CASE REPORT

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# Cross-Reactivity to Meropenem and Ertapenem Without Imipenem

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## ABSTRACT

Carbapenems have a beta-lactam ring that might prone to cause hypersensitivity reactions. We proposed that the clinical cross-reactivity between the individual carbapenems will develop independently from the beta-lactam ring in this case report.

A 75-years-old male patient was admitted to the surgical intensive care unit after whipple procedure for malignant neoplasm of the pancreas. Meropenem and colistin was started because of increased oxygen demand. Most likely drug-induced generalized maculopapular skin rash developed on the first day of the antimicrobial therapy. Followed by discontinuation of meropenem, imipenem-cilastatin therapy was administered without any problem. Because of the increase in the existing infiltrate on the chest x-ray, ertapenem was added as a double-carbapenem strategy. However, it has been discontinued after one dose due to appearing same adverse effects with meropenem.

Besides, the lack of allergy history despite prior ceftazidime usage implies that the hypersensitivity reaction of the patient was unlikely related to the beta-lactam ring.

**Keywords:** Carbapenem Antibiotics, Cross-reactivity, Hypersensitivity, Beta Lactams

## Introduction

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). Carbapenems have a beta-lactam ring with a modified thiazolidine ring. Therefore, these agents might prone to cause hypersensitivity reactions. The most of these allergic reactions are type IV delayed hypersensitivity reactions which present as a maculopapular rash (2). Only a few published data on carbapenem-induced allergic reactions exists in the literature. In a study by Saxon et al., 50% of patients with penicillin sensitivity also reacted to imipenem in skin testing; however, this was performed in only 20 patients (3). The frequency of reported hypersensitivity reactions to carbapenems is estimated to be approximately 2% to 3% per therapeutic exposure (4). Although there are many studies showing cross-reactivity between penicillins and carbapenems, the clinical cross-reactivity between the individual carbapenems has been described only in few studies (4,5). We report a patient who developed an allergic reaction to meropenem and ertapenem and subsequently tolerated a course of imipenem.

## Case

A 75-year-old male patient was admitted to the surgical intensive care unit after whipple procedure for malignant neoplasm of the pancreas. The patient had no known comorbidities at the time of admission. The patient had an allergy history to levetiracetam.

In the post-operative period, fluconazole (intravenous [i.v.] 200 mg daily after loading dose) treatment was initiated by the infectious disease physician because of growth of *Candida parapsilosis* in the urine culture. A few days later, the patient showed increased oxygen demand and a new infiltrate on chest x-ray. Meropenem (i.v. 500 mg twice daily) was started and colistin (i.v. 56.25 mg twice daily after loading dose) was added to the treatment two days later because of growth of pan-resistant *Pseudomonas aeruginosa* in deep tracheal aspirate culture. Subsequent antibiotic doses were adjusted according to the glomerular filtration rate (GFR) (11.4 ml/min). In addition, those two antibiotics, he received insulin, dopamine, enoxaparin, ranitidine and amlodipine as co-medications.

A generalized maculopapular skin rash developed on the first day of the antimicrobial therapy and the primary physician started cetirizine and pheniramine. Review of the patient chart revealed that the patient had received ceftazidime uneventfully during his previous hospitalization. The consulting dermatologist interpreted the rash to be most likely drug-induced and recommended the addition of a topical corticosteroid. Since the most recent medication that the patient was placed on was meropenem and colistin, meropenem was discontinued, and the patient was switched to intravenous imipenem-cilastatin. The imipenem dose was adjusted to 250 mg twice daily according to the body weight and GFR. Within several days of discontinuation of meropenem, the rash improved and disappeared subsequently.

On the 2nd day of imipenem therapy, intravenous colistin had to be changed to inhalational (50 mg twice daily) route because of worsening renal function.

On the 7th day of therapy, the patient developed leukocytosis and a repeat chest x-ray demonstrated an increase in the existing infiltrate. Inhaled colistin was stopped and ertapenem (i.v. 1000 mg daily) was added with the purpose of double-carbapenem strategy. Ertapenem-induced drug eruption developed on the 8th day of therapy and ertapenem treatment was discontinued. Tigecycline (i.v. 50 mg twice daily after loading dose) was added to the treatment when tigecycline-sensitive *Klebsiella pneumoniae* was isolated in deep tracheal aspirate culture on the 14th day of therapy. Antimicrobial medications were stopped after 18 days of imipenem and 10 days of tigecycline administration.

Seven days later, the patient was re-consulted to the infectious disease team because of fever and growth of *Klebsiella pneumoniae* and *Enterococcus faecalis* in the blood culture. Imipenem-cilastatin (i.v. 250 mg twice daily), tigecycline (i.v. 50 mg twice daily after loading dose) and teicoplanin (i.v. 12mg/kg every 72 hours after loading dose) were started. On the 3rd day of treatment, the patient developed hypotension. He did not respond to norepinephrine and dopamine infusions and died.

## Discussion and Conclusion

Carbapenems are structurally similar to penicillin antibiotics with their beta-lactam ring. This similarity may result an immune-mediated response to carbapenems in patients with penicillin allergy. Cross-reactivity between carbapenems and penicillin have been frequently described, but cross-reactivity between the individual carbapenems has described only in few studies.

Although the side chains of ertapenem and meropenem have a pyrrolidine ring, this ring is absent in imipenem's structure (Figure 1). The cross-reactivity between meropenem and ertapenem but not imipenem can be explained with this structural difference. In addition, the lack of a history of prior ceftazidime allergy implies that it is unlikely that the hypersensitivity reaction of the patient was related to the beta-lactam ring.

We found two similar case reports in the literature who had imipenem intolerance where meropenem was a safe alternative (4, 5) or vice versa (4).

In conclusion, the clinicians should monitor their patients while administering a carbapenem antibiotic even if they have no history of penicillin allergy. Switching meropenem with imipenem (or vice versa) may be considered if carbapenem therapy is necessary. Further studies are needed to clarify the presence and lack of cross-reactivity between certain carbapenems.

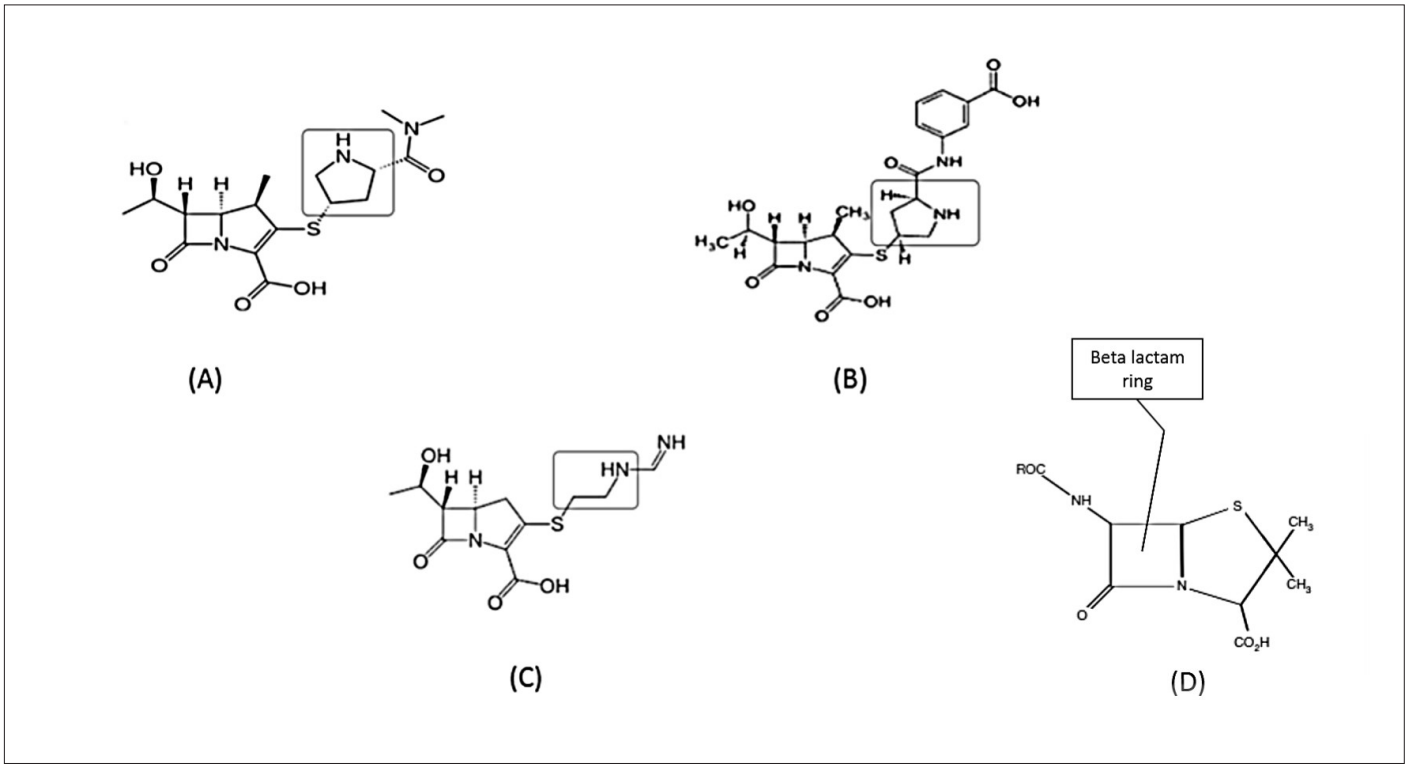


**Figure 1.** Chemical structure of meropenem (A), ertapenem (B), imipenem (C), penicillin (D). The difference between the side chains of carbapenems is shown with the box.

AUTHOR CONTRIBUTIONS:

**Concept:** PB, ÖU; **Design:** PB, EK, AY; **Supervision:** ÖU, KD; **Data Collection and/or Processing:** PB, EK, AY; **Analysis and/or Interpretation**: PB, EK, AY, KD, ÖU; **Literature Search:** PB, EK; **Writing Manuscript**: PB, EK; **Critical Review:** ÖU, KD.

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**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** Authors have no conflicts of interest to declare.

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