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An unusual case of delayed-type hypersensitivity to ceftriaxone and meropenem

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Summary
Recent studies have demonstrated a low cross-reactivity between β-lactam antibiotics and carbapenems in IgE-mediated reactions. There are no studies on cross-reactivity of meropenem in patients with non-immediate hypersensitivity to cephalosporins.
We describe a case of a 13-year-old male, admitted in Neurosurgery with a severe extradural empyema complicating frontal sinusitis, submitted to an emergent bifrontal craniotomy. A generalized maculopapular exanthema, fever and malaise, appeared by the 7th day of meningeal doses of ceftriaxone, clindamycin and vancomycin. Those were replaced by meropenem, with posterior worsening of the reaction and mucosal involvement. A new scheme with amikacin, metronidazole and linezolid was done with improvement. Skin prick, intradermal and patch tests to penicillins, ceftriaxone and meropenem were negative. Lymphocyte transformation test was positive to ceftriaxone and negative to meropenem.
Non-immediate T cell mechanism seems to be involved. Diagnosis work-up couldn't exclude cross-reactivity between ceftriaxone and meropenem.

Introduction

Depending on their chemical structure, β-lactam (BL) antibiotics are classified into 2 major classes, penicillins and cephalosporins, and 4 minor classes, monobactams, carbapenems, oxacephems and clavams (1). Cephalosporins and penicillins are the most widely used antibiotics for the treatment of common infections. Each one has a 4-membered β-lactam ring, but the 5-membered dihydrothiazine ring of penicillins is replaced by the 6-membered dihydrothiazine ring in the cephalosporins nucleus. Monobactams contain a monocyclic ring structure, whereas carbapenems have a bicyclic nucleus comprised of β-lactam ring with an association 5-membered ring (2).
Meropenem is a broad-spectrum carbapenem with potent antimicrobial activity against a broad range of Gram-negative, Gram-positive and anaerobic bacteria. The second parental carbapenem to be introduced worldwhile, meropenem has been in clinical use since 1994 and showed a favorable safety profile (3).
β-lactam (BL) antibiotics are referred as the most frequent elicitors of drug hypersensitivity reactions. The skin is the organ most frequently involved in hypersensitivity reactions to BLs, sometimes accompanied by systemic symptoms (1).
The frequency of carbapenem associated hypersensitivity in the general population is estimated to be in maximum 3% (0.3 to 3%) (4,5,6,7,8), mostly reported as rash, pruritus or urticaria (4).
The structural similarity between penicillin and carbapenem antibiotics is the bicyclic core, composed of a 5-membered ring attached to the β-lactam ring, which is generally believed to be responsible for the cross-reactivity between these classes of antibiotics. However, there is no consensus on the rate of hypersensitivity in individuals also allergic to penicillins. Several studies have evaluated the cross-sensitivity between carbapenems and penicillins on IgE-mediated reactions. The results range widely, from 0.9 to 47.4% (4-13), mainly due to different studies methodologies. Recent pro-

spective studies, that confirmed penicillin allergy by standardized procedures and tested for carbapenem allergy by administering a full therapeutic dose to carbapenem skin test-negative patients, showed rates of cross-reactivity around 1% (11,12,13).
Studies concerning the tolerability of carbapenems in subjects with hypersensitivity to cephalosporins are lacking, with exception of a prospective study that pointed to cross-reactivity between cephalosporins and carbapenems inferior to 5%, in IgE mediated-reactions (2).
Cross-reactivity between carbapenems and other β-lactams has been poorly investigated in patients with delayed-type cell-mediated allergy to β-lactams, with a recent prospective study showing a rate of 5.5% of cross-reactivity between imipenem-cilastatin and other β-lactams (14).
As far as we know, there are no studies on cross-reactivity and tolerability of meropenem in patients with delayed-type, cell-mediated hypersensitivity to cephalosporins.

Case Report

The authors report a case of a 13-year-old non-atopic adolescent male, admitted in Neurosurgery Department with a severe extradural empyema complicating frontal sinusitis, despite amoxicillin and acid clavulanic oral treatment. He was submitted to an emergent bifrontal craniotomy in order to drain empyema and to a simultaneous ethmoidectomy by ENT. Meningeal doses of intravenous antibiotic with ceftriaxone, clindamycin and vancomycin were prescribed. By the 7th day, he presented a pruriginous generalized maculopapular exanthema, fever and malaise, with no analytical changes like leucocitosis, neutrophilia or eosinophilia and with PCR reducing values. Antibiotherapy was replaced by meropenem without further treatment, namely corticosteroids. An initial improvement of the symptoms occurred, followed by posterior reappearance of the malaise and fever, worsening of the cutaneous lesions (without blistering) and appearance of oral mucosal lesions, at the third day of treatment. No analytical changes were found, also at this stage. Meropenem withdrawn and β-lactams eviction was advised. None of the cutaneous reactions were compatible with a Steven Johnson Syndrome. The absence of analytical changes excluded a DRESS Syndrome (Drug rash and eosinophilic systemic syndrome).
A new antibiotherapy scheme with amikacin, metronidazole and linezolid was done during the following week, with good clinical response and resolution of mucocutaneous lesions.
The allergy diagnosis work-up was performed 8 weeks after hospital discharge, in the Drug Allergy Unit, according to ENDA guidelines (15,16) and after a patient's legal responsible signed informed consent. Skin prick tests (SPT) and intradermal tests (ITD) to penicillins and ceftriaxone, including delayed reading at 48 hours, were negative. Meropenem at 1 mg/ml was tested beginning with SPT and followed by ITD. SPT (1 mg/ml) and ITD (1/1000 - 1/10 dilutions) to meropenem were negative (immediate and delayed reading), but ITD at 1 mg/ml was positive in immediate reading (15 mm medium diameter wheal, with surrounding erythema). Patch tests were negative to all antibiotics.
In *vitro* tests were performed, namely lymphocyte transformation test (LTT), with positive results to ceftriaxone (3.1 mcg/ml) and negative to meropenem. Specific IgE to meropenem (CAP-FEIA) performed at *Phadia,* Uppsala, Sweden, was negative (< 0.10 KU/L).
Due to the severity of the reaction, drug provocation tests with beta-lactam antibiotics weren't performed.
SPT (pure drug) and ITD (1/1000 - 1/1 dilutions) to meropenem were repeated one year after. As in the first time, all the tests were negative, with exception of IDT with pure drug, which remained positive in immediate reading (8.5 mm papule diameter).

Discussion

The clinical presentation of the reaction and the time of occurrence are suggestive of non-immediate T cell mechanism, supported by LTT positive result to ceftriaxone. The negative LTT to meropenem doesn't allow the exclusion of this mechanism to this antibiotic, since the LTT has a sensitivity of just 74% to BLs (16,17).
The absence of published standardized concentrations to meropenem skin tests was also a difficulty in this case. In a case report, SPT and ITD were done with maximum concentration of meropenem 25 mg/ml (8). In more recent prospective studies with larger series of patients (104, 108 and 98 respectively) meropenem was used at a concentration of 1 mg/ml of normal saline, but with no reference to the used dilutions (11,12,13). Based on those larger series, we decided to perform SPT and ITD tests with meropenem at 1 mg/ml (dilutions from 1/1000 to 1/1). The positivity in ITD with pure meropenem could be irritative, since the mechanism didn't seem to be IgE-mediated. To clarify this result, SPT and ITD tests to meropenem were performed in 10 controls with the described concentrations with negative results, except in one patient previous exposed to meropenem. This result could be a sign of exposure rather than a sensitization. The result of the specific IgE to meropenem and the reduction on the wheal size on the test performed one year after, also suggest that. This last result could also be in consonance with the decrease of sensitivity of the skin tests to penicillins over time (1,16,18,19).
The negative results of skin tests (SPT and ITD at delayed reading, and patch tests) to penicillins and ceftriaxone don't exclude a cell-mediated mechanism to these antibiotics. For non-immediate allergic reactions to BLs, skin tests appear to be less sensitive than for immediate allergic reactions (16). Delayed reading of intradermal and/or patch tests have been used for many years in the evaluation of non-immediate reactions to BLs, particularly to penicillins. ENDA recommendations advise a combined approach (16), since sensitivity to these procedures

ranging from 2.6% (patch tests) (20) to 37.8% (patch tests and/or delayed reading IDTs) (21).

The severity of the reaction in our patient contra-indicated a provocation diagnostic test, which remains the gold standard in the drug allergy diagnosis (although the known limitations in non-immediate reactions). In this case, cross-reactivity between ceftriaxone and meropenem couldn't be clearly established, in spite of the allergy diagnosis work-up performed according to recommendations. Moreover, the described limitations during allergy diagnosis procedures and the particularities of this unusual case became an interesting challenge.

Published data show a very low incidence of carbapenem-associated hypersensitivity in general population, which is estimated to be less than 3% (4,5,6,7,8) and low cross-reactivity between carbapenems and other BLs (2,11,12,13,14).

Although first studies showed an important cross-reactivity between carbapenems and penicillins in IgE-mediated reactions (5,6,9,10), recent prospective studies, that confirmed penicillin allergy by standardized procedures and tested for carbapenem allergy by administering a full therapeutic dose to carbapenem skin test-negative patients, showed low rates of cross-reactivity (around 1%), with all carbapenem skin test-negative patients tolerating the challenge (11,12,13).

Studies concerning the tolerability of carbapenems in subjects with hypersensitivity to cephalosporins are lacking, with exception of a prospective study, which demonstrated the tolerability of meropenem in 97 of a total of 98 patients with well-demonstrated, IgE-mediated hypersensitivity to cephalosporins (2).

Cross-reactivity between carbapenems and other β-lactams has been poorly investigated in patients with delayed-type cell-mediated allergy to β-lactams, with a recent prospective study showing a rate of 5.5% of cross-reactivity between imipenem-cilastatin and other β-lactams (14).

As far as we know, there are no studies on cross-reactivity and tolerability of meropenem in patients with delayed-type, cell-mediated hypersensitivity to cephalosporins.

This case reports an unusual case of hypersensitivity to ceftriaxone and meropenem that seems to be cell-mediated, although the diagnosis work-up performed didn't establish clearly cross-reactivity between them. However, the severity of the reaction combined with a suggestive history, still advice the eviction of these ATB in this patient.

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