

Anaphylactic shock to meropenem with ertapenem tolerance: A case report



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Clinical Implications

- We report an anaphylactic shock to meropenem (with positive skin prick test) with ertapenem tolerance highlighting the need of an extensive allergy investigation to offer the most appropriate antibiotic coverage in multiresistant bacterial infections.

TO THE EDITOR:

We present the case of a 48-year-old man with Marfan syndrome. He had no previous drug allergies and was currently on angiotensin-converting enzyme inhibitors for hypertension. Because of a type A aortic dissection, he suffered an ischemic medullary infarction that caused a complete D3 level sensitive-motor tetraplegia in 2012. Furthermore, he presented multiple urinary tract infections with isolation of *Escherichia coli* with extended-spectrum β -lactamase resistance but sensitive to carbapenems, quinolones, and amikacin, all of which he had received on different occasions. Also in September 2017, he received and tolerated 2 full courses of amoxicillin-clavulanic acid and piperacillin-tazobactam for biliary tract infections.

In October 2017, the patient was admitted in the emergency department for a septicemia. Under the suspicion of a biliary or urinary origin and considering previous *E. coli* isolations, intravenous meropenem was prescribed. Immediately after starting meropenem infusion (3 mL/30 mg accumulated), the patient developed itching of palms and soles, generalized erythema, hypotension, loss of consciousness, and cardiorespiratory arrest. Meropenem infusion was stopped; cardiopulmonary resuscitation was initiated together with standard treatment for anaphylactic shock (intramuscular adrenaline, intensive saline serum infusion, and intravenous noradrenaline), achieving patient stabilization. Total serum tryptase was determined, with a peak at the first hour of 62.00 $\mu\text{g/L}$, second hour 10.20 $\mu\text{g/L}$, and 4.75 $\mu\text{g/L}$ at 12 hours ($N < 12.4 \mu\text{g/L}$).

The infection was treated with ciprofloxacin, and all β -lactam antibiotics were avoided until he was assessed for the suspected drug allergy.

The patient was initially evaluated by an allergy consultant the day after the anaphylactic shock. After written informed consent, antibiotic skin testing was performed 6 days after the anaphylaxis and 5 days after histamine therapy was stopped. Skin prick test (SPT) and intradermal testing (IDR) with 1 mg/mL meropenem were negative. To overcome a potential refractory period, he was rescheduled 4 weeks later. Cutaneous tests (SPT and IDR) to β -lactams were performed with the following agents and

concentrations: penicilloyl-poly-L-lysine (Diater, Madrid, Spain) (SPT and IDR at 5×10^{-5} mM), minor determinant mixture (Diater) (SPT and IDR at 2×10^{-2} mM), amoxicillin (SPT and IDR at 20 mg/mL), amoxicillin-clavulanic acid (SPT and IDR at 20-2 mg/mL), benzylpenicillin (SPT and IDR at 10,000 UI/mL), and cefuroxime (SPT and IDR at 2 mg/mL). Immediate and delayed readings were negative. SPT with meropenem was positive at 1 mg/mL. Wheal diameter was 6 mm and flare was 20 mm, whereas both SPT and IDR tests with imipenem-cilastatin (SPT and IDR at 4/0.5 mg/mL) and ertapenem (SPT and IDR at 10 mg/mL) were negative. Despite that the recommended concentrations for skin testing with carbapenems are 0.5 to 1 mg/mL,¹ our group has not found an irritant effect of concentration up to 10 mg/mL with meropenem and ertapenem and 4/0.5 mg/mL for imipenem/cilastatin.

A biliar liquid culture was positive for *E. coli* with the production of AmpC plasmidic type cefamandime sensitive to imipenem, ertapenem, and amikacin and resistant to the rest of antibiotics tested including ciprofloxacin. In line with these results and because of the preferential requirement of a carbapenem for an adequate antibiotic coverage in a complex patient with multiple urinary and biliary tract infections, a controlled challenge test with ertapenem was performed. Under intensive surveillance, ertapenem was administered by an infusion pump starting at 5 mL/h of a dilution of 10 mg/mL during 10 minutes (0.83 mg accumulated), 10 mL/h during 5 minutes (1.66 mg accumulated), 30 mL/h during 5 minutes (4.16 mg accumulated), 60 mL/h during 5 minutes (9.16 mg accumulated), and finally 200 mL/h during 26 minutes until a full dose of 1 g was reached with good tolerance. He subsequently completed a 21-day treatment course. Amoxicillin-clavulanic tolerance was also confirmed in a different challenge, and has also been prescribed to the patient on several occasions after the anaphylactic shock with meropenem.

This case illustrates a selective IgE-mediated hypersensitivity to meropenem (anaphylactic shock, with tryptase elevation, and strong positive meropenem SPT). The allergy workup yielded negative for other carbapenems (ertapenem and imipenem) and the rest of β -lactams, and subsequent tolerance to ertapenem and amoxicillin-clavulanic acid was proven, highlighting the importance of a thorough evaluation, especially in selected patients with a high need of antibiotics.

Imipenem, meropenem, and ertapenem are commercially available in Spain. They are β -lactam antibiotics usually reserved for known or suspected multidrug-resistant bacterial infections. They have a β -lactam ring attached to a modified thiazolidine ring and 2 different side chains. The chemical structure of meropenem's side chain has a methyl group in C1 and a dimethylcarbamoylpyrrolidinyl group in C2,² both different from those of ertapenem, because of a prolyl-3-aminobenzoic acid (Figure 1).³

There are several cases reported in the literature demonstrating the low cross-reactivity between carbapenems and other β -lactams,⁴⁻⁸ mainly penicillins and cephalosporins. Also a few reports have shown lack of cross-reactivity between imipenem and meropenem in delayed reactions.^{4,9} Chen et al⁹ reported an anaphylactic reaction to imipenem with a positive skin test to

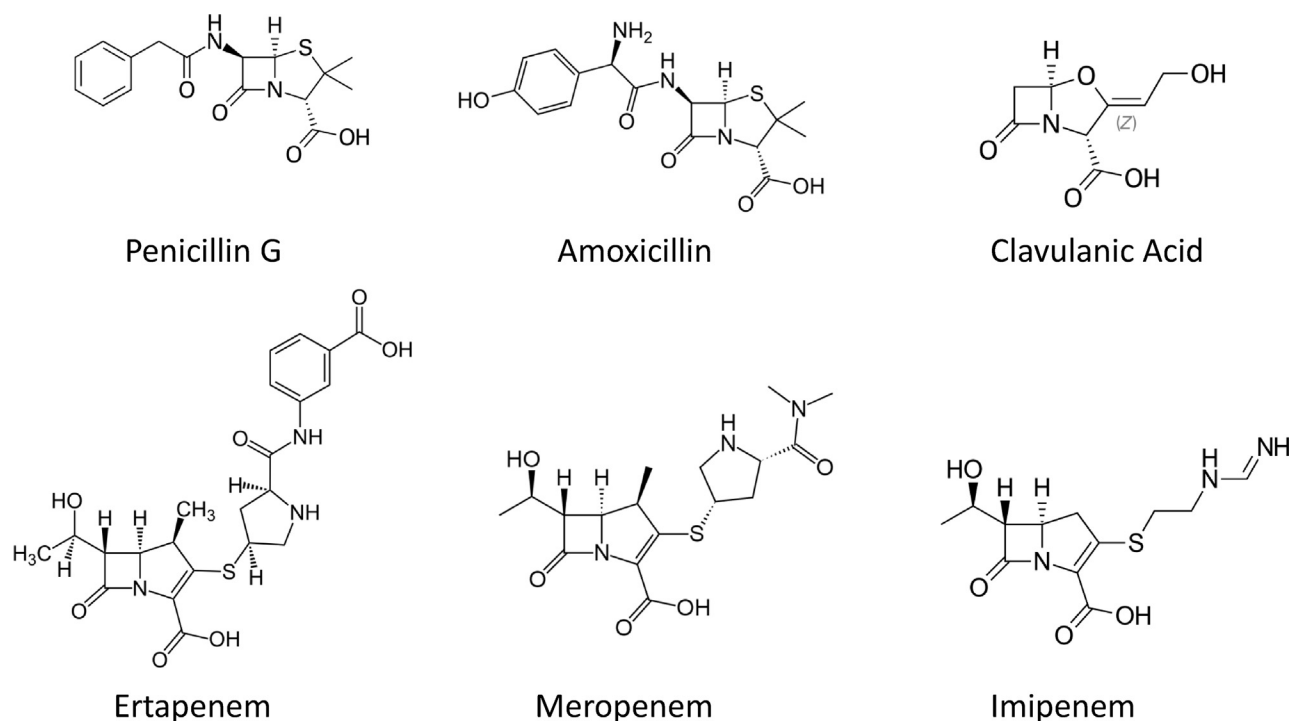


FIGURE 1. Chemical structure of penicillins and carbapenems.

this antibiotic but negative to the other carbapenems, but the authors did not perform challenge tests to prove tolerance.

In conclusion, this is the first case of confirmed meropenem-associated anaphylaxis in which acute tolerance to ertapenem was demonstrated. This patient also tolerated amoxicillin-clavulanic acid, providing additional support for the lack of clinically significant immunologically mediated cross-reactivity between carbapenems and penicillins.

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REFERENCES

1. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs—an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013;68:702-12.
2. Noguerado-Mellado B, Pinto Fernandez C, Pineda-Pineda R, Martinez Lezcano P, Alvarez-Perea A, De Barrio Fernandez M. Cross-reactivity between carbapenems: two case reports. *J Allergy Clin Immunol Pract* 2014;2:816-7.
3. Singh SB, Rindgen D, Bradley P, Suzuki T, Wang N, Wu H, et al. Design, synthesis, structure-function relationship, bioconversion, and pharmacokinetic evaluation of ertapenem prodrugs. *J Med Chem* 2014;57:8421-44.
4. Lakhal K, Lortat-Jacob B, Neukirch C, Pajot O, Wolff M. Safe use of meropenem in a patient with a possible non immediate allergy to imipenem. *Pharmacotherapy* 2007;27:1334-8.
5. Gaeta F, Valluzzi RL, Alonzi C, Maggioletti M, Caruso C, Romano A. Tolerability of aztreonam and carbapenems in patients with IgE-mediated hypersensitivity to β -lactams. *J Allergy Clin Immunol* 2015;135:972-6.
6. Bauer SL, Wall GC, Skoglund KJ, Peters LK. Lack of cross-reactivity to meropenem in a patient with an allergy to imipenem-cilastatin. *J Allergy Clin Immunol* 2004;113:173-5.
7. Buonomo A, Pascolini L, Rizzi A, Aruanno A, Pecora V, Ricci AG, et al. Cross-reactivity and tolerability of ertapenem in patients with IgE-mediated hypersensitivity to β -lactams. *J Investig Allergol Clin Immunol* 2016;26:100-5.
8. Prescott WA Jr, DePestel DD, Ellis JJ, Regal RE. Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy. *Clin Infect Dis* 2004;38:1102-7.
9. Chen Z, Baur X, Kuttcha-Lissberg F, Merget R. IgE-mediated anaphylactic reaction to imipenem. *Allergy* 2000;55:92-3.

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