



Enfermedades Infecciosas y Microbiología Clínica

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Editorial

Current approach to fosfomycin: From bench to bedside[☆]

Uso actual de la fosfomicina: del laboratorio a la práctica clínica

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The need to use effective antimicrobials to treat multidrug-resistant (MDR) infections has driven the pharmaceutical industry to design new molecules, as well as to rediscover molecules which were already known about, such as colistin and fosfomycin. Indeed, use of fosfomycin, which is only approved in some European and Latin American countries, has seen unprecedented growth in the last four years. Fosfomycin, which is only approved by the US Food and Drug Administration as fosfomycin trometamol for the treatment of uncomplicated cystitis, is currently pending approval in intravenous form as disodium salt. In 2013, a randomised, multi-centre, open-label, controlled phase 3 clinical trial to evaluate the efficacy of fosfomycin *versus* meropenem in the targeted treatment of bacteraemic urinary tract infection due to extended-spectrum beta-lactamase-producing *Escherichia coli* (*E. coli*) (FOREST study) began in Spain.¹ In 2017, another multi-centre, randomised, double-blind, phase 2/3 non-inferiority study to evaluate the safety and efficacy of intravenous fosfomycin *versus* piperacillin-tazobactam in the treatment of adult hospitalised patients with complicated urinary tract infections (ZEUS study) began in the United States.²

Fosfomycin was discovered in Spain by an integrated research team from the now defunct *Compañía Española de Penicilina y Antibióticos* [Spanish Company of Penicillin and Antibiotics] (CEPA) from an isolate of *Streptomyces fradiae* collected in 1966 in Jávea (Alicante). As a phosphoenolpyruvate (PEP) analogue, it irreversibly inhibits the cytosolic enzyme MurA (N-acetylglucosamine enolpyruvyl-transferase), which plays a key role in the formation of N-acetylmuramic acid found in the peptidoglycan layer of the cell wall. It also reduces the formation of penicillin-binding proteins (PBP).³ Fosfomycin is water soluble, has a low molecular mass (138) and binds negligibly to proteins, which is why it has excellent tissue diffusion properties.^{4,5} It also penetrates and diffuses in biofilms in experimental models at concentrations equal to or higher than ciprofloxacin or co-trimoxazole.⁶ The pharmacokinetic-pharmacodynamic efficacy

parameter to take into account to achieve the therapeutic target with fosfomycin is the ratio between the area under the curve at 24 h and the MIC. It also shows postantibiotic effect at lower concentrations.⁷ Some of the resistance mechanisms reported include reduced intracellular transport of the antibiotic (mutations in transporter genes and AMPc *glpT* or *uhpT* regulators), change of target caused by *murA* expression mutations or abnormalities and, finally, the direct inactivation of the antibiotic by metalloenzymes (FosA, FosB and FosX) or by kinases (FormA and FormB).³

The lack of consistency between the CLSI (≥ 64 mg/l) and EUCAST (≥ 32 mg/l) breakpoints, the fact that some microorganisms have a naturally higher MIC (*Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *Pseudomonas aeruginosa*) due to the expression of chromosomal genes homologous to FosA and FosB that interact with fosfomycin, and the varying effective concentrations of the drug for Gram-positive and Gram-negative bacteria explains why the dosage recommendations for the treatment of MDR infections range from 8 to 12 g/day when Gram-positive microorganisms are involved, and from 16 to 24 g/day when treating Gram-negative bacteria.^{8,9} It has recently been established that *E. coli* colonies that grow in the inhibition halos of diffusion tests, and whose presence is not related to clinical failure, are mutants with loss of GlpT and UhpT transporter expression.¹⁰ Given that the selection frequency of mutants with higher fosfomycin MIC values than those obtained with a wild strain depends on the concentration of fosfomycin present in the medium (5.5×10^5 CFU/ml with concentrations 5 times the MIC and $>1.2 \times 10^9$ CFU/ml with concentrations 256 times the MIC), the use of high doses of the drug, particularly if prescribed in monotherapy, would avoid this selection window.¹¹ Furthermore, most of these mutants, particularly those selected with a lower fosfomycin concentration, would not be stable in successive passages, impacting on the high MIC values.¹² Finally, a recent meta-analysis¹³ found just 3.4% onset of resistance (95% CI, 1.8%–5.1%) during treatment with fosfomycin in monotherapy, which would presumably be lower or non-existent with combination therapy.

Fosfomycin has at least an additive effect, or even a synergistic effect in combination with almost all the antimicrobials tested thanks to its high diffusion and unique mechanism of action. In this edition of the journal, Coronado-Alvarez et al.¹⁴ present an interesting study that highlights the synergistic activity *in vitro* of

DOI of original article: <https://doi.org/10.1016/j.eimc.2018.10.002>

[☆] Please cite this article as: Candel FJ, Cantón R. Uso actual de la fosfomicina: del laboratorio a la práctica clínica. Enferm Infecc Microbiol Clin. 2019;37:1–3.

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fosfomycin at suprainhibitory concentrations (above the MIC) in combination with other antimicrobials (daptomycin, vancomycin, imipenem or linezolid) against strains of methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA). Previous studies had demonstrated an additive effect of fosfomycin at subinhibitory concentrations (below the MIC). Coronado-Alvarez et al.¹⁴ also show the clinical correlation of their observations *in vitro* in patients administered fosfomycin in combination to treat bacteraemia caused by MRSA and MSSA, as well as by *Enterococcus faecium*. The most active combinations *in vitro* were those containing daptomycin or imipenem, while those with vancomycin or linezolid were less effective. The clinical results also revealed greater efficacy with daptomycin (93% therapeutic success) when compared with vancomycin (47% therapeutic success). In all cases, sterilisation of blood cultures was observed 48 h after initiating combination therapy with fosfomycin. Although a variety of regimens were used, no significant differences were observed when the combination therapy was administered at baseline *versus* 72 h after the onset of bacteraemia.

The results published by Coronado-Alvarez et al.¹⁴ corroborate those already published by other authors with combinations of fosfomycin with daptomycin¹⁵ or with imipenem.¹⁶ The current guidelines on the treatment of persistent infection, or infection complicated by MRSA, issued by the *Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica* [Spanish Society of Infectious Diseases and Clinical Microbiology], recommend the combination of fosfomycin and daptomycin.¹⁷ This recommendation is expected to be further reinforced when the results of an ongoing trial comparing the combined activity of fosfomycin and daptomycin *versus* daptomycin in monotherapy for the treatment of MRSA infection are published.¹⁸

Furthermore, the combination of fosfomycin with other antimicrobials has also demonstrated synergy *in vitro* against multidrug-resistant Gram-negative microorganisms,¹⁹ and there is published clinical evidence of its use at high doses and in combination with other agents in the treatment of carbapenemase-producing enterobacteriaceae^{20–22} and extensively-drug resistant *Pseudomonas* spp.²³

Fosfomycin is considered to be a relatively safe and well-tolerated antimicrobial. Nevertheless, cases of intolerance caused by sodium overload have been reported in exceptional cases. One gram of fosfomycin sodium contains 0.33 g (14.4 meq) of sodium,²⁴ which means that treatment with 12–24 g of fosfomycin provides the extracellular compartment with 4–8 g of sodium. Cases of heart failure have been reported in patients being treated with fosfomycin, including patients with a normal ejection fraction, requiring the drug to be withdrawn.^{14,16,25} Monitoring sodium overload in patients treated with high doses of fosfomycin (16–24 g/day) could be complicated in comorbid patients with water retention (cirrhosis, heart or kidney failure) as the neurohormonal expression of soluble factors (norepinephrine, vasopressin, atrial natriuretic peptides, etc.) could trigger an episode of volume overload in the extracellular compartment.²⁶ In standard practice, the stability of fosfomycin at room temperature has led to its use in continuous infusion, particularly to treat MDR infections, striving for relatively low doses (12–16 g/day) that guarantee plasma trough concentrations above 32 mg/l, thereby reducing the total salt overload that would require the administration of fractionated doses. This could be particularly beneficial for patients suffering from the water retention conditions referred to above.

In conclusion, although this molecule is not new, its positioning has yet to be fully defined. The more we find out about fosfomycin, the more potential benefits it seems to reveal. Given its safety and activity, the most attractive therapeutic model is probably that proposed by Coronado-Alvarez et al.,¹⁴ featuring the synergistic

combination with other antimicrobials to treat complicated MDR infections.

Conflicts of interest

FJC and RC have participated in training activities sponsored by Laboratorios ERN.

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