

Short communication

Tolerability of meropenem in children with IgE-mediated hypersensitivity to penicillins

Background: Administration of meropenem to penicillin-allergic patients who might benefit from this treatment is usually avoided because of a 47.4% rate of cross-reactivity to imipenem, the prototype of the carbapenem class of β -lactam antibiotics, demonstrated in a single study on the basis of positive responses to skin tests with imipenem reagents. However, recent studies of ours have demonstrated a very low rate of cross-reactivity between penicillins and both meropenem and imipenem in adults.

Objective: To assess cross-reactivity and tolerability of meropenem in children with documented penicillin allergy.

Methods: One hundred and eight consecutive children who had suffered a total of 129 immediate reactions (120 urticarial and/or angioedematous manifestations and 9 anaphylactic shocks) to penicillins and had positive results to skin tests for at least one of the penicillin reagents tested underwent skin tests with meropenem and negative subjects were challenged with it.

Results: One subject (0.9%) displayed a positive intradermal test to meropenem. The remaining 107 subjects with negative skin tests to meropenem tolerated challenges. Challenges were not followed by full therapeutic courses.

Conclusions: Our results demonstrate a low rate of cross-reactivity between penicillins and meropenem. Therefore, the practice of avoiding meropenem in children with immunoglobulin E-mediated hypersensitivity could be abandoned; in those who especially require meropenem treatment, prophylactic skin tests are advisable, because negative results indicate tolerability.

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Key words: cross-reactivity; meropenem; penicillin allergy; skin tests; tolerability.

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Accepted for publication 26 July 2007

Meropenem is a carbapenem with a broad spectrum of antibacterial activity exceeding that of most other antimicrobial classes, which is used mainly in the treatment of serious polymicrobial infections (1). Administration of meropenem to patients with immunoglobulin E (IgE)-mediated hypersensitivity to penicillins who might benefit from this treatment is considered potentially harmful (2) because of a 47.4% rate of cross-reactivity to imipenem, demonstrated in a single study (3). In this study, nine out of 19 patients with histories of penicillin hypersensitivity and skin test positivity to penicillin reagents had also presented positive responses to skin tests with imipenem reagents.

In subsequent retrospective studies (4–6), the rate of cross-reactivity between penicillins and carbapenems, specifically meropenem, was found to be lower than 10%. In two of them (5, 6), the rate of hypersensitivity reactions to meropenem and/or imipenem/cilastatin among patients with histories of penicillin allergy was about 9%, while among patients without such histories it was lower than 4% (Table 1).

Recently, we had found a 0.9% rate of positive responses to skin tests with imipenem/cilastatin or

meropenem among 112 and 104 adults, respectively, with a well-demonstrated IgE-mediated hypersensitivity to penicillins (7, 8). All negative subjects who had accepted imipenem/cilastatin or meropenem challenges tolerated them: 110 imipenem/cilastatin and 103 meropenem, respectively.

The present prospective study was conducted to evaluate the possibility of using meropenem in children with documented penicillin allergy, who especially require this treatment. To address this question, a large group of well-characterized penicillin-allergic subjects was evaluated by skin tests with meropenem to assess the cross-reactivity. Moreover, subjects who had displayed negative results in meropenem skin tests were challenged to ascertain, if negative results could be a reliable indicator of its tolerability.

Methods

Patient selection

Children ranging in age from 3 to 14 years were recruited prospectively from a large outpatient population with a history of

Table 1. Rate of adverse reactions to meropenem in retrospective studies regarding both patients with and without a history of penicillin allergy

Study (Reference)	Patients (n)	Positive history of penicillin allergy (n)	Reactions, n (%)	Negative history of penicillin allergy (n)	Reactions n (%)
Ciofu et al. (4)	62 (with cystic fibrosis)	57	8/114 courses* (7)	5	1/10 courses (10)
Prescott et al. (5)	110	51	5 (9.8)	59	1 (1.6)
Sodhi et al. (6)†	266	163	15 (9.2)	103	4 (3.8)

Adapted from Romano et al. (8).

*51 of the 114 courses were meropenem monotherapies, 31 were combined with tobramycin, 11 were combined with ciprofloxacin, and 21 were combined with both tobramycin and ciprofloxacin.

†In this study, patients were administered either imipenem/cilastatin or meropenem; the authors did not specify the carbapenem responsible for each reaction.

immediate reactions to at least one penicillin. This population was evaluated between January 2005 and March 2007 in the University Children's Hospital of Belgrade. The inclusion criterion required positive skin tests to one or more of the classic penicillin reagents and/or to one or more of the semi-synthetic penicillins. Sensitization to meropenem was evaluated using skin tests with the parent drug. In case of negative results, patients were administered meropenem. The exclusion criteria consisted in severely compromised cardiovascular, renal, or respiratory functions. Prior to the study, the parents of all the children received information about the possible risks of skin and challenge tests, and written informed consent was obtained from them. The protocol was approved by the institutional review board.

Skin tests

The skin testing with the classic penicillin reagents (penicilloyl-polylysine, minor determinant mixture, and benzyl-penicillin), ampicillin, and amoxicillin was performed on two different days, as previously described (9, 10). Meropenem (Meronem, AstraZeneca, Luton, UK) was used on the third day at a concentration of 1 mg/ml in normal saline.

Skin tests and readings were performed as previously described (11, 12); reagents were assessed first by prick tests and, in case of negative results, by intradermal tests. Positive controls for prick and intradermal tests were performed with histamine (at 10 and 1 mg/ml, respectively). As a negative control for prick and intradermal tests, normal saline was used. Prick and intradermal tests with meropenem were also administered to 20 healthy control children.

In vitro tests

Assays (UniCAP System; Phadia, Uppsala, Sweden) were performed for specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, and amoxicilloyl. A positive result was defined as a value ≥ 0.35 kU/l. Blood samples were obtained when patients were evaluated and sera were kept at -20°C until assayed.

Meropenem test dosing

On a different day, controlled administrations of therapeutic doses of meropenem (Meronem, intravenously) were also performed in subjects who displayed negative results in skin testing. We administered an initial dose of one-hundredth of the therapeutic one (150 mg–1 g, depending on children's weight). In cases with negative results, 1 h later we administered a dose of one-tenth and, if the result was again negative, after another hour a full dose. After the first 30 challenges, we modified this challenge work-up, adminis-

tering an initial dose of one-tenth of the therapeutic one and, if the result was negative, 1 h later a full dose. Each patient was carefully monitored during test dosing, and complete equipment for cardiopulmonary resuscitation was immediately available. Subjects with positive skin test responses to meropenem were not challenged, because such positivity could indicate a sensitization.

Results

We examined a total of 108 children (52 females and 56 males), with histories of immediate reactions to penicillins. Our work-up was performed with intervals ranging from 1 to 120 months (median: 5.50) after the most recent reaction. None of these cases had any exclusion criterion.

Our 108 patients had experienced a total of 126 reactive episodes to penicillins and three to cephalosporins (Table 2). The majority (87 patients, 80.5%) had suffered only one reaction, whereas 21 subjects had had two distinct reactions to either different penicillins (18 patients) or to penicillins and cephalosporins (three patients) in separate episodes. The penicillins responsible for the reactions and the clinical manifestations are shown in Table 2. Sixty subjects (55.5%) reported adverse reactions to benzyl-penicillin; most of the clinical manifestations were urticarial eruptions.

All subjects had positive skin tests to at least one of the penicillin reagents tested: 51 were positive only to the classic penicillin reagents, 25 to both the classic penicillin reagents and semi-synthetic penicillins, and 32 only to the latter. Of our total of 108 patients, 107 displayed negative skin tests to meropenem and 1 (0.9%) was skin-test positive. He was a 5-year-old boy who had suffered an urticarial reaction to amoxicillin. He displayed a positive response to intradermal testing with amoxicillin at a concentration of 1 mg/ml (maximum wheal diameter of 7 mm, surrounded by erythema), as well as a positive reaction to the intradermal test with meropenem (maximum wheal diameter of 5 mm, surrounded by erythema). There were no positive reactions to meropenem in control subjects. *In vitro* assays were positive in 16 (14.8%) of the 108 children; 14 of them had specific IgE to penicilloyl G and/or penicilloyl V. All the 107 patients with negative skin tests to meropenem who underwent meropenem challenges tolerated them.

Table 2. Clinical data and allergologic-test results of patients

Age (years), mean (SD)	All patients (n = 108)
Women, n (%)	8.15 (3.7)
Time since last penicillin reaction*, median (range) [25th, 75th percentile]	52 (48.15) 5.5 (1–120) [3, 10.5]
Family history of allergic diseases, n (%)	13 (12)
Personal history of allergic diseases, n (%)	10 (9.2)
Culprit β-lactams, n (%)	All reactions (n = 129)
Benzyl-penicillin	60 (46.5)
Amoxicillin	52 (40.3)
Ampicillin	13 (10)
Phenoxymethyl-penicillin	1 (0.8)
Cephalosporins	3 (2.4)
Manifestations, n (%)	All reactions (n = 129)
Urticaria	101 (78.2)
Urticaria and angioedema	18 (14)
Anaphylactic shock	9 (7)
Angioedema	1 (0.8)
Positive skin-test results to penicillins, n (%)	All patients (n = 108)
Penicilloyl-polylysine	52 (48.1)
Minor determinant mixture	54 (50)
Benzyl-penicillin	70 (64.8)
Ampicillin	27 (25)
Amoxicillin	46 (42.6)
Positive skin-test results to meropenem, n (%)	1/108 patients (0.9)
Positive specific IgE assay results, n (%)	All patients (n = 108)
Penicilloyl G	13 (12)
Penicilloyl V	11 (10.5)
Ampicilloyl	6 (5.5)
Amoxicilloyl	4 (3.7)

*Time elapsed between the last penicillin reaction and the allergologic examination.

Discussion

The rate of positive responses to skin tests with meropenem detected in the present study was 0.9%, which is identical to that of skin tests with imipenem/cilastatin or meropenem found in the previously mentioned studies of ours, regarding penicillin-allergic adults (7, 8). The present study differs from the latter (7, 8) not only because of the age of the patients assessed, but also because of the fact that the great majority of adults of the previous studies had experienced immediate reactions to aminopenicillins, and <10% had reacted to benzyl-penicillin or benzathine-penicillin, while 65 (60.2%) of the children of the present study had reacted to amoxicillin and/or ampicillin and 60 (55.5%) to

benzyl-penicillin. Therefore, the characteristics of the children evaluated in the present study are more similar to those of the adults assessed by Saxon et al. (3) than are the characteristics of the adults of our previous studies (7, 8). In any case, our studies performed both in adults and in children did not confirm the results of Saxon et al. (3). Unlike these researchers, we challenged patients displaying negative results to carbapenem skin testing and all those who underwent challenges tolerated them.

With regard to the aforesaid retrospective studies (4–6), two of them (5, 6) indicate that patients with histories of penicillin allergy are at greater risk for hypersensitivity reactions to meropenem than patients without such histories (Table 1). We must consider, however, that retrospective studies rely mainly on the patient's history. Furthermore, one (6) of the previously mentioned three studies (4–6) did not specify the carbapenem (imipenem/cilastatin or meropenem) responsible for each hypersensitivity reaction. Moreover, most of the hypersensitivity reactions reported in these studies (4–6) were rashes, which usually are not IgE-mediated; a few patients experienced hives and only one suffered an anaphylactic shock to meropenem (5). In any case, none of the patients in these retrospective studies (4–6) underwent skin testing with penicillin reagents, and it has been estimated that as many as 80–90% of all patients who claim to have a penicillin allergy are not truly allergic (13).

In conclusion, our results demonstrate a very low rate of cross-reactivity between penicillins and meropenem. Therefore, the practice of avoiding meropenem in patients with IgE-mediated hypersensitivity could be abandoned. In children with such hypersensitivity who especially require meropenem treatment, we recommend prophylactic skin tests, because negative results indicate its tolerability. In penicillin-allergic patients with negative skin tests to meropenem, we suggest, in any case, a graded challenge until further studies have been performed to fully establish the negative predictive value of such tests. Because the power of meropenem courses to sensitize penicillin-allergic patients is not well known, it seems advisable to retest meropenem before any subsequent course.

Acknowledgments

This study was funded by MURST, (Italian) Ministry for University, Scientific and Technological Research.

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