

Letter to the Editor

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

To the Editor:

Until recently, administration of imipenem/cilastatin to patients with IgE-mediated hypersensitivity to penicillins who might benefit from this treatment was considered potentially harmful¹ because a single study² found a 47.4% rate of cross-reactivity to imipenem.

Subsequent retrospective studies³⁻⁵ did not find such a high rate of cross-reactivity between penicillins and carbapenems, specifically imipenem, but 2 of them^{4,5} indicate that patients with histories of penicillin allergy are at greater risk for hypersensitivity reactions to imipenem than patients without such histories (Table I). However, recent studies of ours, performed on samples larger than 100 subjects with a well-demonstrated IgE-mediated hypersensitivity to penicillins, have demonstrated a 0.9% rate of cross-reactivity between penicillins and both imipenem⁶ and meropenem⁷ in adults, as well as between penicillins and the latter carbapenem in children.⁸

We evaluated 124 children (age range, 3-14 years) with a well-demonstrated IgE-mediated hypersensitivity to penicillins to assess the cross-reactivity with imipenem/cilastatin and to evaluate its tolerability in subjects with negative skin test results. These 124 children constituted 45% of an outpatient population of 275 subjects recruited prospectively between January 2005 and June 2008 in the University Children's Hospital of Belgrade on the basis of histories of immediate reactions (ie, occurring within 1 hour after the last drug administration) to at least 1 penicillin. The inclusion criterion required positive skin test responses to 1 or more of the penicillin reagents tested. A clinical indication for imipenem/cilastatin treatment was not an inclusion criterion because we assessed imipenem/cilastatin cross-reactivity and tolerability in our patients only for research purposes. The protocol was approved by the institutional review board.

Skin tests with the penicillin reagents were performed on 2 different days, as previously described by us.^{8,9} On the first day, prick and intradermal tests were carried out with penicilloyl-polylysine (DAP; Diater, Madrid, Spain), minor determinant mixture (DAP; benzylpenicillin, sodium benzylpenicilloate, and benzylpenicilloic acid), and benzylpenicillin (Sanavita Pharmaceuticals GmbH, Werne, Germany). The final concentrations were, respectively, 1.07×10^{-2} mmol/L, 1.5 mmol/L, and 10,000 IU/mL.

Ampicillin (Pentrexyl; Bristol-Myers Squibb Srl, Sermoneta, Italy) and amoxicillin (Bactox; Innothera Group, Chouzy, France), at concentrations of 1 and 20 mg/mL, respectively, after dilution in normal saline were used on the second day.

Imipenem/cilastatin (Tienam; Merck Sharp & Dohme, Whitehouse, NJ) was used on the third day, with each component at a concentration of 0.5 mg/mL in normal saline. Skin tests and readings were performed as previously described.^{8,9} reagents were assessed first by using prick tests and, in case of negative results, by using intradermal tests. Positive controls for prick and intradermal tests were done with histamine (at 10 and 1 mg/mL, respectively). As a negative control for prick and intradermal tests, normal saline was used.

Of the 124 children, 82 also participated in another study of patients with penicillin allergy,⁸ which examined the cross-reactivity and tolerability of meropenem.

Our 124 patients had experienced a total of 154 reactive episodes to penicillins. The responsible β -lactams and the clinical manifestations are shown in Table II. All subjects had positive skin test responses to at least 1 of the penicillin reagents tested; 16 (12.9%) had positive specific IgE assay results (Table II). Only 1 (0.8%) subject displayed a positive intradermal test result to imipenem/cilastatin (maximum wheal diameter of 6 mm surrounded by erythema). He was a 5-year-old boy who had an urticarial reaction to amoxicillin 3 months before the allergologic work-up and presented with a positive intradermal test result to amoxicillin at a concentration of 1 mg/mL (maximum wheal diameter of 7 mm surrounded by erythema).

In the 123 children with negative skin test results, we performed tolerability tests with imipenem/cilastatin, administering intravenously or intramuscularly one hundredth of the therapeutic dose (from 220 mg up to 0.5 g of each component, depending on the child's weight), and if no symptoms developed, a one-tenth dose was used. Finally, the full dose was used at 1-hour intervals. After the first 30 tests, we modified this work-up, administering an initial dose of one tenth of the therapeutic dose, and if the result was negative, a full dose was administered 1 hour later. No child had a clinical reaction.

The results of the present study confirm those of our previous studies concerning cross-reactivity between penicillins and carbapenems (imipenem and meropenem) in both adults and children.⁶⁻⁸ The rate of cross-reactivity to imipenem/cilastatin detected in our study (1/124 [0.8%] patients) is much lower than that found by Saxon et al² (9/19 [47.4%]). Such different results might derive, to a certain extent, from the characteristics of the samples assessed and the diagnostic methods of the 2 studies. All patients evaluated by Saxon et al had reacted to benzylpenicillin, whereas in the present study only 67 (43.5%) of the 124 subjects had so reacted. Moreover, we performed skin tests only with the parent drug (imipenem/cilastatin), whereas Saxon et al used the imipenem determinants (imipenemoyl and imipenemoate) in addition to the parent drug. In the Saxon et al study, however, skin testing with the parent drug produced positive results in 7 of the 10 patients given diagnoses of cross-reaction to imipenem/cilastatin. In any case, unlike Saxon et al, we challenged children with negative results to imipenem/cilastatin skin testing, and all 123 subjects who underwent challenges tolerated these tests.

It is interesting to note that the characteristics of the Serbian children of the present study, as well as the previous one,⁸ are more similar to those of the adults assessed in the study by Saxon et al² than are the characteristics of the adults in our previous studies.^{6,7} In effect, more than 40% of the Serbian children evaluated in the present study and in the previous one⁸ had reacted to benzylpenicillin, whereas most of our Italian adults had experienced immediate reactions to aminopenicillins, and fewer than 10% had reacted to benzylpenicillin.

The rate of cross-reactivity to imipenem/cilastatin detected in the present study is also lower than the rate of hypersensitivity reactions to imipenem/cilastatin or meropenem among patients with histories of penicillin allergy observed in the aforementioned retrospective studies (Table I).³⁻⁵ However, retrospective studies

TABLE I. Rate of adverse reactions to imipenem/cilastatin therapy in children with or without a history of penicillin allergy

Study	No. of patients	Positive history of penicillin allergy (n)	Reactions, no. (%)	Negative history of penicillin allergy (n)	Reactions, no. (%)
McConnell et al ³	63	63	6 (9.5)	0	0
Prescott et al ⁴	101	49	6 (12.2)	52	2 (3.8)
Sodhi et al ^{5*}	266	163	15 (9.2)	103	4 (3.9)

*In the study of Sodhi et al,⁵ patients were given either imipenem/cilastatin or meropenem. The authors did not specify the carbapenem that was responsible for each reaction.

TABLE II. Clinical data and allergologic test results of patients

	All patients (n = 124)
Age (y), mean (SD)	7.68 (3.54)
Female sex, no. (%)	55 (44.35)
Time since last penicillin reaction,* median (range [25th-75th percentile])	5.5 (2-120 [3-10])
Family history of allergic diseases, no. (%)	7 (5.6)
Personal history of allergic diseases, no. (%)	6 (4.8)
Culprit β -lactams, no. (%)	All reactions (n = 154)
Benzylpenicillin	67 (43.5)
Amoxicillin	58 (37.7)
Ampicillin	17 (11)
Phenoxymethyl penicillin	9 (5.85)
Cephalexin	1 (0.65)
Ceftriaxone	1 (0.65)
Cefaclor	1 (0.65)
Manifestations, no. (%)	All reactions (n = 154)
Urticaria	124 (80.5)
Urticaria and angioedema	19 (12.3)
Anaphylactic shock	11 (7.2)
Positive skin test results to penicillins, no. (%)	All patients (n = 124)
Penicilloyl-polylysine	52 (42)
Minor determinant mixture	56 (45.2)
Benzylpenicillin	71 (57.2)
Phenoxymethyl penicillin	21 (17)
Ampicillin	28 (22.5)
Amoxicillin	51 (41.1)
Positive skin test results to imipenem/cilastatin, no. (%)	1/124 (0.8%) patients
Positive specific IgE assay results, no. (%)	All patients (n = 124)
Penicilloyl G	8 (6.4)
Penicilloyl V	8 (6.4)
Ampicilloyl	4 (3.2)
Amoxicilloyl	3 (2.4)

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

rely mainly on the patient's history. In any case, none of these patients underwent skin tests with penicillin reagents, and studies indicate that as many as 80% to 90% of all patients who report a penicillin allergy are not truly allergic.¹⁰

It is difficult to establish whether the boy with positive skin test results to amoxicillin had such a response to imipenem/cilastatin because of cross-reactivity or because of a coexisting sensitivity. This boy also participated in another study concerning cross-reactivity with meropenem⁸ and displayed positive skin test responses to the latter carbapenem. In any case, he had never been treated with imipenem/cilastatin or meropenem.

In conclusion, our results demonstrate a very low rate of cross-reactivity between penicillins and imipenem/cilastatin. Therefore it is possible to abandon the practice of avoiding the administration of imipenem/cilastatin in patients with IgE-mediated hypersensitivity to penicillins; in those who especially require

imipenem/cilastatin treatment, prophylactic skin tests and, in the case of negative results, graded challenges can be performed. The latter are advisable until further studies have been performed to fully establish the negative predictive value of such tests.

Because the power of imipenem/cilastatin courses to sensitize patients with penicillin allergy is not well known, it seems advisable to retest imipenem/cilastatin before any subsequent course.

Marina Atanasković-Marković, MD^a

Francesco Gaeta, MD^b

Marija Gavrović-Jankulović, PhD^c

Tanja Čirković Veličković, PhD^c

Rocco Luigi Valluzzi, MD^b

Antonino Romano, MD^{b,d}

From ^athe Department of Allergology and Pulmonology, University Children's Hospital, Belgrade, Serbia; ^bthe Department of Internal Medicine and Geriatrics, UCSC-Allergy Unit, Complesso Integrato Columbus, Rome, Italy; ^cthe Department of Biochemistry, Faculty of Chemistry, University of Belgrade, Belgrade, Serbia; and ^dIRCCS Oasi Maria S.S., Troina, Italy. E-mail: antoninoromano@h-columbus.it.

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