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The role of fosfomycin in osteoarticular infection

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ABSTRACT

Osteoarticular infections include septic arthritis and osteomyelitis, with Gram-positive microorganisms isolated most frequently. In recent years, there has been an increase in the number of resistant strains in this type of infection, which complicates the treatment. Fosfomycin is active against a large percentage of Gram-positive and Gram-negative pathogens, including multidrug-resistant strains, and its properties include low protein binding, low molecular weight and good bone dissemination. In this article, we discuss fosfomycin's activity *in vitro*, its pharmacokinetic and pharmacodynamic parameters of interest in osteoarticular infections, the experimental models of osteomyelitis and foreign body infection and the clinical experience with these types of infections.

Keywords: fosfomycin, arthritis, osteomyelitis

BACKGROUND

Osteoarticular infections include septic arthritis and osteomyelitis. For septic arthritis, we can differentiate between monoarticular (the knee being the most commonly affected joint) and polyarticular forms, the latter of which usually involves small peripheral joints. Osteomyelitis has been classified according to the degree of impairment of the bone's anatomical structure (medullar, superficial, localized or diffuse) and the pathophysiology of the infection. The latter classification includes the hematogenous infections, which mainly affect the axial skeleton (spine) in adults and long bones in children, which correspond to medullary forms of the anatomical classification. Infections by contiguity include osteomyelitis secondary to bone exposure due to loss of skin integrity (diabetic foot, pressure ulcer) and initially correspond to superficial anatomical forms, although they can progress to localized or diffuse forms if not treated promptly. Lastly, we have osteomyelitis by direct inoculation of the microorganism, which encompasses infections secondary to open fractures and to contamination during the surgical act. The risk of osteomyelitis after an open fracture depends on the severity of the injury; more than 20% of severe cases are still complicated by osteomyelitis. However, the most common form of osteomyelitis at present is the result of bacterial contamination during surgery to place orthopedic material for fractures or for prosthetic joints to treat osteoarthritis. The etiology of osteoarticular infections is dominated by Gram-positive cocci (GPC), although in recent years Gram-negative bacilli (GNB) are on the increase, particularly in infections related to the placement of orthopedic material [1-3].

Prosthetic joint infections (PJI) occur in 1-3% of cases according to data from the Catalonian Nosocomial Infection Surveillance Program (VINCAT), which included more than 7000 annual procedures performed in various hospitals [4]. The aging of the population, with high indices of comorbidity (diabetes mellitus, obesity), and an increase in resistant microorganisms that could potentially contaminate the surgery leads to the prediction that infection rates will not decrease, which will result in significant economic costs [5]. GPC are still the most commonly isolated pathogens, mainly *Staphylococcus aureus* and coagulase-negative staphylococci (CNS). Recent data show that methicillin-resistance rates are approximately 20% and >60%, respectively, for *S. aureus* and CNS; for fluoroquinolones, the resistance rates are >30% in a series in our setting [3, 6]. This fact is important because the best results have been achieved with a combination of levofloxacin and rifampicin, thanks to their increased activity versus bacterial biofilms [7, 8]. An epidemiological study of these infections in 19 Spanish hospitals between 2003 and 2012 showed an increase in GNB and their increased resistance to fluoroquinolones [3],

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a relevant finding because, in these cases, the inclusion of a quinolone in the treatment also improves the prognosis, once again thanks to its increased activity versus biofilms [9,10]. The most worrying fact of the study, however, is that 16% of the infections were caused by a multidrug-resistant Gram-positive or Gram-negative microorganism. This situation warrants an analysis of therapeutic alternatives, which include fosfomycin due to its good activity against multidrug-resistant GPC [11] and GNB [12], its good bone dissemination and activity against *S. aureus*, enterococcus and GNB in various foreign body infection models when fosfomycin is combined with other antibiotics. It is therefore worth reviewing fosfomycin's characteristics in terms of its *in vitro* and *in vivo* activity, as well as the clinical experience in osteoarticular infections with the aim of identifying its indications and forms of administration.

CHARACTERISTICS OF FOSFOMYCIN'S *IN VITRO* ACTIVITY

Fosfomycin is a broad-spectrum, time-dependent bactericidal antibiotic that acts by inhibiting the synthesis of N-acetylmuramic acid and blocking the synthesis of the bacterial wall [13], although its activity is lower in the presence of a high inoculum (10^8 colony-forming units/mL), as can be found in some forms of osteomyelitis [14], suggesting the need for employing fosfomycin in combination. The minimum inhibitory concentration required to inhibit the growth of 90% (MIC_{90}) of staphylococci (regardless of methicillin sensitivity) is <16 mg/L, <8 mg/L against *E. coli* and ≤32-64 mg/L against 50% of strains of *K. pneumoniae*, *Enterobacter*, *Serratia* and *Proteus* and 20% of *P. aeruginosa* strains. One of the peculiarities of fosfomycin's activity is that it maintains an acidic pH [5-7], even in anaerobiosis. There are numerous mechanisms that determine the bacterial resistance within the biofilm, but one of the characteristics of these structures is that the environment in the deeper strata is acidic and oxygen-poor [15]. These data could explain the good results obtained *in vitro* with fosfomycin against biofilms of *S. aureus* and CNS [16, 17]. Although not all of the *in vitro* models demonstrated the efficacy of fosfomycin against biofilms [18], there is greater unanimity in the synergy between fosfomycin and vancomycin, teicoplanin, linezolid and fusidic acid against biofilms of methicillin-resistant *S. aureus* (MRSA). A number of the models showed superior results for fosfomycin compared with those obtained with the combination of these antibiotics and rifampicin [19]. There are also data indicating synergy between ciprofloxacin and fosfomycin (both at concentrations 3 times the MIC) against *P. aeruginosa* biofilms [20]. In the pathogenesis of osteomyelitis, there is increasing evidence of the role of intracellular forms of *S. aureus* that adapt to this location through the formation of small colony variants that present tolerance to multiple antibiotics [21]. Fosfomycin has shown efficacy against intracellular forms of *S. aureus* at therapeutic concentrations, although fosfomycin was unable to prevent the selection of small colony variants, unlike ofloxacin and rifampicin, which suggests the need to employ fosfomycin combinations for this type of infection [22]. These results have been transferred to animal models of osteomyelitis and foreign body infection, with good results as we will discuss later.

PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS OF FOSFOMYCIN

There are 3 presentations of fosfomycin: the disodium salt for intravenous administration, the calcium salt and trometamol for oral administration. The oral bioavailability of the calcium salt and trometamol is <20% and <40%, respectively. Therefore, only the intravenous presentation is recommended for treating osteoarticular infections. The intravenous administration of 4-8 g achieves a serum concentration of 200-400 mg/L and an elimination half-life of 3 h. The protein binding is <5%, and the molecular mass is 138 g/mol. The fosfomycin concentration in bone and subcutaneous cell tissue was measured using microdialysis in 9 patients with diabetes and osteomyelitis who were administered a single 100-mg/kg dose. The patients underwent surgery to excise necrotic tissue, leaving the microdialysis needle in the vicinity of the infected bone tissue and subcutaneous cell tissue [23]. The area under the curve (AUC) described by the concentration in the bone and subcutaneous cell tissue was 43% and 76% of the plasma AUC, respectively. The maximum concentration reached in the bone was 96 mg/L, and in all cases the concentration at 6 h remained above 32 mg/L. Considering that the pharmacodynamic parameter that predicts fosfomycin's efficacy is a time above the MIC ≥50%, these data suggest that the dosage of 100 mg/kg (according to the adjusted weight) every 8 h is appropriate for microorganisms with MICs ≤32 mg/L. In the presence of a suppurative collection, especially if it cannot be drained immediately, the recommendation is a loading dose of 10 g to avoid delays in reaching the desired concentration [24]. These data could partly explain the results of experimental models of osteomyelitis that are described in a subsequent section.

Fosfomycin has been classically assumed to easily select resistant mutations, given that it has been determined in the laboratory that the frequency of these mutations in *S. aureus* is relatively high (10^{-6}-10^{-5}), and the mutant prevention concentration (MPC) is 64 mg/L, which, according to the bone dissemination data, suggests that the risk of selecting mutations is high. However, an *in vivo* foreign body model that exposed animals to concentrations between the MIC and MPC (mutagenic window) was unable to select resistant mutations [14]. Similarly, mutations were not selected during treatment of infections caused by *E. coli* [25]. The authors did not identify a loss of competence in the resistant strains, and therefore the reason for this finding should be sought in another characteristic of fosfomycin. It has recently been shown that the bactericidal activity of neutrophils and macrophages is performed not only after phagocytosis in the interior of phagolysosomes through oxidative reactions but also at the extracellular level through the release into the medium of a DNA mesh and molecules with antimicrobial action (elastase, myeloperoxidase) that trap microorganisms and have bactericidal action [26].

Fosfomycin has been shown *in vitro* to potentiate both bactericidal activity pathways of the immune system [27], which could explain the lack of selection *in vivo* of resistant mutations, even when the concentration is within the mutagenic window.

EXPERIENCE WITH FOSFOMYCIN IN EXPERIMENTAL MODELS OF OSTEOMYELITIS AND FOREIGN BODY INFECTION

An experimental model of chronic osteomyelitis by MRSA [28] showed that monotherapy with fosfomycin achieves curing rates >90% and was more effective than daptomycin at a dosage corresponding to 6 mg/kg/24 h. Fosfomycin-resistant mutations were not selected in any case. Foreign-body infection models that seek to simulate infection related to orthopedic implants (osteosynthesis material, prosthetic joints) include the model that introduces a titanium needle into the tibia of a rat that was subsequently contaminated with a high bacterial inoculum. A second model, known as the box model, consists of subcutaneously placing a multiperforated Teflon box containing the inoculated study microorganism into the animal. For the first model, there are 2 studies that assessed the efficacy of fosfomycin, vancomycin, daptomycin and the combination of daptomycin and fosfomycin against MRSA [29, 30]. In monotherapy, fosfomycin was significantly more effective than vancomycin and daptomycin, and the combination with daptomycin was synergistic. Fosfomycin-resistant mutations were not selected in any case, and it is worth noting that all models described herein employed fosfomycin dosages that, in the animal, involved levels lower than those that can be achieved in humans with a dosage of 8 g/8 h.

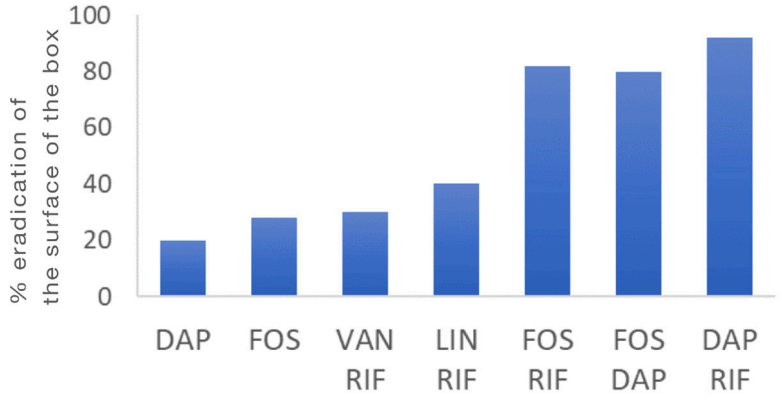

Figure 1 Percentage eradication of an methicillin-resistant *Staphylococcus aureus* biofilm in the animal model of foreign body infection [32-38].

DAP, daptomycin; FOS, fosfomycin; VAN, vancomycin; RIF, rifampicin; LIN, linezolid.

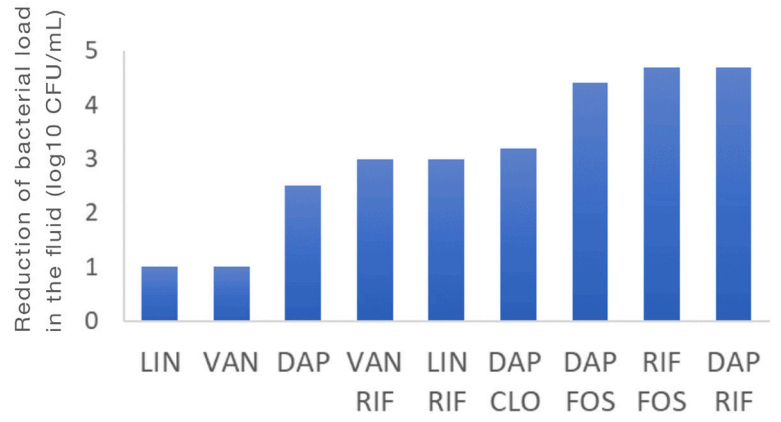

Figure 2 Decrease in bacterial load in the interior of the box of the foreign body animal model by methicillin-resistant *Staphylococcus aureus* [32-38].

CLO, cloxacillin; DAP, daptomycin; FOS, fosfomycin; LIN, linezolid; RIF, rifampicin; VAN, vancomycin.

Table 1 Summary of the clinical experience with fosfomycin in osteoarticular infections

Author/ year	Study type	No. of patients / Infection type	Isolated microorganism, %	Fosfomycin dosage	Combination	Mean intravenous antibiotic duration, days	Mean follow-up, months	Remission n/total evaluated, %
Portier/ 1985 [38]	Prosp.	6 patients: 4 arthritis 2 OM	MRSA (100)	50 mg/kg, 6-8 h	Cefotaxime	15	-	100
Meissner/ 1989 [39]	Prosp.	60 / chronic OM	*S. aureus* (56,7) SCN (25) *P. aeruginosa* (16,7)	5 g / 8 h (loading of 5 or 10 g)	-	13.9	37	73,6
Corti/2003 [40]	Retrosp.	103 children / acute OM	*S. aureus* (60,5)[a] SCN (15,8) *S. pyogenes* (7,9)	-	3 groups: - fosfomycin (23) - fosfomycin + another antibiotic (47) - nonfosfomycin antibiotic (33)	17.5 21.7 26.6	-	23/23 46/47 (98) 32/33 (97)
Luengo/2018 [41]	Retrosp.	1/ chronic hip prosthesis infection	Multidrug-resistant *S. epidermidis*	2 g / 6 h	daptomycin 700 mg / day	42	24	100

CNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; OM, osteomyelitis; Prosp, prospective study; Retrosp, retrospective study.
[a]Calculated for 38 patients with a microbiological isolate.

The box model evaluated 2 factors: 1) the reduction of microorganisms inside the box (planktonic population) and 2) the number of sterilized boxes or the number of microorganisms attached to the box, in the event sterilization was not achieved (sessile population). The efficacy of fosfomycin in monotherapy was limited against MRSA, unlike that observed in models of osteomyelitis; however, the combination with daptomycin and rifampicin was highly synergistic, and both combinations were more effective in reducing the planktonic and sessile populations, with box sterilization rates >70% [31, 32]. Figures 1 and 2 summarize the activity of various antibiotics against MRSA described in several studies conducted with the box model [32-38]. Once again, the selection of a resistant mutation was exceptional.

The box model has been employed to study the efficacy of fosfomycin against *E. faecalis* and extended-spectrum beta-lactamase (ESBL)-producing *E. coli*. Against *E. faecalis*, fosfomycin in monotherapy sterilized 43% of the boxes and increased significantly with the combination of gentamicin to 58% [39]. Against ESBL-producing *E. coli*, fosfomycin in monotherapy was more effective than tigecycline, gentamicin and colistin, but the combinations with fosfomycin improved the results. Specifically, the combination of fosfomycin and colistin achieved sterilization of the box in 67% of the cases [40]. Studies with this model have not been conducted for other microorganisms with few therapeutic alternatives, such as vancomycin-resistant *E. faecium* (VRE), methicillin-resistant CNS, other ESBL/carbapenemase-producing enterobacteria and *P. aeruginosa*, for which *in vitro* data have shown interesting results with fosfomycin in combination with daptomycin against VRE [41] or with carbapenem against *P. aeruginosa* [42, 43].

CLINICAL EXPERIENCE IN TREATING OSTEOARTICULAR INFECTIONS WITH FOSFOMYCIN

The clinical experience with employing fosfomycin in osteoarticular infections is limited to the small case series listed in table 1. In the first series [44], the authors studied the *in vitro* bactericidal activity of several cephalosporins in combination with netilmicin, amikacin, vancomycin and fosfomycin in 10 strains of MRSA. The combination of cefotaxime and fosfomycin was the most active and was assessed in 6 patients with osteoarticular infection (4 with septic arthritis and 2 with osteomyelitis) by MRSA. The treatment consisted of 25-mg/kg cefotaxime administered intravenously and 50 mg/kg/6-8 h of fosfomycin for a mean of 15 days. All patients tolerated the treatment well and presented clinical and microbiological cure with no recurrence, although the authors did not specify the duration of the follow-up after completing the antibiotic regimen. The authors confirmed that the combination was synergistic against the strains isolated from the 6 patients. A second study assessed the addition of 5 g of fosfomycin every 8 h intravenously (with an initial bolus of 5 or 10 g) to antibiotic

therapy for 60 patients with chronic post-traumatic osteomyelitis [45]. The microorganisms isolated most frequently were *S. aureus* (56.7%), CNS (25%) and *P. aeruginosa* (16.7%), all of which were sensitive to fosfomycin. After a mean follow-up of 37 months, 54.7% of the patients had an excellent treatment response, while 26.4% experienced treatment failure. In 19 cases, the fosfomycin concentration could be determined in the bone, and all were higher than the MIC_{90} value of the isolated microorganism. Lastly, Corti et al. [46] assessed 103 children between the ages of 1 month and 15 years with acute hematogenous osteomyelitis, caused mainly by *S. aureus*. The patients who underwent treatment with fosfomycin in monotherapy (n=23) were compared with those treated with fosfomycin in combination with another antibiotic (94% with a beta-lactam) (n=47) and with those who were administered any other regimen without fosfomycin (n=33). The mean intravenous treatment duration was 2.5, 3.1 and 3.8 weeks for the 3 groups, respectively, and only 1 patient in the fosfomycin group required surgical drainage during hospitalization. All patients progressed favorably during the therapy, with C-reactive protein levels normalizing at 2 weeks, except for 1 patient (2%) in the combination group and 1 patient (3%) in the group without fosfomycin who experienced a recurrence.

The clinical experience with the use of fosfomycin in prosthetic joint infections is limited to a single recently reported case of infection by multidrug-resistant *S. epidermidis* treated with debridement, daptomycin (10 mg/kg) and fosfomycin (2 g every 6 h), whose outcome at 2 years of follow-up was favorable [47].

CONCLUSIONS

Fosfomycin maintains good activity against Gram-positive and Gram-negative microorganisms, even for a large percentage of multidrug-resistant strains. Fosfomycin also has good bone dissemination, and an animal model of foreign body infection and numerous *in vitro* studies have demonstrated its activity against biofilms. The antibiotic has noteworthy synergistic activity with daptomycin, rifampicin, vancomycin, linezolid and fusidic acid against biofilms of Gram-positive pathogens, as well synergistic activity with colistin and ciprofloxacin against Gram-negative pathogens. Although clinical experience is limited, fosfomycin employed in combination can be effective in treating osteoarticular infections.

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