

Letters

ANAPHYLAXIS INDUCED BY FOSFOMYCIN

Fosfomycin or L-cis-1,2-epoxypropylphosphoric acid has a unique mechanism of antimicrobial action that involves the inhibition of UDP-N-acetylglucosamine enolpyruvyl transferase, an enzyme that catalyzes the first step in bacterial cell wall synthesis within the cell.¹ Fosfomycin is a unique antibiotic that is chemically unrelated to any other known antimicrobial agent.² Fosfomycin has a broad spectrum of antimicrobial activity, including gram-negative and gram-positive aerobic bacteria.¹

A 29-year-old woman with no history of atopy or allergy drug was treated with fosfomycin (Ern SA, Barcelona, Spain), 500 mg 3 times a day, for a urinary tract infection. One hour after the ingestion of the second tablet, she developed a generalized erythema with pruritus, hives, eyelid angioedema, and diarrhea. Use of medication was discontinued, and the skin lesions resolved completely in 3 hours with systemic corticosteroids and antihistamines. She had previously tolerated this antibiotic.

Six months later, she was referred to our allergy department for study. We performed a skin prick test (100 mg/mL in saline solution) and an intradermal test (1 and 10 mg/mL in saline solution) with fosfomycin sodium, both with negative results. Histamine (10-mg/mL solution) and buffered saline were used as positive and negative controls, respectively. The basal tryptase level was 3.66 µg/L, and the total specific IgE level was 63 kU/L.

Because of the widespread use of fosfomycin, the negative skin test results, and the few cases of sensitization to fosfomycin previously reported, we decided to perform a single-blind oral challenge. After the patient's written informed consent was obtained, we performed a single-blind oral challenge with fosfomycin sodium with a positive result: 45 minutes after receiving 125 mg of fosfomycin, the patient presented with generalized pruritus with hives in her neck and trunk and angioedema on the hands.

The clinical features of the adverse reaction experienced by the patient and the positive result of the oral challenge make us suspect an IgE-mediated mechanism despite the negative skin test results. Therefore, as previously described,³ a determination of drug-specific basophil activation by flow cytometry was performed by using CD63 expression as the activation marker and anti-IgE antibody as the basophil marker. This was performed by stimulating the basophil with fosfomycin at concentrations of 10, 5, 2.5, 1.25, 0.62, and 0.15 mg/mL. Results were considered positive when the stimulation index, calculated as the ratio between the percentage of degranulated basophils with the haptens and the negative control, was greater than 2. The basophil activation test was performed 1 month after the oral challenge with positive results at all the concentrations assayed and with negative results (stimulation index lower than 2) in the 2 controls with a prior negative challenge result to fosfomycin. Fosfomycin has

been in clinical use for more than 40 years¹ and has been found to be generally well tolerated.⁴

Previous studies have demonstrated that fosfomycin inhibits IgE-mediated histamine release from peripheral blood basophils⁵ and pulmonary histamine release from lungs isolated from guinea pigs.⁶ In fact, fosfomycin is used in the clinical practice combined with steroids to reduce the dose of these drugs in patients with severe bronchial asthma, although the mechanism is unknown.⁷

There is only 1 case reported of sensitization to fosfomycin.⁴ Rosales and Vega⁴ described a patient with anaphylactic shock after the ingestion of fosfomycin. They performed prick and intradermal tests, at concentrations of 10 mg/mL, with positive results. Results of the histamine release test were not conclusive. In our case, skin test results were negative, but basophil activation test and single-blind oral challenge results were positive.

In summary, we describe a patient with an immediate anaphylaxis due to fosfomycin. We suggest an IgE-mediated mechanism, as demonstrated by a positive oral challenge result with fosfomycin, despite the negative results of skin tests. To our knowledge, this is the first case of immediate hypersensitivity reaction due to fosfomycin with a positive basophil activation test result.

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1. Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum betalactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis*. 2010;10:43–50.
2. Morikawa K, Oseko F, Morikawa S. Immunomodulatory effect of fosfomycin on human B-lymphocyte function. *Antimicrob Agents Chemother*. 1993;37:270–275.
3. Torres MJ, Padial A, Mayorga C, et al. The diagnostic interpretation of basophil activation test in immediate allergic reactions to betalactams. *Clin Exp Allergy*. 2004;34:1768–1775.
4. Rosales MJ, Vega F. Anaphylactic shock due to fosfomycin. *Allergy*. 1998;53:905–907.
5. Lda S, Shindoh Y, Takishima T. Effect of antibiotics on immediate hypersensitivity reactions in vitro: suppression of IgE-mediated histamine release from peripheral blood basophils by fosfomycin. *Microbiol Immunol*. 1987;31:975–984.
6. Pertelli A, Giovannini L, Berteilli A. In vitro effects of fosfomycin on intracellular cyclic nucleotides and histamine releases. *Drugs Exp Clin Res*. 1979;5:363–365.
7. Mue T, Otsu H, Taniguchi Y, et al. Antibiotic therapy of bronchial asthma: a clinical effect of fosfomycin administration. *Prog Med*. 1993;3:1582–1588.

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