mg of benzyl-penicillin 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 (12).

Immediate-type skin tests were carried out with the preparation for parenteral use first by prick and, if negative, intradermally; for SPT of drugs unavailable on the market for parenteral use, the tablets were ground in a mortar and the powder was dissolved in saline. The concentrations of drugs used for immediate-type skin and patch tests are listed in Table 1. Reactions at least 3 mm > than controls in diameter for prick tests and 5 mm > for intradermal tests were considered positive (13). 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 was considered a delayed positive reaction (14).

Patch tests

Patch tests were carried out using the same drugs as for skin tests. All drugs were mixed in petrolatum at 25% w/w (15) for ampicillin and amoxicillin and at 20% w/w for other drugs. Patches were applied on the interscapular region and evaluated after 72 h. Patch results were scored according to ENDA indications (14): 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

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

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

reaction (+++); intense erythema, induration and coalescing vesicles – an extremely positive reaction (+++). Negative controls were performed with petrolatum. We also performed patch tests with imipenem in 20 healthy control participants who tolerated penicillins.

In vitro tests

Specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, amoxicilloyl and cefaclor were also detected (UniCAP, Pharmacia, Uppsala, Sweden) at evaluation. 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.

Imipenem test dosing

Challenges with intramuscular imipenem-cilastatin were performed in patients who had negative delayed intradermal tests and negative patch tests.

Imipenem-cilastatin test dosing was performed on two days, with a week-interval: on the first day patients received increasing doses of 10, 20 and 40 mg every half an hour; on the second day they received increasing doses of 80, 160 and 260 mg every half an hour (15). Patients undergoing the intramuscular challenge tests were monitored during and for 3 h after the end of the imipenem-cilastatin test dosing and again after 24 and 72 h, should any delayed reaction occur.

Results

We studied 73 patients ranging in age from 15 to 74 years, with histories of non-immediate reactions to β -lactams. We performed the allergy testing after intervals ranging from 1 to 360 months since the most recent reaction. These patients had experienced a total of 94 reactive episodes to β -lactams. The responsible drugs and clinical manifestations are showed in Table 1.

All participants had a positive patch test and/or a positive delayed reading intradermal test to at least one β -lactam antibiotic (Table 2) and 4 out of 73 had also

Tolerability of imipenem in patients with delayed allergy to betalactams

Table 2. Clinical data of the patients

Variable	Value
All patients, <i>n</i>	73
Mean age (SD) [25th, 75th percentile], <i>y</i>	43.7 (16.9) [29, 57]
Men, <i>n</i>	23 (31.5%)
Median time since last penicillin reaction (range) [25th, 75th percentile], months	96.5 (1–360) [12, 147]
Reactions, <i>n</i> *	94
Culprit β-lactams, <i>n</i>	
Amoxicillin	32 (34%)§
Ampicillin	24 (25.5%)¶
Bacampicillin	18 (19.1%)
Penicillin G	9 (9.6%)
Unknown β -lactam	5 (5.3%)
Benzathine-penicillin	2 (2.1%)
Topical penicillin	2 (2.1%)
Ceftriaxone	1 (1.1%)
Cephalexin	1 (1.1%)
Manifestations, <i>n</i>	
Urticaria	30 (31.9%)
Maculopapular rash	13 (13.8%)
Erythema	13 (13.8%)
Urticaria + angioedema	13 (13.8%)
Maculopapular rash + angioedema	12 (12.8%)
Angioedema	8 (8.5%)
Erythema + angioedema	3 (3.2%)
Contact dermatitis	1 (1.1%)
Stevens-Johnson syndrome	1 (1.1%)

*Fifty-three of 73 patients had only one reaction, whereas 18 patients had distinct reactions to either the same β -lactam (five patients) and different β -lactams (13 patients) in separate episodes.

§Of these reactions, 10 were with amoxicillin + clavulanic acid.

¶Of these reactions, three were also with cloxacillin.

a positive patch test with imipenem-cilastatin showing cross-reactivity (Table 3). These patients did not undergo imipenem-cilastatin test dosing because of the high risk of an adverse reaction.

All 20 control subjects who had previously tolerated at least 1 β -lactam compound (mainly aminopenicillins and third generation ral cephalosporins) had no positive patch tests to imipenem.

Thirty-one patients had a selective delayed-type allergy to aminopenicillins (positive patch tests with amoxicillin, ampicillin and bacampicillin) and one had a delayed-type allergy to aminopenicillins and two aminocephalosporins (cefactor and cephradine).

Skin prick and intradermal tests were all negative at the 20 min reading. Delayed reading of intradermal test results are shown in Table 3.

Five patients with negative patch tests to imipenem-cilastatin refused to undergo the intramuscular test dosing; the remaining 64 underwent imipenem-cilastatin test dosing and none of them experienced any adverse reaction.

The negative predictive value of patch tests with imipenem-cilastatin was 100% in patients with delayed-type allergy to β -lactams.

Table 3. Allergy testing results in 73 patients

	<i>n</i> (%)
Positive patch test results to penicillins	
Bacampicillin	66 (90.4)
Amoxicillin	65 (89)
Ampicillin	65 (89)
Penicillin V	34 (46.6)
Penicillin G	31 (42.5)
Ticarcillin	15 (20.5)
Piperacillin	14 (19.2)
Mezlocillin	11 (15.1)
Cefaclor	6 (8.2)
Minor determinant mixture	5 (6.8)
Cephalexin	5 (6.8)
PPL	2 (2.7)
Cefadroxil	2 (2.7)
Cefixime	2 (2.7)
Cephradine	2 (2.7)
Cefuroxime axetil	2 (2.7)
Cefoperazone	1 (1.4)
Cephalotin	1 (1.4)
Cefamandole	1 (1.4)
Cefuroxime	1 (1.4)
Positive patch tests to imipenem-cilastatin	4/73 (5.5)
Positive specific IgE assay results, <i>n</i>	0
Positive delayed-reading immediate-type skin tests	
Amoxicillin	65 (89)
Ampicillin	65 (89)
Penicillin G	31 (42.5)
Ticarcillin	15 (20.5)
Piperacillin	14 (19.2)
Mezlocillin	11 (15.1)

Discussion

In our study we prospectively determined the rate of cross-reactivity between β -lactams and imipenem-cilastatin in patients with cell-mediated allergy to β -lactams. The rate of such cross-reactivity was 5.5% and which is higher than has been demonstrated (6, 8) recently for IgE-mediated allergy to penicillins. This could be explained by the fact that T lymphocytes recognize different determinants than those recognized by IgE.

We would like to underline that 32 patients had a delayed-type allergy to aminopenicillins (one of them also to cefaclor and to cephradine) and in this case the α -amino side chain is responsible of cross-reactivity. This determinant is shared by aminopenicillins and aminocephalosporins and it is not shared by imipenem. This may explain the lack of cross-reactivity in this particular group of patients.

Patients with positive patch tests to imipenem-cilastatin also had positive patch tests to many other β -lactam antibiotics. It can be hypothesized that in these patients the BLR is the main epitope recognised by T lymphocytes and this may be considered the common antigenic determinant (Table 4). On the other hand, in our study there are other subjects with similar patterns of cross-reactivity and with good tolerance of imipenem-cilastatin:

Table 4. Characteristics of patients with cell-mediated allergy to imipenem and other β -lactams

Nº.	Sex and age	Episodes	Responsible drugs	Symptoms	Positive patch test results	Delayed reading of intradermal tests
1	M-32	2	Oral amoxicillin Intramuscular penicillin G	Maculopapular rash Maculopapular rash	Penicillin G, penicillin V, ampicillin, amoxicillin, bacampicillin, piperacillin, mezlocillin, ticarcillin, cephalixin, cefaclor, cefuroxime axetil, imipenem	Penicillin G, ampicillin, amoxicillin, ticarcillin, piperacillin, mezlocillin
2	F-42	2	Oral ampicillin (+ cloxacillin) Oral ampicillin (+ cloxacillin)	Urticaria Angioedema + urticaria	Penicillin G, penicillin V, ampicillin, amoxicillin, bacampicillin, piperacillin, cephalixin, cefaclor, imipenem	Penicillin G, ampicillin, amoxicillin, piperacillin
3	M-34	1	Oral amoxicillin	Urticaria	Penicillin G, penicillin V, ampicillin, amoxicillin, bacampicillin, mezlocillin, ticarcillin, imipenem	Penicillin G, ampicillin, amoxicillin, mezlocillin, ticarcillin
4	F-43	2	Oral ampicillin Oral amoxicillin	Angioedema + urticaria Angioedema + urticaria	Penicillin G, penicillin V, ampicillin, amoxicillin, bacampicillin, piperacillin, mezlocillin, ticarcillin, cephalixin, cephalotin, cefadroxil, cefoperazone, imipenem	Penicillin G, ampicillin, amoxicillin, piperacillin, ticarcillin, mezlocillin

in these cases, the lack of cross-reactivity with imipenem-cilastatin may be explained by the fact that the BLR is not the only antigenic determinant and that other structures of the molecule (such as the side chains, the thiazolidine or the dihydrothiazine rings) may be involved (Fig. 1). However, when comparing our results with those of Romano et al. (6), we did not find any statistically significant difference.

In previous retrospective studies the rate of carbapenem hypersensitivity reactions in patients with histories of penicillin allergy was about 9% (3–5). We would like underline that these authors did not perform any allergy testing and their studies rely only on patients' clinical history and from 80% to 90% of patients who claim to be allergic to penicillin is not (16).

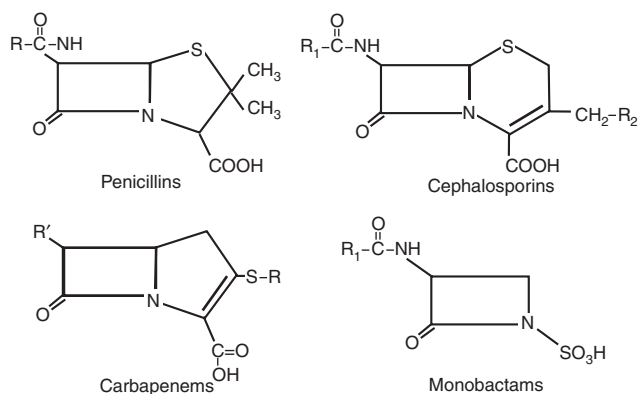
Saxon et al. found a 47% cross-reactivity rate between penicillins and imipenem-cilastatin but patients with negative immediate-type skin tests did not undergo any

imipenem-cilastatin test dosing to ascertain clinical tolerability (1). Our different results may be explained by the fact that we investigated patients with cell-mediated allergy to β -lactams and we did not use imipenem metabolites for our investigation.

All patients with positive patch tests with ampicillin, amoxicillin, penicillin G, piperacillin, mezlocillin and ticarcillin showed positive delayed reading immediate-type skin tests too. Even if other authors put in evidence a greater sensitivity of delayed reading of intradermal tests than patch tests (17), our data confirm the usefulness of patch tests when diagnosing non-immediate reactions to β -lactams (18). Positive patch tests and delayed reading intradermal tests share the same immunological mechanism, as demonstrated by skin biopsies (17, 18) and so, in our opinion, they both should be considered as valuable instruments for the diagnosis of non immediate reactions to β -lactams.

Patch tests with imipenem represent a simple and reliable diagnostic tool with a high negative predictive value, as already demonstrated in our previous papers in patients with delayed type allergy to aminopenicillins and other β -lactams (18). However, in patients with cell-mediated allergy to β -lactams and a negative patch test with imipenem-cilastatin, we suggest a graded challenge test until the negative predictive value of patch tests is confirmed by larger studies. Challenges were not followed by full therapeutic courses and this is the main limitation of our study.

In conclusion, our study confirms the low cross-reactivity between β -lactams and imipenem-cilastatin. Patients with cell-mediated allergy to β -lactams should undergo patch tests and a graded challenge test and, if negative, do not need to avoid imipenem-cilastatin.

Figure 1. Chemical structure of β -lactam molecules.

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