Official journal of the Spanish Society of Chemotherapy

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New evidence on the use of fosfomycin for bacteremia and infectious endocarditis

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ABSTRACT

There is growing concern regarding the increased resistance rates of numerous pathogens and the limited availability of new antibiotics against these pathogens. In this context, fosfomycin is of considerable interest due to its activity against a wide spectrum of these microorganisms. We will review the encouraging data on this issue regarding the use of fosfomycin in treating Gram-negative bacterial infections. We will also cover fosfomycin's role against 2 of the main causal agents of bacteremia and endocarditis worldwide (nosocomial and community-acquired): enterococci, whose growing resistance to glycopeptides and aminoglycosides represents a serious threat, and methicillin-resistant *Staphylococcus aureus*, whose infection, despite efforts, continues to be associated with high morbidity and mortality and a high risk of complications. Thanks also to its considerable synergistic capacity with various antibiotics, fosfomycin is a tool for extending the therapeutic arsenal against these types of infections.

Keywords: Fosfomycin, Bacteremia, Infectious endocarditis, Methicillin-resistant *Staphylococcus aureus*, Gram-negative.

BACKGROUND

There has been a worrying increase in the rates of antibiotic resistance among Gram-positive and Gram-negative pathogens, representing an increase in mortality and hospital stays, thereby impelling the search for alternative treatment strategies. Given the limited availability of new antimicrobials, the reassessment of earlier compounds appears to be an interesting option. Fosfomycin has raised considerable interest, given that, despite being an older antibiotic, it remains active against a wide spectrum of problematic pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-resistant enterococci and multidrug-resistant enterobacteria. Fosfomycin's single mechanism of action, along with its broad spectrum and synergistic potential with other antibiotics, makes it a promising candidate for treating patients with complex systemic infections.

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FOSFOMYCIN

Discovered in Spain in 1969 [1], fosfomycin is a bactericidal drug that inhibits cell wall synthesis [2], preventing the formation of the N-acetylmuramic acid of the bacterial wall peptidoglycan. This inhibitory action occurs in one step prior to the action of beta-lactams and glycopeptides. Fosfomycin is a water-soluble agent with a low molecular weight (138 g/mol) and very low protein binding, which provides it with high tissue dissemination. Fosfomycin also penetrates and disseminates adequately in biofilms, not only acting on microorganisms but also changing their structure [3]. Fosfomycin is eliminated almost exclusively through glomerular filtration. The pharmacokinetic-pharmacodynamic effectiveness parameter to consider for achieving the therapeutic objective is the area under the curve/minimum inhibitory concentration; fosfomycin also presents a postantibiotic effect.

Fosfomycin's spectrum is broad and covers most Gram-positive and Gram-negative bacteria, including numerous antibiotic-resistant varieties, such as *Staphylococcus aureus*, including MRSA [4], enterococci, including those resistant to vancomycin [5], *Enterobacteriaceae*, including extended-spectrum beta-lactamase (ESBL) producers [6] and *Pseudomonas aeruginosa* (with varying rates of intrinsic resistance) [7]. Fosfomycin exerts immunomodulatory effects by changing the function of lymphocytes, monocytes and neutrophils, as well as the acute response of inflammatory cytokines *in vitro* and *in vivo*. These effects provide greater bactericidal capacity to neutrophils in the presence of fosfomycin compared with other antimicrobi-

als [8]. Fosfomycin's single mechanism of action makes cross-resistance uncommon and enables synergy with other antimicrobials [9], as demonstrated by numerous studies in the literature that will be discussed later. In general, fosfomycin is considered a safe drug. Nevertheless, there have been reported cases of heart failure secondary to sodium overload after the administration of fosfomycin's intravenous formulation [10].

GRAM-NEGATIVE BACTEREMIA

Most data that support the use of fosfomycin in infections caused by multidrug-resistant Gram-negative microorganisms originate from observational studies that involved a very limited number of patients, in which fosfomycin was generally employed as part of a regimen in combination with other agents. All this, coupled with the lack of an additional comparator group, limit the conclusions that can be extracted from the available data.

Bacteremic infections caused by multidrug-resistant Gram-negative microorganisms have a poor prognosis. The early diagnosis and start of optimal antimicrobial therapy are essential for improving results. A cohort study conducted in a Spanish hospital from 2010 to 2012 that included 40 patients with bacteremia by OXA-48 carbapenemase-producing *Enterobacteriaceae* observed a mortality rate of 65%. The patients were mostly elderly with significant comorbidities (57.5% with underlying malignancy) and had been exposed to antibiotics and invasive procedures during their hospitalization. The most common source of bacteremia was urinary. Amikacin, colistin and fosfomycin were the antibiotics that most often maintained their effectiveness against OXA-48 isolates, but none were uniformly active in isolation. The patients were treated mostly with combinations of antibiotics active against the involved pathogen, employing monotherapy only in highly selected cases (patients with less severe infection and controlled foci). Of the 5 patients who were treated with intravenous fosfomycin (4 underwent combined therapy with colistin, and 1 underwent combined therapy with tigecycline), death due to the infection was reported in 2 [11].

Role of fosfomycin. Preliminary data on the use of fosfomycin in combination with other agents for treating bacteremic infections by multidrug-resistant Gram-negative microorganisms are encouraging. There is an ongoing clinical trial whose main objective is to demonstrate the clinical noninferiority of fosfomycin compared with meropenem in the targeted treatment of bacteremic infections caused by ESBL-producing *Escherichia coli*. The multicenter study included patients with bacteremia secondary to urinary tract infection caused by ESBL-producing *E. coli*. Using a randomized assignment system, the patients were assigned to one of the following treatment arms: intravenous fosfomycin disodium 4 g/6 h or intravenous meropenem 1 g/8 h. The secondary endpoints included hospital mortality, mortality at 30 days, recurrence rate, length of stay, safety and the development of fosfomycin resistance [12].

BACTEREMIA/INFECTIOUS ENDOCARDITIS DUE TO *S. AUREUS*

Staphylococcal bacteremia is a severe entity with high morbidity and mortality and a high risk of complications such as hematogenous dissemination and endocarditis. Staphylococcal bacteremia is one of the main causes of bacteremia worldwide (both nosocomial and community-acquired), with an incidence rate that ranges from 10 to 30 cases per 100,000 person-years. Despite efforts to manage this infection, staphylococcal bacteremia continues to present high mortality, as demonstrated by a recent multinational observational study that analyzed databases from several European institutions. The study showed a mortality rate of 29% at 90 days, although this rate varied with patient age, patient characteristics and focus of infection [13]. In addition to high mortality, these infections are associated with high morbidity and healthcare costs due to prolonged hospitalizations and antibiotic therapies. The factors that influence the prognosis of staphylococcal bacteremia can be divided into 2 categories:

First, we have unmodifiable factors that include those associated with the host (e.g., age, comorbidities), with the pathogen (MRSA) and with the focus of infection, where infectious endocarditis is especially prominent (with its currently mortality rate of 16-25%) and where *S. aureus* has become the leading cause of staphylococcal bacteremia in the developed world [14]. It is also worth noting the global increase in the prevalence of MRSA infections and the associated epidemiological changes, which mainly include an increase in age, the presence of more comorbidities and nosocomial acquisition. Additionally, MRSA infection has been identified as an independent risk factor for mortality, as observed in a large, observational, multicenter Spanish study that included more than 600 episodes of MRSA bacteremia, with a mortality rate >30% regardless of the type of antibiotic therapy administered [15].

Secondly and in terms of modifiable factors, we have those related to the management, early diagnosis, control of foci and appropriate antibiotic therapy. Circumstances, such as the location of the infection, a high bacterial load and the presence of foreign material, as occurs in valve vegetations and abscesses, are especially important because they can hinder management and therapeutic efficacy.

Role of fosfomycin. According to the recommendations of the latest guidelines [16, 17], vancomycin is currently considered the first treatment option for MRSA bacteremia and endocarditis, along with daptomycin (both in monotherapy). However, therapeutic failures have been reported in the literature, as well as the emergence of resistances both to vancomycin and to daptomycin that can reach 15% [18, 19]. Specifically, MRSA strains with MICs for vancomycin ≥2 mg/L have increased from 5.6% in 2004 to 11.1% in 2009 and are associated with poorer results [20, 21].

In this context, fosfomycin can play an important role in broadening the therapeutic arsenal against this type

of infection because it presents very good activity versus methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA, with susceptibility rates >95%.

Combined therapy. Several studies have also analyzed the synergistic capacity of fosfomycin with various antibiotics [10]. In the specific case of MRSA, studies have observed that MRSA reduces PBP2A expression in the presence of fosfomycin, thereby increasing the susceptibility to beta-lactams. Experimental models of endocarditis (*in vitro* and *in vivo*) have therefore evaluated the effectiveness of fosfomycin combined with various beta-lactams against MRSA and strains intermediate to glycopeptides. Of these combinations, the one with imipenem is the most active [22]. This multicenter study assessed the clinical efficacy and safety of fosfomycin combined with imipenem as rescue therapy for 16 patients with MRSA endocarditis or complicated bacteremia. The blood cultures became negative 72 h after the first doses in all cases, and the cure rate was 69%, with only 1 death attributable to MRSA. The combination was safe in 94% of the cases, although a patient with hepatic cirrhosis died of multiorgan failure secondary to sodium overload [23]. More recently, the same team conducted a randomized clinical trial to assess the safety and efficacy of imipenem combined with fosfomycin in treating MRSA bacteremia and endocarditis, compared with vancomycin alone. Although the study had defects in its recruitment, and the final sample did not allow for a robust analysis, the study provided a proof-of-concept that warrants future investigations [24].

Although the experience is limited, synergistic *in vitro* activity has been observed between fosfomycin and daptomycin, and some cases have been treated successfully [25, 26]. A clinical trial currently underway [27] randomized patients with MRSA bacteremia to treatment with daptomycin in monotherapy or in combination with fosfomycin. There are also studies on the synergistic activity with linezolid, with good *in vitro* results [28].

In 2013, the guidelines of the Spanish Society of Chemotherapy on the treatment of staphylococcal infection [29] placed fosfomycin as a therapeutic option to consider in MRSA endocarditis on native valves. More recently, other guidelines [18, 30] have included the use of fosfomycin as an alternative in combination with cloxacillin, daptomycin or imipenem for treating infections complicated by MSSA or MRSA.

Bacteremia by *S. aureus*, including infectious endocarditis, entails high mortality, and up to 50% of patients experience failure with the initial therapy with vancomycin and require rescue therapy. New strategies (including the use of fosfomycin) are therefore needed to effectively treat these patients and could require combined therapies such as rescue therapy.

BACTEREMIA/INFECTIOUS ENDOCARDITIS DUE TO *ENTEROCOCCUS* SPP.

Enterococcus spp. has become the third leading cause of nosocomial bacteremia, which is significantly associated with the risk of developing infectious endocarditis [15]. Infectious enterococcal endocarditis is mainly caused by *Enterococcus faecalis* (90% of cases) and, more rarely, by *E. faecium* (5%). The medical treatment of enterococcal endocarditis is a challenge for 2 reasons: 1) Enterococci are highly resistant to antibiotic-induced death, and suppressing enterococci requires extended administration (up to 6 weeks) of synergistic bactericidal combinations of 2 cell-wall inhibitors (ampicillin plus ceftriaxone) or a cell-wall inhibitor with aminoglycosides, and 2) enterococci are resistant to numerous antibiotics such as penicillins and cephalosporins and have a growing resistance to glycopeptides and aminoglycosides [31]. The combination of high-dose penicillin or ampicillin and an aminoglycoside (streptomycin or gentamicin) typically cures enterococcal endocarditis; however, resistance to aminoglycosides is a significant problem and threat. New therapeutic options such as synergistic combinations should be assessed [10]. Fosfomycin could therefore have a useful role, and its combination with ceftriaxone could be considered a therapeutic option in the antibiotic treatment of endocarditis by *E. faecalis* [32].

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