

Clinical Communications

Cross-reactivity between carbapenems: two case reports

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Clinical Implications

- Lack of cross-reactivity in hypersensitivity reactions between imipenem and meropenem suggests that the involvement of the side chains may play an important role.
- If carbapenem therapy is unavoidable, then it may be possible to cautiously administer this drug to patients with hypersensitivity to one of them.

TO THE EDITOR:

Carbapenems (imipenem, meropenem, and ertapenem) (Figure 1) are broad-spectrum β -lactam antibiotics. They are typically used as second-line treatment for severe polymicrobial and resistant bacterial infections in hospitals. The antimicrobial spectrum of imipenem and meropenem is similar, with coverage of most of the gram-positive cocci, gram-negative bacilli, and anaerobic microorganisms.¹ Imipenem is inactivated in the kidneys and produces a nephrotoxic metabolite, so it is formulated (in 1:1 proportion) with cilastatin, an enzymatic inhibitor of human dehydropeptidase-I, that blocks its metabolism in the kidneys, which increases levels of drug in the urine and reduces its toxicity. Meropenem and ertapenem are compounds with a methyl group at C1 and are resistant to the kidney enzymes that inactivate imipenem.¹⁻³ The frequency of reported hypersensitivity reactions to carbapenems is estimated to be approximately 2% to 3% per therapeutic exposure.³ It is unknown if there is significant T-cell-mediated immunologic cross-reactivity between individual carbapenems. We present 2 cases of delayed onset, apparently T-cell-mediated, serious cutaneous adverse reactions associated with imipenem and meropenem use.

CASE 1

A 65-year-old man with a delayed-onset micropapular exanthema (Figure 2) associated with imipenem exposure was seen by our service in 2006. The delayed reading of the results of his intradermal (ID) imipenem skin test were positive. The diagnosis of a T-cell-mediated hypersensitivity to imipenem was made, and, at that time, it was recommended that he avoid all β -lactam antibiotics in the future. In February 2012, the patient was hospitalized for acute pancreatitis and required intensive care unit care. Because of a lack of response to other antibiotics and his worsening clinical condition, it was decided to cautiously administer meropenem. The patient completed the meropenem treatment with good tolerance. This was considered a negative challenge test. The patient was then re-evaluated for T-cell-mediated hypersensitivity to β -lactams. He again had a positive results of delayed reading

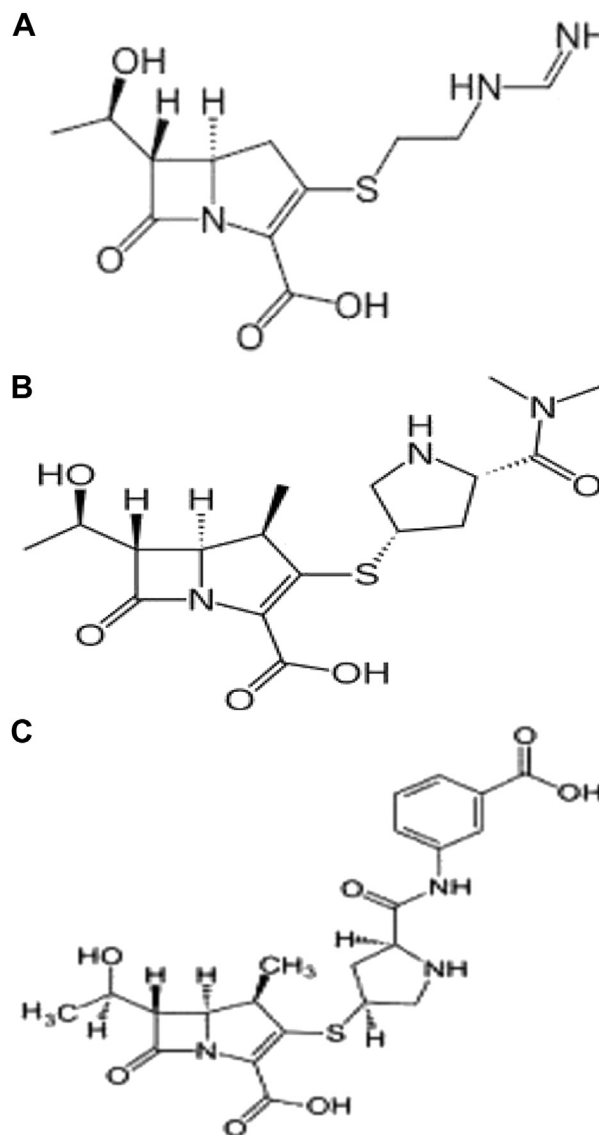


FIGURE 1. A, Chemical structure of imipenem. B, Chemical structure of meropenem. C, Chemical structure of ertapenem.

ID skin tests to imipenem-cilastatin when using a concentration of 2 mg/mL.⁴ The results of his delayed reading ID skin tests were negative to bencilpenicilil, minor determinant mixture, penicillin G, amoxicillin, cefuroxime, ceftriaxone, meropenem (2 mg/mL), and cilastatin (in a 5% saline solution prepared by the pharmacology laboratory of our hospital). Afterward, patch testing with imipenem-cilastatin (50 mg/mL) and cilastatin (5% saline solution) were performed, with negative results for both. Results of challenge tests with amoxicillin, cefuroxime, ceftriaxone, and penicillin V were negative.

CASE 2

A 61-year-old woman was hospitalized in September 2012 because of nausea, uncontrollable vomiting, polymyalgias, and



FIGURE 2. Exanthema in case 1.

high fever without any identifiable site of a bacterial infection. She was empirically treated with amikacin and meropenem, and quickly improved. During her hospital admission, 3 to 4 days after initiating the antibiotic therapy, she developed a generalized scaly erythematous rash, which affected the oral, vaginal, and rectal mucosa. The rashes resolved acutely with antihistamine and corticosteroid treatment. Unfortunately, she then had desquamation of approximately 60% to 70% of her body surface area. Her skin recovered in approximately 25 days.

Delayed reading ID skin testing was performed 60 days after the resolution of the desquamation with meropenem (2 mg/mL),⁴ imipenem-cilastatin, amikacin, penicillin G, minor determinant mixture, phenoxymethylpenicillin, amoxicillin, cefuroxime, and ceftriaxone. She had a positive delayed reading to meropenem, with a 15 × 11-mm infiltration and surrounding erythema. Results of all other delayed reading ID skin tests were negative. Subsequently, challenge test results were negative to imipenem-cilastatin, amikacin, amoxicillin, cefuroxime, and ceftriaxone.

Imipenem and meropenem share similar chemical structures with penicillins. Carbapenems have a β -lactam ring attached to a modified thiazolidine ring and 2 different side chains. The side chain of imipenem is joined to the β -lactam ring in the *trans* direction; meropenem has a similar chemical structure, with a methyl group in C1 and with a dimethylcarbamoylpyrrolidinyl group in C2, which substitutes the imipenem lateral chain (Figure 1).¹ According to previous studies, T-cell-mediated immunologic cross-reactivity between carbapenems could be expected, but *in vivo* or *in vitro* studies have not demonstrated its cross-reactivity until now. In a previous review of 5000 patients in 1999 by Norrby and Gildon,⁵ that investigated the safety of meropenem, found that the frequency of skin reactions was approximately 1.4%, similar to that found with imipenem.

Reported cases of possible immunologic, T-cell-mediated or IgE-mediated, monosensitization to a single carbapenem are rare. In 1995, Giner Almaraz et al² published a case of a patient without a history of previously known drug intolerance, who, 48 hours after intravenous imipenem-cilastatin, presented with both a generalized micropapular rash and erythematous hives on the buttocks and lower limbs. With suspecting intolerance to imipenem-cilastatin, levofloxacin and aztreonam were then administered. Because the patient rapidly progressed to a

critical situation, levofloxacin and aztreonam were discontinued, and then meropenem was given for 14 days, without any further adverse reactions. No immunologic workup was carried out because the patient died of postsurgical complications.²

There is 1 published case⁶ of imipenem-cilastatin anaphylaxis in which an immunologic workup showed positive immediate-type skin test results and specific serum IgE to imipenem and imipenem-cilastatin, with negative results to meropenem and cilastatin. They concluded that the patient had selective immediate-type hypersensitivity to imipenem without cross-reactivity with meropenem.³⁻⁶ Cases of selective sensitization to cilastatin have not been published.

We currently present 1 case of a patient with delayed onset eczematous rash associated with imipenem, who then demonstrated good tolerance to meropenem and other β -lactams, and another case of a patients with an erythematous scaly eruption associated with selective type IV hypersensitivity to meropenem and with tolerance to imipenem-cilastatin and other β -lactams. To our knowledge, these selective type IV hypersensitivities to carbapenems are the first well-documented cases. A lack of cross-reactivity between imipenem and meropenem indicates that the side chains of each carbapenem in these delayed-type hypersensitivity reactions may play an important role.

Therefore, based on previous published cases and our current observations, we can propose that, in special situations such as serious infections or antibiotic resistance to other drugs, cautious administration of an alternative carbapenem could be considered for patients with previous nonimmediate allergy to another antibiotic of this same group. However, the lack of cross-reactivity between these carbapenems should be confirmed in future studies.

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