Official journal of the Spanish Society of Chemotherapy

Current key topics in fosfomycin

Alicia Rodríguez-Gascón[1,2]
Andrés Canut-Blasco[3,4]

Deciphering pharmacokinetics and pharmacodynamics of fosfomycin

[1]Pharmacokinetics, Nanotechnology and Gene Therapy Group (PharmaNanoGene), Faculty of Pharmacy, University of the Basque Country UPV/EHU, Vitoria-Gasteiz, España.
[2]Centro de Investigación Lascaray ikergunea, University of the Basque Country UPV/EHU, Vitoria-Gasteiz, España.
[3]Microbiology Service, Hospital Universitario de Álava, Servicio Vasco de Salud Osakidetza, Vitoria-Gasteiz, España.
[4]Instituto de Investigación Biosanitaria (BIOARABA), Servicio Vasco de Salud Osakidetza, Vitoria-Gasteiz, España.

ABSTRACT

Fosfomycin, a low molecular weight and hydrophilic drug with negligible protein binding, is eliminated almost exclusively by glomerular filtration, whose clearance is subject to patient renal function. The volume of distribution approximates to the extracellular body water (about 0.3 L/Kg) in healthy volunteers, but it is increased in critically ill patients with bacterial infections. Fosfomycin presents a high ability to distribute into many tissues, including inflamed tissues and abscess fluids. Based on PK/PD analysis and Monte Carlo simulations, we have evaluated different fosfomycin dosing regimen to optimize the treatment of septic patients due to *Enterobacterales* and *Pseudomonas aeruginosa*. As PK/PD targets, we selected $\%T_{>MIC}$ > 70% for all pathogens, and AUC_{24}/MIC > 24 and AUC_{24}/MIC > 15 for net stasis of *Enterobacterales* and *P. aeruginosa*, respectively. Pharmacokinetic parameters in critically ill patients were obtained from the literature. Several dosing regimens were studied in patients with normal renal function: fosfomycin 2-8 g given every 6-12 hours, infused over 30 minutes- 24 hours. At the susceptibility EUCAST breakpoint for *Enterobacterales* and *Staphylococcus* spp. (MIC ≤ 32 mg/L), fosfomycin 4 g/8h or higher infused over 30 minutes achieved a probability of target attainment (PTA) > 90%, based in both $\%T_{>MIC}$ and AUC_{24}/MIC. For MIC of 64 mg/L, fosfomycin 6 g/6h in 30-minute infusion and 8 g/ 8h in 30-minute and 6 hours infusions also achieved PTA values higher than 90%. No fosfomycin monotherapy regimen was able to achieve PK/PD targets related to antimicrobial efficacy for *P. aeruginosa* with MICs of 256-512 mg/L.

Key words: fosfomycin, pharmacokinetic/pharmacodynamic, Monte Carlo simulation, critically ill patients

Correspondence:
Andrés Canut-Blasco.
Microbiology Service, Edificio Consultas Externas, Hospital Universitario de Álava. c/Francisco Leandro de Viana, s/n. 01009. Vitoria-Gasteiz, Spain.
Phone: +34 945 007564; Fax: +34 945 007555
E-mail: andres.canutblasco@osakidetza.eus

PHARMACOKINETICS

Fosfomycin, currently produced by a synthetic method, is a low-molecular weight (138 g/mol), highly polar phosphonic acid derivative (cis-1,2-epoxypropyl phosphonic acid) that represents its own class of antibiotics [1,2]. Fosfomycin was initially marketed as both a calcium salt formulation (fosfomycin calcium) for oral administration and a more hydrophilic salt (fosfomycin disodium) for parenteral administration. Fosfomycin tromethamine, which provides a higher bioavailability (30-40%) [3], was later marketed and has become the standard formulation for oral administration [4].

The pharmacokinetics of fosfomycin, as in general of any antibiotic, is conditioned by pathophysiological changes that occur in the critically ill patient. These changes can impact the concentrations at the site of infection, which may potentially reduce the bactericidal activity [5]. Actually, after intravenous injection, variable peak, mean and trough concentrations have been reported in humans [6]. Table 1 shows the main pharmacokinetic parameters of fosfomycin in critically ill patients [7].

Distribution and tissue penetration. Fosfomycin, a hydrophilic drug with low molecular weight and negligible protein binding (ca. 0%) [8], is highly distributed throughout body tissues, including inflamed tissues and abscess fluids [2]. The volume of distribution (V_d) is consistent with extracellular body water (approximately 0.3 L/Kg) in healthy volunteers [7]. The V_d in critically ill patients with bacterial infections is increased (by as much as 50% in comparison to healthy subjects) probably due to alterations of the vascular endothelium, turning in an increase of capillary permeability [9].

In Intensive Care Unit (ICU) patients with soft tissue infections, fosfomycin has shown to exhibit good penetration into muscle [7], and also into subcutaneous tissues regardless of the presence of inflammation [10]; however, the penetration into abscesses seems to depend on morphological characteristics, such as the permeability of the outer wall or the vascular-

Table 1 **Pharmacokinetic parameter of fosfomycin in septic patients [7].**

Study population	No. of patients	Fosfomycin dose	Pharmacokinetic parameter				
			Vd (L)	t1/2 (h)	Cl (L/h)	C_{max} (mg/L)	AUC_{0-4} (mg h/L)
Sepsis	12	8 g i.v.	31.5±4.5	3.9±0.9	7.2±1.3	357±28	721±66

ity of the surrounding tissues [11]. Fosfomycin administered by intravenous route seems also to exhibit good penetration into infected lung tissue, reaching adequate levels in pleural fluid [12,13]. Severe lung inflammation during bacterial pneumonia seems not impair fosfomycin penetration, which supports its use in severe pulmonary infections [13]. Different studies confirm that fosfomycin presents also a favorable penetration into tissue sites traditionally considered to be associated with low penetration, which supports its potential for use in many difficult-to-treat infection sites [5, 14]. Thus, fosfomycin has the ability to cross the blood-brain barrier, and in case of meningeal inflammation, the concentration in cerebrospinal fluid increases [15]. Fosfomycin is also able to penetrate in both cortical and cancellous bone [16], and in aqueous humor [17].

Clearance. Glomerular filtration is almost the only elimination route of fosfomycin, with total clearance being highly correlated with the glomerular filtration rate, measured as creatinine clearance [8]. Actually, variations in renal function among patients justifies pharmacokinetic variability of fosfomycin in critically ill patients [18]. In spite that fosfomycin is almost entirely eliminated unchanged by the kidney, limited information exists on the clearance of fosfomycin in renally-impaired patients. By intravenous route, dose adjustment is recommended in patients with CrCl < 50 mL/min [19]. A recent study including 2 patients undergoing intermittent hemodialysis and extended dialysis showed that, in spite of the efficient tissue penetration of fosfomycin, the extracorporeal elimination can lead to a dramatic decrease of the fosfomycin serum levels [20]. Another study with 12 anuric ICU patients treated with continuous venovenous haemofiltration (CVVH) and receiving 8 g of fosfomycin every 12 h showed a longer mean half-life than found in ICU patients without renal therapy; additionally, the plasma area under the concentration-time curve (AUC) was higher in patients undergoing CVVH than in critically ill patients without CVVH. After a 12 h haemofiltration process, about 77% of fosfomycin was removed. Fosfomycin concentrations in blood resulted to be enough to eradicate relevant pathogens [21]. In any case, additional pharmacokinetic studies regarding dosing in critically ill patients undergoing different dialysis modalities are needed.

PHARMACODYNAMICS

Fosfomycin exerts bactericidal antimicrobial activity against susceptible pathogens by blocking the early stage of bacterial cell wall synthesis [22]. It has a broad spectrum of *in vitro* activity against a variety Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), and drug-resistant *Enterobacterales* and *Pseudomonas aeruginosa* varieties, including extended-spectrum-β-lactamase (ESBL)-producing and carbapenem-resistant (CR) organisms [19, 23]. Given that there are few available therapeutic options, fosfomycin seems an attractive alternative for the treatment of serious systemic infections caused by multidrug-resistant (MDR) bacteria.

Mutation frequency studies indicated the presence of an inherently fosfomycin resistant *Escherichia coli* subpopulation (agar MIC = 32-64 mg/L) within the standard starting inoculum of a susceptibility test. Given that the inherently fosfomycin-resistant subpopulation has a frequency of 3.5×10^5 and $>1.2 \times 10^9$ at 5 times and 256 times the baseline fosfomycin MIC, respectively, the administration at high dose should be recommended, especially in monotherapy [24]. A recent meta-analysis showed that resistance emerged during fosfomycin monotherapy at rates ranging from < 3% to 17.9% (pooled estimate 3.4%). The authors confirm the generally noted discrepancy between high rates of *in vitro* emergence of resistance and its evidently low clinical relevance [25].

The EUCAST [26] defines the susceptibility breakpoint as ≤ 32 mg/L for *Enterobacterales* and *Staphylococcus* spp. for intravenous formulation. Fosfomycin has exhibited a prolonged post-antibiotic effect (PAE) *in vitro* against strains of *E. coli* and *Proteus mirabilis*, varying between 3.4-4.7 h, and shorter against isolates of *P. aeruginosa* (0.3-5.5 h) and *S. aureus* (0.5-1.4 h) [27, 28].

PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

Pharmacokinetic/pharmacodynamic (PK/PD) analysis in combination with Monte Carlo simulation is a very useful tool to optimize the dosing regimens of antibiotics in order to conserve their therapeutic value. The quantitative relationship between a pharmacokinetic parameter and a microbiological parameter (MIC, minimum inhibitory concentration) is known as a PK/PD index. The three main PK/PD indices associated with the effect of the antibiotics are: $\%T_{>MIC}$, that is the percent of the dosing interval in which the drug concentration remains above the MIC; C_{max}/MIC, which is the peak concentration divided by the MIC; and AUC_{24}/MIC, which is the area under the

concentration-time curve measured over a 24-h period divided by the MIC [29].

There is confusion in the literature about whether fosfomycin displays time- or concentration-dependent bactericidal activity. Roussos et al [28] refer that the type of activity may be organism dependent. Fosfomycin exhibits concentration-dependent killing activity against strains of *E. coli, P. mirabilis* and *Streptococcus pneumonie* and time-dependent bactericidal activity against *S. aureus* and *P. aeruginosa* [27,28].

PK/PD analysis and Monte Carlo simulation allow estimating the probability that a certain PK/PD index reaches the value required for antimicrobial efficacy. In this analysis, two different estimations of the clinical outcome can be done. On the one hand, the probability of target attainment (PTA) is defined as the percentage of simulated patients with an estimated PK/PD index equal to or higher than the value related to the efficacy of the antibiotic against a pathogen with a certain MIC. This cut-off value is known as the parmacodynamic target (PDT). As an example, the PK/PD indexes and the PDTs associated with the efficacy of fosfomycin against *Enterobacterales* are $\%T_{>MIC}$ > 70% [30] and AUC_{24}/MIC > 23 (for net stasis) [31].

On the other hand, the cumulative fraction of response (CFR) is defined as the expected probability of success of a dosing regimen against bacteria in the absence of the specific value of MIC, and thus, the population distribution of MICs of country, sanitary area or health center is used. As an example, for the MIC distribution of non-MDR *P. aeruginosa* reported by Asuphon et al. in Bangkok, Thailand, fosfomycin 16 g continuous infusion combined with prolonged infusion of meropenem (1-2 g infusion over 3 hours every 8 hours) achieved CFR > 88% [30]. PTA and CFR ≥ 90% are considered optimal against a bacterial population, whereas a CFR between 80% and 90% are associated with moderate probabilities of success [29].

Based on PK/PD analysis and Monte Carlo simulations, we have evaluated different fosfomycin dosing regimen to optimize the treatment of septic patients due to *Enterobacterales* and *P. aeruginosa*. As PK/PD targets, we selected $\%T_{>MIC}$ > 70% for all pathogens, and AUC_{24}/MIC > 24 and AUC_{24}/MIC > 15 for net stasis of *Enterobacterales* and *P. aeruginosa*, respectively. These targets were selected based on the study by Lepak et al. [31] who demonstrated, in a neutropenic murine thigh infection model, that maximal animal survival was observed at AUC_{24}/MIC ratio exposures comparable to the stasis targets observed in the same infection model. Pharmacokinetic parameters were obtained from a study carried out Joukhadar et al. in critically ill patients [7]. Several dosing regimens were studied in simulated patients with normal renal function: fosfomycin 2-8 g given every 6-12 hours, infused over 30 minutes- 24 hours. Ten-thousand subject Monte Carlo simulations were conducted for each dosing regimen using Oracle® Crystall Ball Fusion Edition v.11.1.1.1.00 (Oracle USA Inc., Redwood City, CA). A log-normal distribution was assumed for Cl and V_d, according to statistical criteria.

Table 2 shows the PTA values obtained for every dosing regimen. At the susceptibility EUCAST breakpoint for *Enterobacterales* and *Staphylococcus* spp. (MIC ≤ 32 mg/L), fosfomycin 4 g/8h or higher infused over 30 minutes, achieved PTA > 90%, based in both $\%T_{>MIC}$ and AUC_{24}/MIC. For MIC of 64 mg/L, fosfomycin 6 g/6h in 30-minute infusion and 8 g/8h in 30-minute and 6 hours infusions also achieved PTA values higher than 90%. In this regard, it is important to bear in mind that the fosfomycin MIC_{90} usually reaches values of 32 mg/L in ESBL-producing *E. coli*, 64 mg/L in ESBL-producing *K. pneumoniae* and MRSA and 512 mg/L in *P. aeruginosa* [32-34]. No fosfomycin monotherapy regimen was able to achieve PK/PD targets related to antimicrobial efficacy for *P. aeruginosa* with MICs of 256-512 mg/L.

A previous study [7] in which the target site penetration properties of fosfomycin was investigated, revealed that after the administration of 8 g IV to patients with sepsis, the concentration in the interstitium and in plasma remained ≥ 70 mg/L during a 4-hours observation period. Considering that the plasma half-life of fosfomycin is <3.5 h, the target site concentrations will reach < 35 mg/L 8 hours after drug administration. Therefore for a MIC of 32 mg/L, twice-daily dosing might be insufficient, unless that fosfomycin is administered in combination with other antibiotics.

Critically ill patients have been shown higher V_d values and a high level of interpatient variability than seen in non-critically ill patients and high doses may be necessary [18]. Although 24 g/day of fosfomycin achieved the PK/PD targets, it may cause side effects, such as hypokalemia and saline overload. Provided that it has been reported that hypokalemia was more frequent when fosfomycin disodium was administered in 30- or 60-minutes infusions compared with a 4-hours infusion and the high doses of fosfomycin can produce overload of sodium, especially in elderly patients with heart failure or cirrosis or in those who are receiving haemodialysis [35, 36].

In view of these results and in agreement with Parker et al. [5], it seems to be opportune for dosing critically ill patients, to increase the daily dosage over the first 24-48 hours (by using loading doses to counter the increased V_d) and then to continue frequent but lower doses, based on estimates of renal function. Another strategy of dosing can be the use of a loading dose and to continue using not so high doses (12-16 g/day) by continuous perfusion, which as observed in table 2, maintain the steady state concentration (C_{ss}) > 32 mg/L.

The combination of fosfomycin and meropenem is synergistic and prevents the emergence of drug resistance in severe infections caused by ESBL-producing *Enterobacterales* and *P. aeruginosa* strains. Docobo-Pérez et al. [37] examined the utility of fosfomycin alone (4 g/q8h) at the very dense inoculum of 10^{10} CFU/mL against ESBL-producing *E. coli* strain with a fosfomycin MIC of 1 mg/L. Fosfomycin as monotherapy reduced the bacterial concentration by 3 $\log_{10}$ CFU/mL. However, mutants able to grow at 256 mg/L appeared after 48 h of treatment and, 24 h later, the resistant mutants replaced the susceptible population. The combination of fosfomycin (4 g/q8h) and meropenem (1 g/q8h) produced a 10-$\log_{10}$ CFU/mL bacterial reduction and sterilization of the bacterial inoculum

Table 2 **The probability of target attainment (%PTA) of various fosfomycin monotherapy regimens.**

	Probability $\%T_{>MIC}>70\%$							
	infusion 30 minutes						infusion 6 hours	
CMI (mg/L)	2 g/6 h	4 g/12 h	4 g/8 h	4 g/6 h	6 g/6 h	8 g/8 h	4g/8 h	8g/8 h
0.03	100	100	100	100	100	100	100	100
0.06	100	100	100	100	100	100	100	100
0.13	100	100	100	100	100	100	100	100
0.25	100	100	100	100	100	100	100	100
0.50	100	100	100	100	100	100	100	100
1	100	100	100	100	100	100	100	100
2	100	100	100	100	100	100	100	100
4	100	100	100	100	100	100	100	100
8	100	100	100	100	100	100	100	100
16	100	97	100	100	100	100	100	100
32[a]	78	20	98	100	100	100	100	100
64	0	0	11	79	100	98	49	100
128	0	0	0	0	23	11	0	50

	Probability $AUC_{24}/MIC > 24$ (for Enterobacterales)				Probability $AUC_{24}/MIC > 15$ (for P. aeruginosa)			
CMI (mg/L)	4 g/12 h	4 g/8 h	4 g/6 h	6g/6h 8g/8h	4 g/12 h	4 g/8 h	4 g/6 h	6g/6h 8g/8h
0.03	100	100	100	100	100	100	100	100
0.06	100	100	100	100	100	100	100	100
0.13	100	100	100	100	100	100	100	100
0.25	100	100	100	100	100	100	100	100
0.50	100	100	100	100	100	100	100	100
1	100	100	100	100	100	100	100	100
2	100	100	100	100	100	100	100	100
4	100	100	100	100	100	100	100	100
8	100	100	100	100	100	100	100	100
16	100	100	100	100	100	100	100	100
32[a]	98	100	100	100	100	100	100	100
64	4	71	99	100	**81**	100	100	100
128	0	0	4	71	0	24	**82**	100
256	0	0	0	0	0	0	0	24

Continuous infusion	12 g/day	16 g/day
Probability C_{ss} > 32 mg/L	100	100
Probability C_{ss} > 64 mg/L	70	98
Probability C_{ss} > 128 mg/L	0	4

In gray, values ≥90%, in bold, values ≥80 and <90%. [a]Fosfomycin EUCAST breakpoint.

after 48 h of treatment. In addition, the combination completely suppressed all clones resistant to fosfomycin at a dose of 12 g/day when employed as monotherapy.

The use of intravenous fosfomycin as monotherapy for systemic infection caused by *P. aeruginosa* may be problematic because the bacterial killing is virtually eliminated at high inoculum, suggesting that combination with other antibiotics is required for this organism [27]. In *in vitro* studies, the combination of fosfomycin with carbapenems has shown good synergistic effects against *P. aeruginosa* isolates. Asuphon et al. [30] through synergy studies using an E-test strips of fosfomycin in combination with meropenem have reported that MIC_{90} for non-MDR *P. aeruginosa* were 512 mg/L for fosfomycin monotherapy, 128 mg/L for fosfomycin combined with meropenem, 8 mg/L for meropenem monotherapy and 3 mg/L for meropenem combined with fosfomycin. The same authors calculated the PTAs for fosfomycin and meropenem used alone or in combination. For non-MDR *P. aeruginosa*, fosfomycin 16 g continuous infusion combined with meropenem 1-2 g, 3-hour infusion every 8 hours achieve approximately 80% PTA for MIC_{90} 128 mg/L of fosfomycin and 3 mg/L of meropenem. However, the loading dose of fosfomycin needed in a continuous infusion regimen will apply. Considering the carbapenem-resistant *P. aeruginosa* subgroup, MIC_{90} were >1,024 mg/L for fosfomycin monotherapy, 192 mg/L for fosfomycin combined with carbapenems, > 32 mg/L for meropenem monotherapy and 6 mg/L for meropenem combined with fosfomycin. For PTA of > 90% of meropenem in combination with fosfomycin, the dosage should be fosfomycin 8 g every 8 hours infusion over 6 hours in combination wtih meropenem 2 g every 8 hours prolonged infusion at MIC_{90} less than 128 mg/L of fosfomycin and less than 6 mg/L for meropenem. In this regard, Sauermann et al. [11] reported, in an *in vivo* study, that the average concentration at steady state of fosfomycin in the abscess fluid after the administration of 8 g every 8 hours was 184 mg/L. This concentration was higher than the MIC_{90} (128 mg/L) of non-MDR *P. aeruginosa* and carbapenem-resistant *P. aeruginosa* against fosfomycin combined with meropenem [30].

Synergism has been also documented between fosfomycin and glycopeptides, linezolid and daptomycin against MRSA and *Enterococcus* spp. [38, 39].

Until more data are available, fosfomycin should not be used as monotherapy to treat systemic infections with either high MICs or with high bacterial densities [27, 37].

REFERENCES

1. Popovic M, Steinort D, Pillai S, Joukhadar C. Fosfomycin: an old, new friend? Eur J Clin Microbiol Infect Dis 2010;29:127-42. doi: 10.1007/s10096-009-0833-2.
2. Dijkmans AC, Zacarías NVO, Burggraaf J, Mouton JW, Wilms EB, van Nieuwkoop C, et al. Fosfomycin: Pharmacological, Clinical and Future Perspectives. Antibiotics (Basel) 2017;6. pii: E24. doi: 10.3390/antibiotics6040024.
3. Neuner EA, Gallagher JC. Pharmacodynamic and pharmacokinetic considerations in the treatment of critically Ill patients infected with carbapenem-resistant Enterobacteriaceae. Virulence 2017;8:440-52. doi: 10.1080/21505594.2016.1221021.
4. Bergan T. Degree of absorption, pharmacokinetics of fosfomycin trometamol and duration of urinary antibacterial activity. Infection 1990;18 Suppl 2:S65-9.
5. Parker S, Lipman J, Koulenti D, Dimopoulos G, Roberts JA. What is the relevance of fosfomycin pharmacokinetics in the treatment of serious infections in critically ill patients? A systematic review. Int J Antimicrob Agents 2013;42:289-93. doi: 10.1016/j.ijantimicag.2013.05.018.
6. Samonis G, Vardakas KZ, Tansarli GS, Dimopoulou D, Papadimitriou G, Kofteridis DP, et al. Fosfomycin. Clin Microbiol Rev 2016;29:321-47. doi: 10.1128/CMR.00068-15.
7. Joukhadar C, Klein N, Dittrich P, Zeitlinger M, Geppert A, Skhirtladze K, et al. Target site penetration of fosfomycin in critically ill patients. J Antimicrob Chemother 2003;51:1247-52.
8. Kirby WM. Pharmacokinetics of fosfomycin. Chemotherapy 1977;23 Suppl 1:141-51.
9. Udy AA, Roberts JA, De Waele JJ, Paterson DL, Lipman J. What's behind the failure of emerging antibiotics in the critically ill? Understanding the impact of altered pharmacokinetics and augmented renal clearance. Int J Antimicrob Agents 2012;39:455-7. doi: 10.1016/j.ijantimicag.2012.02.010.
10. Legat FJ, Maier A, Dittrich P, Zenahlik P, Kern T, Nuhsbaumer S, et al. Penetration of fosfomycin into inflammatory lesions in patients with cellulitis or diabetic foot syndrome. Antimicrob Agents Chemother 2003;47:371-4. http://dx.doi.org/10.1128/AAC.47.1.371-374.2003.
11. Sauermann R, Karch R, Langenberger H, Kettenbach J, Mayer-Helm B, Petsch M, et al. Antibiotic abscess penetration: fosfomycin levels measured in pus and simulated concentration-time profiles. Antimicrob Agents Chemother 2005;49:4448-54. http://dx.doi.org/10.1128/AAC.49.11.4448-4454.2005.
12. Farago E, Kiss IJ, Nabradi Z.. Serum and lung tissue levels of fosfomycin in humans. Int J Clin Pharmacol Ther Toxicol 1980;18:554-8.
13. Matzi V, Lindenmann J, Porubsky C, Kugler SA, Maier A, Dittrich P, et al. Extracellular concentrations of fosfomycin in lung tissue of septic patients. J Antimicrob Chemother 2010;65:995-8. http://dx.doi.org/10.1093/jac/dkq070.
14. Falagas ME, Vouloumanou EK, Samonis G, Vardakas KZ. Fosfomycin. Clin Microbiol Rev 2016;29:321-47. doi: 10.1128/CMR.00068-15.
15. Drobnic L, Quiles M, Rodriguez A. A study of the levels of fosfomycin in the cerebrospinal fluid in adult meningitis. Chemotherapy 1977;23(Suppl 1):S180-8.
16. Sirot J, Lopitaux R, Dumont C, Rampon S, Cluzel R. Diffusion of fosfomycin into bone tissue in man. Pathol Biol (Paris) 1983;31:522-4.
17. Forestier F, Salvanet-Bouccara A, Leveques D, Junes P, Rakotondrainy C, Dublanchet A, et al. Ocular penetration kinetics of fosfomycin administered as a one-hour infusion. Eur J Ophthalmol 1996;6:137-2.

18. Parker SL, Frantzeskaki F, Wallis SC, Diakaki C, Giamarellou H, Koulenti D, et al. Population Pharmacokinetics of fosfomycin in critically ill patients. Antimicrob Agents Chemother 2015;59:6471-6. doi: 10.1128/AAC.01321-15.
19. Michalopoulos AS, Livaditis IG, Gougoutas V. The revival of fosfomycin. Int J Infect Dis 2011;15:e732-9. doi: 10.1016/j.ijid.2011.07.007.
20. Schmidt JJ, Bode-Böger SM, Wilhelmi M, Omar M, Martens-Lobenhoffer J, Welte T, et al. Pharmacokinetics and total removal of fosfomycin in two patients undergoing intermittent haemodialysis and extended dialysis: prescription needs to avoid under-dosing. J Antimicrob Chemother 2016;71:2673-4. doi: 10.1093/jac/dkw187.
21. Gattringer R, Meyer B, Heinz G, Guttmann C, Zeitlinger M, Joukhadar C, et al. Single-dose pharmacokinetics of fosfomycin during continuous venovenous haemofiltration. J Antimicrob Chemother 2006;58:367-71.
22. Kahan FM, Kahan JS, Cassidy PJ, Kropp H. The mechanism of action of fosfomycin (phosphonomycin). Ann N Y Acad Sci 1974;235:364-86.
23. Karaiskos I, Giamarellou H. Multidrug-resistant and extensively drug-resistant Gram-negative pathogens: current and emerging therapeutic approaches. Expert Opin Pharmacother 2014;15:1351-70. doi: 10.1517/14656566.2014.914172.
24. VanScoy BD, McCauley J, Ellis-Grosse EJ, Okusanya OO, Bhavnani SM, Forrest A et al. Exploration of the pharmacokinetic-pharmacodynamic relationships for fosfomycin efficacy using an *in vitro* infection model. Antimicrob Agents Chemother 2015;59: 7170-7. doi: 10.1128/AAC.04955-14.
25. Grabein B, Graninger W, Rodríguez Baño J, Dinh A, Liesenfeld DB. Intravenous fosfomycin-back to the future. Systematic review and meta-analysis of the clinical literature. Clin Microbiol Infect 2017;23: 363-372. doi: 10.1016/j.cmi.2016.12.005.
26. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0, 2018. http://www.eucast.org.
27. Walsh CC, McIntosh MP, Peleg AY, Kirkpatrick CM, Bergen PJ. *In vitro* pharmacodynamics of fosfomycin against clinical isolates of *Pseudomonas aeruginosa*. J Antimicrob Chemother 2015;70: 3042-50. doi: 10.1093/jac/dkv221.
28. Roussos N, Karageorgopoulos DE, Samonis G, Falagas ME. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of fosfomycin for the treatment of patients with systemic infections. Int J Antimicrob Agents 2009;34:506-15. doi: 10.1016/j.ijantimicag.2009.08.013.
29. Asín-Prieto E, Rodríguez-Gascón A, Isla A. Applications of the pharmacokinetic/pharmacodynamics (PK/PD) analysis of antimicrobial agents. J Infect Chemother 2015; 21: 319-329. doi: 10.1016/j.jiac.2015.02.001.
30. Asuphon O, Montakantikul P, Houngsaitong J, Kiratisin P, Sonthisombat P. Optimizing intravenous fosfomycin dosing in combination with carbapenems for treatment of *Pseudomonas aeruginosa* infections in critically ill patients based on pharmacokinetic/pharmacodynamic (PK/PD) simulation. Int J Infect Dis 2016;50: 23-9. doi: 10.1016/j.ijid.2016.06.017.
31. Lepak AJ, Zhao M, VanScoy B, Taylor DS, Ellis-Grosse E, Ambrose PG et al. *In vivo* pharmacokinetics and pharmacodynamics of ZTI-01 (Fosfomycin for Injection) in the neutropenic murine thigh infection model against *Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2017;61. pii: e00476-17. doi: 10.1128/AAC.00476-17.
32. de Cueto M, López L, Hernández JR, Morillo C, Pascual A. *In vitro* activity of fosfomycin against extended-spectrum-beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: comparison of susceptibility testing procedures. Antimicrob Agents Chemother 2006; 50:368-70.
33. Díez-Aguilar M, Morosini MI, del Campo R, García-Castillo M, Zamora J, Cantón R. *In vitro* activity of fosfomycin against a collection of clinical *Pseudomonas aeruginosa* isolates from 16 Spanish hospitals: establishing the validity of standard broth microdilution as susceptibility testing method. Antimicrob Agents Chemother 2013;57:5701-3. doi: 10.1128/AAC.00589-13.
34. Zhanel GG, Zhanel MA, Karlowsky JA. Intravenous fosfomycin: an assessment of its potential for use in the treatment of systemic infections in Canada. Can J Infect Dis Med Microbiol 2018; 2018:8912039. doi: 10.1155/2018/8912039.
35. Florent A, Chichmanian RM, Cua E, Pulcini C. Adverse events associated with intravenous fosfomycin. Int J Antimicrob Agents 2011; 37 :82-3. doi: 10.1016/j.ijantimicag.
36. Candel FJ, Matesanz M, Martín-Sánchez FJ, González Del Castillo JM. Monitoring of high-dose fosfomycin guided by NT-proBNP. Int J Cardiol 2016; 209:131-2. doi: 10.1016/j.ijcard.2016.02.037.
37. Docobo-Pérez F, Drusano GL, Johnson A, Goodwin J, Whalley S, Ramos-Martín V et al. Pharmacodynamics of fosfomycin: insights into clinical use for antimicrobial resistance. Antimicrob Agents Chemother 2015;59:5602-10. doi: 10.1128/AAC.00752-15.
38. 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.
39. Kaye KS, Gales AC, Dubourg G. Old antibiotics for multidrug-resistant pathogens: from *in vitro* activity to clinical outcomes. Int J Antimicrob Agents 2017;49:542-548. doi: 10.1016/j.ijantimicag.2016.11.020.