

BRIEF COMMUNICATION

Absence of cross-reactivity to carbapenems in patients with delayed hypersensitivity to penicillins

A. Romano^{1,2}, F. Gaeta¹, R. L. Valluzzi¹, C. Alonzi¹, M. Maggioletti¹, A. Zaffiro³, C. Caruso¹ & D. Quarantino³

¹Allergy Unit, Complesso Integrato Columbus, Rome; ²IRCCS Oasi Maria S.S., Troina; ³Ambulatorio di Allergologia, IDI-IRCCS, Capranica, Italy

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Keywords

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Correspondence

Prof. Antonino Romano, Unità di Allergologia, Complesso Integrato Columbus, Via G. Moscati, 31 00168 Rome, Italy.
Tel.: +39 06 3503782
Fax: +39 06 3503235
E-mail: antoninoromano@h-columbus.it

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Abstract

Studies performed on subjects with IgE-mediated hypersensitivity to penicillins have demonstrated a 1% rate of cross-reactivity between penicillins and both imipenem and meropenem, while a single study found a 5.5% rate of cross-reactivity with imipenem/cilastatin in subjects with T-cell-mediated hypersensitivity to β -lactams, mostly penicillins. We studied 204 consecutive subjects with a well-demonstrated T-cell-mediated hypersensitivity to assess the cross-reactivity with carbapenems and the tolerability of such alternative β -lactams. All 204 subjects underwent skin tests with imipenem/cilastatin and meropenem; 130 of them were skin-tested also with ertapenem. Subjects with negative test results were challenged with these carbapenems. All subjects displayed negative skin tests to carbapenems and tolerated challenges. These data demonstrate the absence of clinically significant T-cell-mediated cross-reactivity between penicillins and carbapenems. Negative delayed-reading skin testing with carbapenems in individuals with documented T-cell-mediated hypersensitivity to penicillins correlates well with subsequent clinical tolerance of therapeutic doses of carbapenems.

Until the last decade, it was considered potentially harmful to administer carbapenems to patients with IgE-mediated hypersensitivity to penicillins (1), because a single study (2) found a 47.4% rate (9 of 19 subjects) of cross-reactivity to imipenem. Subsequent studies of ours, performed on samples larger than 100 subjects of both adults and children with a documented IgE-mediated hypersensitivity to penicillins, have demonstrated a 1% rate of cross-reactivity between penicillins and both imipenem and meropenem (3–6), causing the alarm connected with a significant allergic cross-reactivity between penicillins and carbapenems to cease (7). However, a recent study (8) found a 5.5% rate (4 of 73 subjects) of cross-reactivity to imipenem/cilastatin in subjects with T-cell-mediated hypersensitivity to β -lactams, mainly penicillins.

This prospective study was conducted to evaluate the possibility of using carbapenems in patients with a documented T-cell-mediated penicillin allergy.

Methods

Between 1997 and 2012, we studied 204 consecutive subjects with a T-cell-mediated hypersensitivity to penicillins,

diagnosed as previously described (9). Before the study, all subjects received information about possible risks of allergologic tests, and a written informed consent was obtained from each patient or the parents of those under 18 years of age. The respective institutional review boards approved the protocol.

Subjects underwent an allergologic workup (9), which includes both immediate- and delayed-reading skin tests, as well as patch tests.

On the first day, prick and intradermal tests were carried out using penicilloyl-polylysine, minor determinant mixture, and benzylpenicillin. Patch tests were also administered with benzylpenicillin, ampicillin, and amoxicillin; piperacillin was also used in subjects with adverse reactions to it, as previously described (10).

Two days later, ampicillin and amoxicillin were used for prick and intradermal tests. Piperacillin was also used in subjects with adverse reactions to it, as previously described (10).

On a different day, all subjects positive to patch and/or delayed-reading skin tests underwent skin testing with imipenem/cilastatin at a concentration of 0.5 mg/ml in 0.9% NaCl for each component and meropenem at a concentration of 1 mg/ml in 0.9% NaCl. Since 2002, when ertapenem was

Table 1 Clinical data of patients

	All patients (<i>n</i> 204)
Age (years), mean (SD)	42.7 (16.7)
Women, <i>n</i> (%)	137 (67.1)
Time since last drug reaction*, median (range) [25th, 75th percentile]	12 (1-540) [4, 96]
Family history of allergic disease, <i>n</i> (%)	77 (37.7)
Personal history of allergic disease, <i>n</i> (%)	44 (21.6)
Responsible β -lactams, <i>n</i> (%)	All reactions 298
Amoxicillin	165 (55.3) [83 plus clavulanic acid]
Ampicillin	87 (29.2) [3 plus sulbactam, 6 plus cloxacillin]
Bacampicillin	28 (9.4)
Piperacillin	7 (2.3)
Benzylpenicillin	3 (1)
Benzathine penicillin	1 (0.3)
Cephalexin	1 (0.3)
Pivampicillin	1 (0.3)
Unspecified	5 (1.7)
Manifestation, <i>n</i> (%)	All reactions 298
Maculopapular exanthema	144 (48.3)
Maculopapular exanthema plus edema	116 (38.9)
Erythema	12 (4)
Bullous exanthema	3 (1)
Erythema plus edema	7 (2.3)
Local reaction	3 (1)
Urticaria	2 (0.7)
Toxic epidermal necrolysis	4 (1.3)
Acute generalized exanthematous pustulosis (AGEP)	3 (1)
Others	4 (1.3)
Positive delayed-reading skin test results, <i>n</i> (%)	All patients (<i>n</i> 204)
Minor determinant mixture	19 (9.3)
Benzylpenicillin	94 (46) [50 (24.5) also patch test positive]
Ampicillin	197 (96.6) [186 (91.1) also patch test positive]
Amoxicillin	197 (96.6) [179 (87.7) also patch test positive]
Piperacillin	7 (3.4) [4 (1.9) also patch test positive]

*Time (months) elapsed between last adverse penicillin reaction and current allergologic examination.

commercialized, participants were skin-tested also with ertapenem at a concentration of 1 mg/ml in 0.9% NaCl.

Readings of skin tests and patch tests were made as previously described (9, 11).

Challenges with carbapenems were also performed in subjects who displayed negative results in skin testing. We administered intravenously at one-week intervals one-hundredth of the therapeutic dose (500 mg of imipenem plus 500 mg of cilastatin, 1 g of meropenem, and ertapenem, each on a different day). In cases with negative results, 1 week later, we administered a dose of one-tenth and, if the result was again negative, after another week a full dose was administered. After the first 30 challenges with each carbapenem, we modified this workup, administering an initial dose of one-tenth of the therapeutic dose, and if the result was negative, 1 week later, we administered a full dose. After 30 additional challenges, we administered an initial dose of one-tenth of the therapeutic dose, and if the result was negative, 1 h later, a full dose was administered.

Patients were carefully monitored during all allergy testing and 6 h after carbapenem challenges.

We collected data prospectively and analyzed them by using SAS software for Windows (SAS Institute, Cary, NC, USA) and Stata (StataCorp, College Station, TX, USA). We reported continuous variables as means (SDs). The frequency of positive results is given as a percentage and exact 95% confidence interval (CI).

Results

We examined a total of 204 subjects ranging in age from 15 to 79 years, who had experienced a total of 298 nonimmediate reactions to β -lactams. One hundred and ninety-six subjects (96.1%) reported hypersensitivity reactions to aminopenicillins and 7 of them also to other β -lactams, such as piperacillin, unspecified penicillins, and cephalexin; 5 subjects had reacted to piperacillin and 3 to benzylpenicillin (one of the latter also to an unspecified penicillin). The most frequent clinical manifestations were maculopapular exanthemas (Table 1).

All subjects had positive patch tests and/or delayed-reading skin tests to at least one penicillin reagent and were negative to carbapenem skin tests.

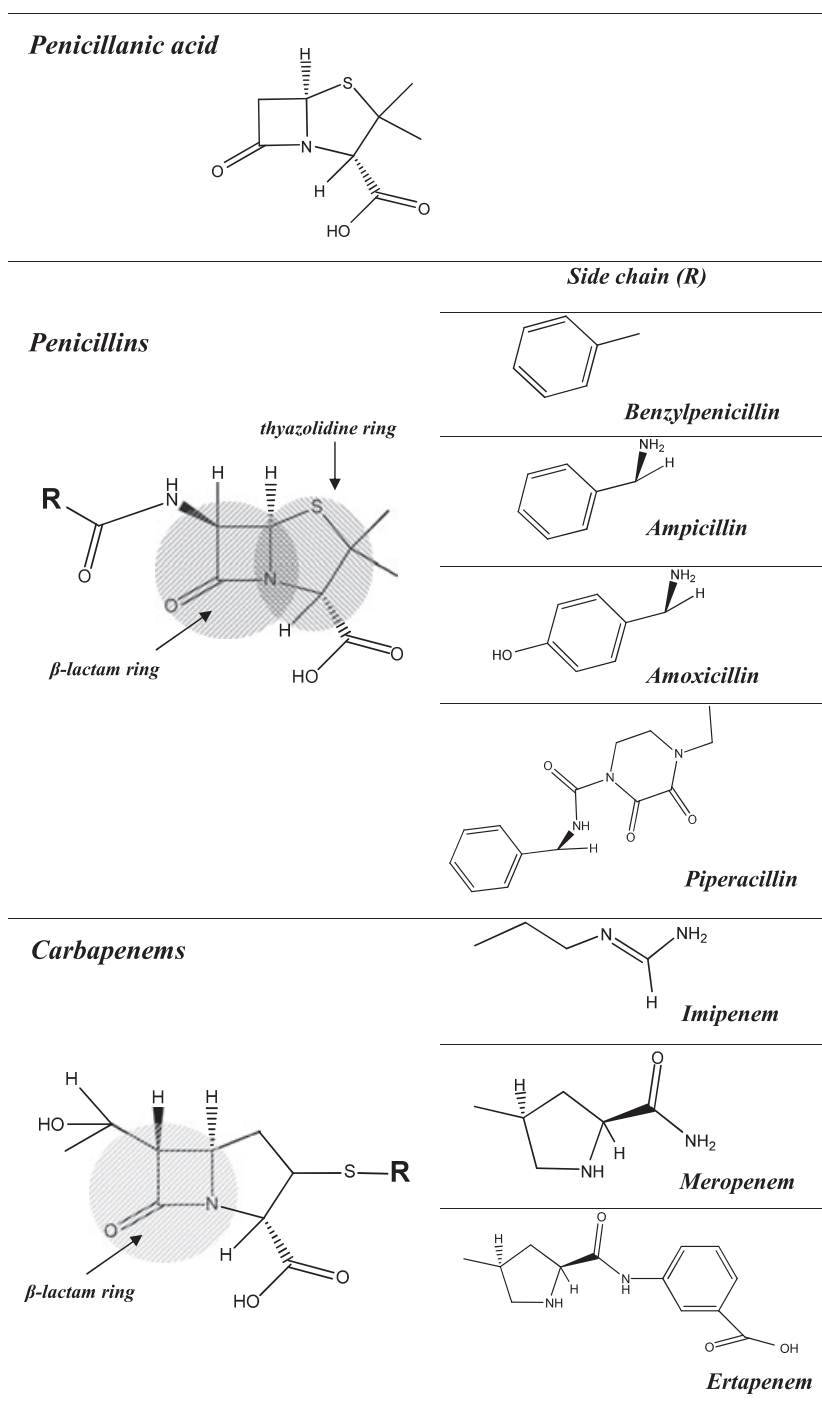


Figure 1 Chemical structures of penicillanic acid, penicillins, and carbapenems, with the common β -lactam ring and the thiazolidine ring highlighted in gray.

All the 204 subjects with negative skin tests to imipenem/cilastatin and meropenem accepted challenges and tolerated them (100% [CI, 98.2% to 100%]); 130 of them were also skin test negative to ertapenem, underwent challenges, and tolerated them (100% [CI, 97.2% to 100%]).

Discussion

These data indicate the absence of cross-reactivity between penicillins and carbapenems in subjects with delayed hypersensitivity to penicillins. Considering the results of the present study, the 5.5% rate of cross-reactivity between β -lactams

and imipenem/cilastatin found by Schiavino et al. (8) appears quite surprising and is difficult to explain with any differences in the characteristics of the samples assessed. In particular, it seems unlikely that all 4 patients of the aforesaid study (8) positive to imipenem/cilastatin patch tests were negative to delayed-reading intradermal tests, which are more sensitive than patch tests in evaluating subjects with delayed hypersensitivity to β -lactams (9). Moreover, the aforementioned study (8) found 2 patch test positivities to penicilloyl-polylysine. Actually, patients with T-cell-mediated hypersensitivity to penicillins present negative responses to penicilloyl-polylysine, because polylysine is a nonimmunogenic carrier, as observed by Levine (12) in delayed reactions to penicillins. Therefore, the positive responses to imipenem/cilastatin patch tests may have been cases of false positivities, as were those to penicilloyl-polylysine.

The present study demonstrates that skin testing and graded challenges with carbapenems can be used safely even in subjects who have suffered severe reactions, such as acute generalized exanthematous pustulosis and toxic epidermal necrolysis.

The absence of cross-reactivity between penicillins and carbapenems found in our study could be explained by the fact that the antigenic epitope of penicillins recognized by T cells consists of both the thiazolidine ring and the side chain structure, as demonstrated *in vitro* by Padovan et al. (13). It should be noted that penicillins do not share common side chains with carbapenems (Fig. 1). In the aforesaid study (13), moreover, the complete absence of the side chain in 6-aminopenicillanic acid (Fig. 1) resulted in the inability to stimulate T-cell clones from penicillin-allergic subjects.

On the other hand, when considering subjects with IgE-mediated hypersensitivity to β -lactams, in studies that demonstrated a very low (around 1%) rate of allergic cross-reactivity between penicillins and carbapenems (3, 4), as well as between cephalosporins and carbapenems (14), the 2 subjects who displayed positive skin tests to both imipenem/cilastatin and meropenem were also positive to all the other β -lactams tested, including aztreonam; therefore, their IgE antibodies were probably directed against a common nuclear determinant, the β -lactam ring, which is shared by all β -lactams. This pattern of sensitization (i.e., selective recognition by T lymphocytes of the β -lactam ring) was not observed either in the present study or in that by Schiavino et al. (8), in which the 4 subjects positive to imipenem/cilastatin were not positive to all the β -lactams tested, including cephalosporins and aztreonam.

In conclusion, our study demonstrated the tolerability of carbapenems in all subjects with T-cell-mediated hypersensitivity to penicillins. Nevertheless, until further studies confirm our data, in patients with such hypersensitivity who need carbapenem therapy, pretreatment skin tests and graded challenges are advisable at least in subjects who experienced severe reactions.

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Conflicts of interest

The authors declare no conflicts of interest.

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