Is high-dose intravenous fosfomycin safe for the treatment of patients prone to heart failure?

¿Es segura la administración de dosis altas de fosfomicina en pacientes con riesgo de insuficiencia cardiaca?

Dear Editor,

Fosfomycin is a well-known and useful oral antibiotic for the treatment of acute uncomplicated cystitis.[1] *In vitro* studies have demonstrated that fosfomycin is active against multidrug resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis*.[2,3] A few case reports describing the synergistic combination of high-dose daptomycin–fosfomycin treatment for *S aureus* endocarditis have been published[4,5] and a clinical trial[6] is underway. Nevertheless, data concerning the efficacy and side effects of such combination is still scarce.

An 81-year-old woman previously diagnosed of chronic hepatitis C virus infection, atrial fibrillation (for which she received oral anticoagulation therapy) and epilepsy (treated with levetiracetam), was admitted to our hospital with the diagnosis of an aortic prosthetic-valve endocarditis due to coagulase-negative *Staphylococcus*. An abscess located on the junction of the aortic annulus and the interatrial septum and a severe aortic regurgitation, due to a perivalvular leak, were also described. At admission, no signs of congestive heart failure were noticed. The serum creatinine was 1.05 mg per deciliter, serum sodium 135 mEq per liter, albumin 3.9 g per deciliter and hemoglobin 9.8 g per deciliter. Intravenous treatment with daptomycin at a dose of 10 mg per kilogram of body weight per day and fosfomycin at a dose of 2 g administered four times daily (total daily dose of 8 g) was prescribed due to failure of initial treatment. Seven days after starting this antibiotic treatment, the patient began complaining of paroxysmal nocturnal dyspnea and a grade 4 peripheral edema was noticed. Although spironolactone (100 mg daily) and a continuous intravenous infusion of furosemide (0.07 mg per kilogram per hour) were prescribed, the patient's symptoms continued to aggravate and three days later, she was unable to recline without severe breathlessness. The combined daptomycin–fosfomycin treatment was continued for one more week, until fosfomycin was finally suspended. Congestive heart failure was completely resolved in six days after fosfomycin was stopped. No other episodes of heart failure were diagnosed during the time the patient was hospitalized.

The progressive worsening of our patient's symptoms in the course of treatment with fosfomycin, followed by the rapid clinical improvement after its discontinuation, establishes a temporal relationship between both events. In the multiple echocardiograms performed, there was no evidence of worsening of our patient's aortic-valve disease or of the left ventricular function. Fosfomycin has high sodium content (each gram of fosfomycin contains 14.35 mEq [330 mg] of sodium).[7] Piperacillin/tazobactam, an antibiotic commonly known for its high sodium content, has only 2.36 mEq per gram of piperacillin administered.[8] We considered that the high daily dose of sodium administered with fosfomycin (almost 115 mEq [2640 mg] daily) was responsible for our patient's episode of congestive heart failure. The National Pharmacovigilance System was notified of this adverse event.

When high doses of fosfomycin are administered for prolonged periods, patients requiring sodium restriction (heart disease, hypertension or previous episodes of pulmonary edema, for example) should be advised to reduce the intake of sodium chloride and physicians should regularly monitor blood concentration of sodium, potassium and chloride.

This side effect of fosfomycin has been previously described.[9] It is possible that in the near future the combined use of daptomycin plus fosfomycin will become widespread for the treatment of methicillin-resistant *Staphylococcus aureus* endocarditis or other type of severe infections produced by this bacterium. In this context, it is important to take into account that high-dose intravenous fosfomycin can trigger heart failure in patients prone to this complication, as those with endocarditis.

Conflict of interest

All authors declare that there are no conflicts of interest.

Acknowledgements

I would like to thank the collaboration and unconditional support to carry out this manuscript to Dr. Jose Miguel Ferrari Piquero.

Bibliografía

1. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52:e103–20.
2. Burke SL, Rose WE. New pharmacological treatments for methicillin-resistant *Staphylococcus aureus* infections. Expert Opin Pharmacother. 2014;15:483–91.
3. Molina-Manso D, del Prado G, Ortiz-Pérez A, Manrubia-Cobo M, Gómez-Barrena E, Cordero-Ampuero J, et al. In vitro susceptibility of *Staphylococcus aureus* and *Staphylococcus epidermidis* isolated from prosthetic joint infections. J Antibiot (Tokyo). 2012;65:505–8.
4. Chen LY, Huang CH, Kuo SC, Hsiao CY, Lin ML, Wang FD, et al. High-dose daptomycin and fosfomycin treatment of a patient with endocarditis caused by daptomycin-nonsusceptible *Staphylococcus aureus*: case report. BMC Infect Dis. 2011;11:152.
5. Miró JM, Entenza JM, Del Río A, Velasco M, Castañeda X, Garcia de la Mària C, et al. High-dose daptomycin plus fosfomycin is safe and effective in treating methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* endocarditis. Antimicrob Agents Chemother. 2012;56:4511–5.
6. ClinicalTrials.gov identifier: NCT01898338. Available at: http://clinicaltrials.gov/ct2/show/NCT01898338?term=BACSARM&rank=1 [accessed 24.02.14].
7. Spanish agency for medicines and health products. Available at: http://www.ern.es/wp-content/uploads/2013/01/FT-Fosfocina-IV-IM.pdf [accessed 24.02.14].
8. U.S. Food and Drug Administration, FDA approved drug products. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/065386lbl.pdf [accessed 24.02.14].
9. Larrodé Leciñena I, Munguiá Navarro P, Palomo Palomo P, Abad Sazatornil MR. Clinical significance of the sodium content of intravenous antibiotic therapy. Farm Hosp. 2014;38:147–8.

Irene Cañamares-Orbis [a,*], José Tiago Silva [b], Francisco López-Medrano [b], Jose Maria Aguado [b]

[a] *Pharmacy Department, University Hospital 12 Octubre, Avda. Cordoba s/n., 28041 Madrid, Spain*
[b] *Infectious Diseases Unit, University Hospital 12 Octubre, Madrid, Spain*

* Corresponding author.
E-mail address: Irene.canamares@gmail.com (I. Cañamares-Orbis).

http://dx.doi.org/10.1016/j.eimc.2014.07.005