

Lack of cross-reactivity to meropenem in a patient with an allergy to imipenem-cilastatin

To the Editor:

For more than a decade the carbapenem class of antibiotics have played an important role in our therapeutic armamentarium. Current carbapenems available in the United States include imipenem-cilastatin (IC), meropenem, and ertapenem. They are among the broadest spectrum antibacterials available and are often used for serious polymicrobial infections or infection from highly resistant organisms.¹ They are among the few agents effective against extended-spectrum β -lactamase-producing gram-negative organisms.² Thus, their importance in treating serious infections, especially in critically ill patients, is apparent. Carbapenem antibiotics have a β -lactam ring attached to a modified thiazolidine ring with 2 side chains. Therefore, these agents share the same general structure as the classic penicillin antibiotics and would be expected to have similar adverse effects and propensity for causing Type I hypersensitivity reactions. In addition, patients who are allergic to penicillin

might be at risk for similar reactions when given a carbapenem antibiotic. However, little published data exist involving allergic reactions and the carbapenems. Indeed, one of the earliest articles reporting that about 50% of patients with penicillin sensitivity also reacted to imipenem was based on skin testing in only 20 patients.³ A more recent retrospective review of patients undergoing bone marrow transplant found about a 10% cross-reactivity of imipenem in patients with a self-reported or confirmed penicillin allergy.⁴ Although assumed to be high, the clinical cross-reactivity between the individual carbapenems has not been described. We report a case of a patient who developed an allergic reaction to imipenem and subsequently tolerated a course of meropenem.

A 41-year-old woman was admitted to a large community teaching hospital's intensive care unit (ICU) after having undergone elective gastric bypass surgery (Roux-en-Y) for morbid obesity. During the immediate postoperative period the patient had become febrile, with a leukocytosis (white blood cell count, 24,000/mm³), mental status deterioration, and hypotension (blood pressure, 90/50 mm Hg). The diagnosis of septic shock as a result of leaking anastomosis was made, and the patient was placed on IC for a presumed intra-abdominal source of infection. The patient's medical history was significant for morbid obesity, depression, gastroesophageal reflux disease, urinary incontinence, and osteoarthritis. She had no known drug allergies, which was confirmed by discussing her drug history with family. In addition to antibiotics, she was placed on the following medications: sucralfate 1 g 4 times daily, dopamine and dobutamine intravenous drips, enoxaparin 40 mg subcutaneously twice daily, lorazepam and morphine intravenous drips, total parenteral nutrition, and hydrocortisone 50 mg intravenously every 6 hours (for presumed relative adrenal insufficiency caused by sepsis). Within 48 hours of starting IC, a large erythematous maculopapular rash with areas of urticaria appeared on the patient's pannus, buttocks, and legs. Because the patient was sedated and intubated, she could not complain of pain or itching. Her hemodynamic parameters remained low, but ventilatory requirements remained relatively stable during the course of the eruption. Suspecting IC as the culprit medication, the patient's antibiotics were changed from IC to aztreonam, metronidazole, and levofloxacin. Within several days of the IC withdrawal the skin eruption faded, and within 10 days the rash and urticaria had dissipated considerably. Unfortunately, the patient's ICU course remained complicated. By week 3 of her ICU stay she had developed adult respiratory distress syndrome, as well as persistent hyperglycemia (requiring intravenous insulin drips) and acute renal failure (requiring hemodialysis). The patient continued to exhibit signs and symptoms consistent with sepsis, including fever (temperatures to 39°C) and leukocytosis (white blood cell count ranging from 22,000/mm³ to 40,000/mm³ with high neutrophil counts and bandemia). At day 22 of her ICU stay the patient was given dotrecogin alfa for 96 hours. No noticeable improvement in her hemodynamic

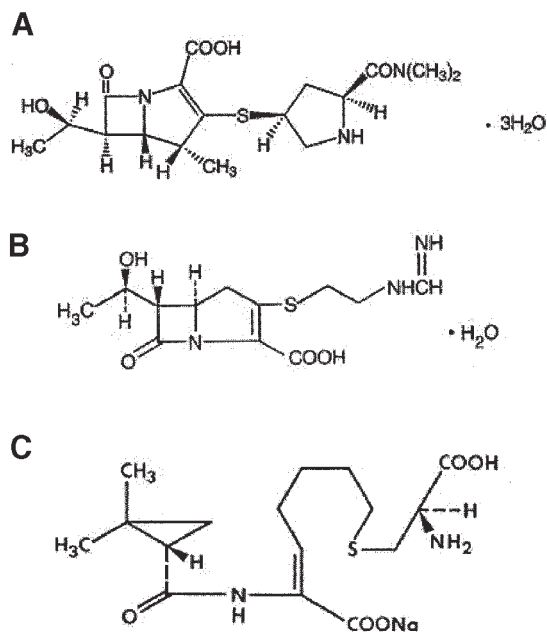


FIG 1. Chemical structures of meropenem (A), imipenem (B), and cilastatin (C).

parameters or ventilator requirements was observed. During the next 7 weeks the patient's course remained largely unchanged. Caspofungin was added to her antibiotic regimen when *Candida glabrata* was cultured from an abdominal abscess. At this point in the patient's course (week 10 in the ICU), computed tomography scans had shown several abdominal abscesses that were then drained percutaneously. One of the routine cultures from these abscesses showed gram-negative rods and gram-positive cocci, later identified as *Enterococcus casseliflavus* that was resistant to nearly all commercially available antibiotics. One of the few antibacterials that had demonstrated in vitro activity against this organism, yet also had activity against gram-negative organisms, was imipenem. After discussion with the family and a joint conference between the infectious disease physicians and clinical pharmacists, it was believed that the benefit of using meropenem (even knowing its decreased activity against *Enterococcus*) outweighed the possible risks to the patient. At this time the patient's other medications remained largely as noted above, with the exception of the addition of erythropoietin for anemia associated with critical illness. The patient received a dose challenge of 125 mg meropenem intravenously during a period of 15 minutes and then was observed by the nursing staff for another 15 minutes for any sign of reaction. This procedure, including doubling the dose of meropenem, was performed every 30 minutes until the target dose of 1 g was achieved. The patient went on to receive a full 14-day course of meropenem with no sign of skin eruptions or significant change in hemodynamic status during the entire course of therapy. About 7 days after the completion of the meropenem course the patient's status had

not improved significantly; her family opted to withdraw care, and she died.

Our case presents a patient with demonstrated allergy to IC who tolerated treatment with meropenem. In our opinion, this represents either a lack of cross-reactivity between imipenem and meropenem or an allergy to cilastatin. The antimicrobial spectra of imipenem and meropenem are quite similar, with each antibiotic covering a wide variety of organisms. This coverage extends to most aerobic gram-positive cocci, gram-negative bacilli, and anaerobic organisms. In vitro studies have shown that imipenem and meropenem share a high degree of cross-susceptibility as measured by dilution test methods. On the basis of this assumption, we concluded that meropenem was a feasible alternative to imipenem in our case.

Imipenem is not commercially available without cilastatin; consequently we are unable to rule out a pure allergy to cilastatin in our case. Cilastatin itself has no antibacterial activity, but it is added to inhibit the dehydropeptidase-1 enzyme in the renal tubule that metabolizes imipenem. Without cilastatin, imipenem is rapidly metabolized and causes toxicity to the proximal tubule.⁵ The literature, however, does not report any cases of true allergy to cilastatin.

Carbapenems such as imipenem and meropenem are structurally related to classic penicillin antibiotics (Fig 1). These similarities might be the basis for an immune-mediated response to imipenem in many patients with penicillin allergy.⁶ Although cross-reactivity between imipenem and penicillin has been demonstrated, it has not been described between imipenem and meropenem. On the basis of their mutual classification as carbapenems, it is logical to conclude that a patient who exhibits an allergy to imipenem will have the same reaction to meropenem. In animal models, anti-meropenem antibodies raised in rabbits and guinea pigs had weak cross-reactivity with imipenem.⁷ Also, one article reports a case of IgE-mediated anaphylaxis in a patient being treated with IC. The results of skin prick testing conducted 2 weeks after this reaction were positive for IC and for imipenem alone, but they were negative for cilastatin alone and for meropenem.⁸ On the basis of this report, one might conclude that the patient had a pure allergy to imipenem, which did not cross over to meropenem. A recent review also comments on the lack of detailed information concerning cross-reactivity among the carbapenems.⁹ Fortunately, patients with a documented allergy to IC are rare. This case demonstrates the safe use of meropenem in a patient who falls into this category. Of course, we are not recommending indiscriminate use of meropenem in patients with a history of imipenem allergy. But if clinical circumstances demand a carbapenem antibiotic in a patient allergic to IC, our case demonstrates that a dose-challenging regimen of meropenem might be considered. To our knowledge, this is the first case to demonstrate the lack of cross-reactivity to meropenem in a patient with a known allergy to IC.

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