

# Brief Communication: Tolerability of Meropenem in Patients with IgE-Mediated Hypersensitivity to Penicillins

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**Background:** Although clinicians avoid giving meropenem to patients with penicillin allergy because of potential cross-reactivity, the rate of cross-reactivity between penicillins and meropenem has not been prospectively determined.

**Objective:** To assess the tolerability of meropenem in patients with documented penicillin allergy.

**Design:** Prospective skin testing and antibiotic challenge.

**Setting:** Allergy units of 2 Italian medical centers.

**Patients:** 104 consecutive participants with immediate hypersensitivity reactions to penicillins and positive skin test results to at least 1 penicillin reagent.

**Measurements:** Skin tests to meropenem and, if results were negative, challenges with escalating doses of meropenem.

**Results:** One participant (0.9% [95% CI, 0.02% to 5.2%]) had a positive intradermal test result to meropenem. The remaining 103 participants with negative skin test results to meropenem tolerated escalating dose challenges.

**Limitation:** Challenges were not followed by therapeutic courses.

**Conclusions:** These data indicate a low rate of cross-reactivity between penicillins and meropenem. Therefore, the practice of avoiding meropenem therapy in penicillin-allergic patients should be reconsidered. In patients who especially require meropenem treatment, the authors recommend pretreatment skin tests because negative results indicate tolerability.

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Meropenem is a carbapenem with a potent antibacterial efficacy against a wide range of pathogens and is used primarily to treat serious polymicrobial infections (1).

No published data examine cross-reactivity to meropenem in patients with documented IgE-mediated hypersensitivity to penicillins. Nevertheless, administration of meropenem to penicillin-allergic patients is considered potentially harmful (2, 3) because of a 47% rate of cross-reactivity to imipenem, the prototype of the carbapenem class of  $\beta$ -lactam antibiotics, demonstrated in a single study (4).

Subsequent retrospective studies (5–7) did not find such a rate of cross-reactivity between penicillins and carbapenems, specifically meropenem (Table 1). No patient in these studies (5–7) had prick or intradermal tests with either penicillin or carbapenem reagents. However, skin testing with native carbapenems may be useful (8). Recently, we reported a very high negative predictive value of imipenem skin testing among 112 patients with well-demonstrated IgE-mediated hypersensitivity to penicillins (9). Of the 111 participants with negative results, 110 agreed to undergo imipenem–cilastatin challenges, which they tolerated.

We conducted this prospective study to evaluate meropenem use in patients with documented penicillin allergy. We evaluated a large group of penicillin-allergic participants by using skin tests with meropenem to assess the cross-reactivity. Participants with negative results were challenged to ascertain if negative results could be a reliable indicator of meropenem tolerability.

## METHODS

### Patient Selection

We studied all participants older than 13 years of age who came to the allergy units of the Complesso Integrato Columbus, Rome, Italy, and Oasi Maria Santissima, Troina, Italy, between January 2002 and June 2006 and had histories of immediate reactions to penicillins. The inclusion criterion was a positive skin test result to at least 1 penicillin reagent. An indication for meropenem treatment was not an inclusion criterion. The exclusion criteria were pregnancy; use of  $\beta$ -blockers; and severe cardiovascular, renal, or respiratory condition. Before the study, all participants received information about possible risks of allergologic tests, and we obtained written informed consent from each patient or from the parents of patients younger than 18 years of age. The respective institutional review boards approved the study protocol.

### Skin Tests

The skin testing with the classic penicillin reagents (penicilloyl polylysine, minor determinant mixture, and benzylpenicillin) and semisynthetic penicillins (ampicillin,

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amoxicillin, and piperacillin) was performed on 2 different days, as previously described (10). Meropenem (Merrem, AstraZeneca, Basiglio, Italy) was used on the third day at a concentration of 1 mg/mL of normal saline.

We performed skin tests and readings as previously described (11), and we assessed reagents first by prick tests and, if results were negative, by intradermal tests. We obtained positive control results for prick and intradermal tests with histamine (at 10 mg/mL and 1 mg/mL, respectively) and negative control results by using normal saline.

We did prick and intradermal tests with meropenem in 20 healthy control participants who tolerated penicillins.

### In Vitro Tests

Assays (UniCAP, Pharmacia Diagnostics AB, Milan, Italy) were performed for specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, and amoxicilloyl. We defined a positive result as a value of 0.35 kU/L or greater. We obtained patient blood samples at evaluation and stored sera at  $-20^{\circ}\text{C}$  until assayed.

### Meropenem Test Dosing

On a different day, challenges with intravenous meropenem were also performed in participants who had negative skin test results. We administered an initial dose of one hundredth of the therapeutic dose. In patients with negative results, we administered a one-tenth dose 1 hour later and, if the result was again negative, a full dose after another hour.

After the first 40 challenges, we administered a one-tenth dose and, if the result was negative, we administered a full dose 1 hour later.

Patients were carefully monitored during all testing and for 2 hours after the meropenem challenges.

Participants with positive skin test results to meropenem were not challenged because this could indicate a sensitization.

Of the 104 participants, some also participated in our other studies in penicillin-allergic patients (9, 10) that examined the cross-reactivity and tolerability of imipenem-cilastatin ( $n = 69$ ) and cephalosporins ( $n = 22$ ).

### Statistical Analysis

We collected data prospectively and analyzed them by using SAS software for Windows (SAS Institute, Cary,

### Context

Frequent cross-reactions between penicillins and imipenem, the prototype carbapenem, may discourage use of other carbapenems in patients with a history of penicillin allergy.

### Contribution

The authors performed skin tests with penicillins and meropenem in 104 patients with a history of immediate reaction to penicillins. All patients had positive skin test results to at least 1 penicillin, while only 1 patient had a positive skin test result with meropenem (prevalence, 0.9% [95% CI, 0.02% to 5.2%]). All 103 patients with a negative meropenem skin test had a negative intravenous meropenem challenge.

### Caution

The patients did not receive a full therapeutic course of meropenem.

### Implications

Allergy to meropenem is uncommon in penicillin-allergic patients.

—The Editors

North Carolina) and Stata software (StataCorp, College Station, Texas). We reported continuous variables as means (SDs). We evaluated differences between percentages by Fisher exact test. For all results, a  $P$  value less than 0.05 was considered significant.

The frequency of positive results is given as a percentage and exact 95% CI (12).

### Role of the Funding Sources

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**Table 1. Rate of Adverse Reactions to Meropenem Therapy Based on the History of Penicillin Allergy\***

Study, Year (Reference)	Patients, <i>n</i>	History of Penicillin Allergy		No History of Penicillin Allergy	
		Patients, <i>n</i>	Reactions, <i>n</i> (%)	Patients, <i>n</i>	Reactions, <i>n</i> (%)
Ciofu et al., 1996 (5)	62 (with cystic fibrosis)	57	8/114 courses (7)*	5	1/10 courses (10)
Prescott et al., 2004 (6)	110	51	5 (9)	59	1 (1)
Sodhi et al., 2004 (7)†	266	163	15 (9)	103	4 (3)

\* Fifty-one of the 114 courses were monotherapy with meropenem, 31 were in combination with tobramycin, 11 were in combination with ciprofloxacin, and 21 were in combination with both tobramycin and ciprofloxacin.

† In Sodhi and colleagues' study (7), patients were given either imipenem-cilastatin or meropenem. The authors did not specify the carbapenem that was responsible for each reaction.

**Table 2. Clinical Data and Allergologic Test Results of Patients**

Variable	Value
All patients, <i>n</i>	104
Mean age (SD), <i>y</i>	47.83 (15.8)
Women, <i>n</i> (%)	66 (63)
Median time since last penicillin reaction (range) [25th, 75th percentile], <i>mo</i> *	6 (1–360) [2, 24]
Family history of allergic diseases, <i>n</i> (%)	34 (32)
Personal history of allergic diseases, <i>n</i> (%)	24 (23)
Reactions, <i>n</i> †	138
Culprit penicillins, <i>n</i> (%)	
Amoxicillin	73 (52)‡
Ampicillin	25 (18)§
Bacampicillin	18 (13)
Piperacillin	16 (11)
Benzathine-penicillin	3 (2)
Benzyl-penicillin	3 (2)
Manifestations, <i>n</i> (%)†	
Anaphylactic shock	85 (61)
Urticaria	29 (21)
Urticaria and angioedema	24 (17)
Positive skin test results to penicillins, <i>n</i> (%)	
Penicilloyl polylysine	27 (25)
Minor determinant mixture	35 (33)
Benzylpenicillin	44 (42)
Ampicillin	63 (60)
Amoxicillin	63 (60)
Piperacillin	44 (42)
Positive skin test results to meropenem, <i>n/n</i> (%)	1/104 (0.9)¶
Positive skin test results to imipenem–cilastatin, <i>n/n</i> (%)	1/69 (1)¶
Positive skin test results to cephalosporins, <i>n/n</i> (%)	3/22 (13)¶
Positive specific IgE assay results, <i>n</i> (%)	
Penicilloyl G	23 (22)
Penicilloyl V	27 (25)
Ampicilloyl	28 (26)
Amoxicilloyl	19 (18)

\* Time that elapsed between the last adverse reaction and current allergologic examination.

† Seventy-two of 104 patients had only 1 reaction, whereas 32 patients had distinct reactions to either the same penicillin (17 patients) or different penicillins (15 patients) in separate episodes.

‡ Of these reactions, 33 were also with clavulanic acid.

§ Of these reactions, 1 was also with sulbactam.

|| Of these reactions, 1 was also with tazobactam.

¶ The denominator is the total number of patients. The same patient had positive skin test results to meropenem, imipenem–cilastatin, and cephalosporins (cephalothin, cefamandole, cefuroxime, ceftazidime, ceftriaxone, and cefotaxime); 2 other patients had positive results to  $\geq 1$  of these cephalosporins.

## RESULTS

We examined a total of 104 participants, ranging in age from 14 to 83 years, with histories of immediate reactions to penicillins. We performed the allergy testing with intervals ranging from 1 to 360 months (median, 6 months) after the most recent reaction (Table 2). No case had any exclusion criterion. These patients had experienced a total of 138 reactive episodes to penicillins. Table 2 shows the responsible penicillins and clinical manifestations.

All participants had positive skin test results to at least 1 penicillin reagent, while only 1 participant (0.9% [95% CI, 0.02% to 5.2%]) presented a positive reaction to the intradermal test with meropenem (maximum wheal diameter of 8 mm, surrounded by erythema). The participant had had an anaphylactic reaction to amoxicillin plus clavulanic acid and had positive results to all penicillin reagents in both in vivo and in vitro tests, as well to skin tests with imipenem–cilastatin and cephalosporins. Control participants had no positive reactions to meropenem.

Of the 104 patients who had in vitro assays, 39 participants (37.5% [CI, 28.8% to 47.1%]) had positive results and 30 of these participants had specific IgE to ampicilloyl, amoxicilloyl, or both.

Of the 103 patients (100% [CI, 96.5% to 100%]) with negative skin test results to meropenem, all accepted challenges with meropenem and tolerated them.

## DISCUSSION

We believe that our study is the first to prospectively determine the rate of cross-reactivity between penicillins and meropenem in patients with well-demonstrated IgE-mediated hypersensitivity to penicillins. The rate of such cross-reactivity is no higher than 5.2%, the upper confidence bound. This low rate can be explained by the fact that IgE antibodies of penicillin-allergic patients recognize specific penicillin determinants rather than a common nuclear determinant, that is, the  $\beta$ -lactam ring, which is shared by penicillins and meropenem.

In 2 of the 3 aforementioned retrospective studies (6, 7) the rate of hypersensitivity reactions to meropenem, imipenem-cilastatin, or both among patients with histories of penicillin allergy was about 9% (Table 1). We must consider, however, that retrospective studies rely mainly on the patient's history. In effect, no patient in the 3 retrospective studies (5–7) had skin testing with penicillin reagents, and as many as 80% to 90% of all patients who claim to be allergic to penicillin are not (13).

In contrast, our study documented penicillin hypersensitivity as well as Saxon and colleagues' study (4). In their study of 19 of 40 patients, Saxon and colleagues found a 47% rate of cross-reactivity to imipenem, but they did not challenge patients who had negative results on skin testing with imipenem reagents. The rate of cross-reactivity to meropenem detected in our present study is identical to that of cross-reactivity to imipenem–cilastatin found in our previous study (9). Such different results between our studies and Saxon and colleagues may derive from differences in the samples assessed. In Saxon and colleagues' study, all patients reacted to benzylpenicillin, while in our studies, most patients experienced immediate reactions to aminopenicillins and fewer than 10% reacted to benzylpenicillin or benzathine penicillin. Moreover, we performed skin testing only with the parent carbapenems, while Saxon and colleagues also used imipenem metabolites.

Of interest, the rate of positive responses to skin tests with meropenem found in the our present study is lower than the rate of positive responses to skin tests with cephalosporins (10.9% [CI, 5.6% to 16.2%]) found in our previous study (10), which assessed 128 patients with an IgE-mediated hypersensitivity to penicillins documented in the same way as in our present study. Furthermore, the upper confidence bound (5.2%) established is not far from the 4.4% rate of cross-reactivity between penicillins and cephalosporins calculated in a recent review (14).

An important limitation of our study is that challenges were not followed by full therapeutic courses, because we studied our patients for research purposes rather than for clinical indications for meropenem treatment. However, skin testing with meropenem is a simple, reliable diagnostic tool, which has a high negative predictive value and could even be used in patients with acute illness. In effect, our data indicate that no more than 3.5% of patients would be expected to have a positive challenge after a negative skin test result. In penicillin-allergic patients who especially require meropenem treatment and have negative skin test results to meropenem, we suggest, in any case, a graded challenge until further studies have been performed to confirm the negative predictive value of such tests.

In conclusion, our data indicate a very low rate of cross-reactivity between penicillins and meropenem. Therefore, the practice of avoiding meropenem in patients with penicillin allergy should be reconsidered. In patients with such hypersensitivity who need meropenem therapy, we recommend pretreatment skin tests and graded chal-

lenges. Considering that the sensitizing power of meropenem courses in penicillin-allergic patients is not well-known, meropenem retesting seems advisable before any subsequent course is pursued.

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