Red Man Syndrome Adverse Reaction following Intravenous Infusion of Cefepime

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We report the first case of cefepime-induced “red-man syndrome,” which appeared 30 min following drug infusion and was confirmed with a rechallenge test. This syndrome is classically associated with vancomycin infusion and is the result of non-IgE mediated mast cell degranulation. While this adverse effect can be easily managed with drug withdrawal and antihistamine administration, it is unknown whether it can be prevented with slower cefepime infusion and preinfusion antihistamines, as is the case with vancomycin.

Cefepime is a broad-spectrum cephalosporin with activity against Gram-negative nosocomial pathogens (e.g., *Pseudomonas aeruginosa*) (5) and often against *Streptococcus* and *Staphylococcus* species (8). It is generally reserved for the treatment of nosocomial infections, especially pneumonias, and is also approved for treatment of complicated and uncomplicated urinary tract infections, skin and soft tissue infections, intra-abdominal infections, and febrile neutropenia (10).

Cefepime is administered via the intravenous or intramuscular route, with suggested dosages of 0.5, 1, and 2 g. Each intravenous dose is diluted in 50 or 100 ml of compatible fluid and is then infused over 30 min. Moderately severe infections, such as pneumonia due to *Pseudomonas* (3), are among the recommended indications for cefepime, for which it is administered at dosages of 1 to 2 g, every 12 h, for 10 days (10).

The most frequently reported adverse effects of cefepime are local reactions (3%), phlebitis (1.3%), and pain or inflammation (0.6%). Nausea, colitis, diarrhea, vomiting, headache, and fever have been reported for less than 1% of the patients; less often, encephalopathy, myoclonus, and seizures have also been observed (1). Furthermore, cefepime is known to cause dermatological adverse effects, such as rash (1.1% when lower doses are administered versus 4% for the 2-g dosage), pruritus (1 to 10%), urticaria, and anaphylaxis in less than 1% (1).

We report the first case of red man (or red neck) syndrome, presenting as an adverse reaction related to intravenous cefepime administration.

Case report. A 25-year-old man suffering from meningococcal meningitis was admitted to the Patras University Hospital intensive care unit (ICU) due to the acute appearance of seizures and cardiac arrest. During his 1-month hospitalization in the ICU he acquired nosocomial infections, such as venous catheter and respiratory infections, which were treated with various antibiotics. During his recovery period in the internal medicine department, he developed intense pruritus and an erythematous-fine maculopapular rash covering the neck and upper torso 30 min after intravenous cefepime infusion (Fig. 1), without any local infusion site erythema; this reaction appeared on the twelfth day of cefepime administration (2 g over 30 min, three times daily) as part of the treatment regimen. Other symptoms, such as dyspnea, tachycardia, and hypotension, were not present. The patient's reaction was completely relieved by intravenous antihistamine ad-

ministration (dimetindene; 0.1 mg/kg). Given the temporal association of this reaction with cefepime infusion (Table 1), the antibiotic was suspected as the underlying cause. In order to assess this hypothesis, administration of all other antibiotics was suspended while we rechallenged him with intravenous cefepime (alone) 8 h later; the same symptoms reappeared and then quickly resolved after the administration of intravenous dimetindene. Thus, we concluded that the observed reaction was an adverse effect induced by cefepime. The patient did not report any history of drug allergy or atopic disease.

The adverse effect of cefepime observed in this patient corresponds to red man syndrome, a combination of pruritic erythematous rash (affecting the face, neck, and upper torso) and possible anaphylaxoid symptoms, classically associated with vancomycin infusion (9). A few cases have also been reported following administration of infliximab (2), teicoplanin, and amphotericin B but not cefepime (9). The reaction observed in our patient occurred 5 days after the last dose of vancomycin (*per os*) was administered for suspected *Clostridium difficile* colitis, making any contribution of this antibiotic to the adverse event described exceptionally implausible.

Vancomycin-related red man syndrome is usually associated with a high infusion rate and appears soon after the initiation of infusion; however, it has been observed with lower infusion rates and following several days of treatment as well (9). Correspondingly, our patient presented this adverse reaction shortly after high-dose cefepime infusion but was asymptomatic during the first 12 days of treatment.

The underlying mechanism of red man syndrome has been found to be IgE-independent degranulation of mast cells brought about by vancomycin, with mast cell-derived histamine being a significant mediator of the observed adverse effect (11). As a re-

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FIG 1 Cefepime-induced red man syndrome in a 25-year-old male.

sult, the established effectiveness of antihistamines in the prevention and treatment of red man syndrome (7), as observed in our patient, is not surprising.

Unlike our description of cefepime-related red man syndrome, two cases of IgE-mediated anaphylaxis with prominent angioedema, airway compromise, and/or circulatory symptoms following cefepime were previously reported (4, 6).

Conclusion. Cefepime can cause an anaphylaxoid reaction, similar to the non-IgE-mediated, vancomycin-related red man syndrome. The relative incidence of red man syndrome among the rashes commonly associated with cefepime is not known. Although this adverse effect can be managed with drug withdrawal and antihistamines, prevention with the latter (along with a lower infusion rate of cefepime) has not been assessed; this may be im-

portant in critically ill patients for whom cefepime is considered a critical antimicrobial.

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TABLE 1 Drug administration times, prior to reaction-inducing infusions of cefepime

Drug	Dose (route) ^a	Time (hospitalization day)
Cefepime	2 g (i.v.)	0600 (51), 1800 (51), 0600 (52), ^b 1400 (52) ^c
Atenolol	25 mg (p.o.)	0600 (51), 0600 (52)
Citalopram	20 mg (p.o.)	0600 (51), 0600 (52)
Lorazepam	2.5 mg (p.o.)	0600 (51), 1800 (51), 0600 (52)
Miconazole	120 mg (oral gel)	0600 (51), 1200 (51), 1800 (51), 0000 (52), 0600 (52)
Omeprazole	40 mg (i.v.)	0600 (51), 0600 (52)
Pregabalin	75 mg (p.o.)	0600 (51), 1800 (51), 0600 (52)
Risperidone	1 mg (p.o.)	0600 (51), 0600 (52)
Tinzaparin	4,500 IU (s.c.)	0600 (51), 0600 (52)
Venlafaxine	75 mg (p.o.)	0600 (51), 0600 (52)

^a i.v., intravenous; p.o., *per os*; s.c., subcutaneous.

^b Initial reaction-associated infusion.

^c Drug rechallenge infusion.