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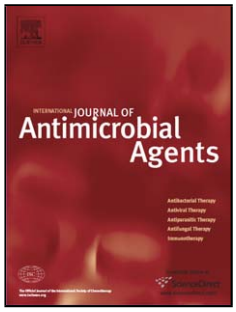

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Antimicrobial susceptibility of Gram-positive non-urinary isolates to fosfomycin

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ABSTRACT

We aimed to evaluate the antimicrobial activity of fosfomycin against Gram-positive non-urinary isolates collected at the microbiological laboratory of the University Hospital of Heraklion, Crete, Greece, in 2008. Susceptibility testing was performed by the disk diffusion method for a total of 1846 isolates; 1275 isolates (69.1%) were susceptible to fosfomycin. Specifically, 416/419 *Staphylococcus aureus* (99.3%) [including 129/130 meticillin-resistant *S. aureus* (MRSA) isolates] and 745/961 coagulase-negative staphylococci (77.5%) were susceptible to fosfomycin. Among 42 *Streptococcus pneumoniae*, 64 *Streptococcus pyogenes* and 93 other streptococcal isolates, 61.9%, 40.6% and 48.4%, respectively, were susceptible to fosfomycin. Fosfomycin was inactive against the 166 enterococcal isolates tested. This old antibiotic may deserve consideration for further studies and use in clinical practice, especially for *S. aureus* (including MRSA) infections.

1. Introduction

Antibacterial agents traditionally used for the treatment of infections caused by Gram-positive cocci are becoming increasingly ineffective [1]. The spread of meticillin-resistant staphylococci and penicillin-non-susceptible *Streptococcus pneumoniae*, in the community or the hospital, and of vancomycin-resistant enterococci, mainly in the hospital, is of great public health importance [2]. Although new antibacterial agents with activity against these pathogens have been developed, each has a specific place in therapy [3]. Thus, expansion of the current therapeutic options against resistant Gram-positive cocci is an important goal.

Novel therapeutic options may sometimes be identified among older, almost neglected antibiotics. Fosfomycin is an agent that might merit re-evaluation for use against contemporary resistant pathogens [4]. It has a unique mechanism of action and a wide spectrum of antimicrobial activity that encompasses both Gram-positive and Gram-negative aerobic bacteria [5]. In this study, we sought to evaluate retrospectively the in vitro antimicrobial activity of fosfomycin against recent Gram-positive non-urinary isolates.

2. Methods

This study included all Gram-positive clinical isolates originating from sites other than the urinary tract collected over a 1-year period (January–December 2008) at

the microbiological laboratory of the 700-bed University Hospital of Heraklion (Heraklion, Crete, Greece). All isolates for which susceptibility testing to fosfomycin had been performed were included. No specific criteria were set throughout the study period for the selection of isolates to be tested for fosfomycin susceptibility. Only the first isolate of the same species for each patient was included.

Routine laboratory methods were used for specimen processing and culture. Bacterial species identification was done by standard biochemical methods, the API system or the Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France) [6]. Antimicrobial susceptibility testing for all antibiotics was performed by the disk diffusion method following the recommendations of the Clinical and Laboratory Standards Institute (CLSI) [7]. Specifically, disks used for determination of susceptibility to fosfomycin contained 200 μg of fosfomycin plus 25 μg of glucose-6-phospate. To interpret susceptibility to fosfomycin, values corresponding to the most relevant CLSI breakpoints were used as provisional breakpoints, i.e. those for *Enterococcus faecalis* urinary tract isolates.

3. Results

A total of 1846 Gram-positive, non-urinary, first-patient isolates for which susceptibility to fosfomycin had been tested during the study period was evaluated, representing 87.2% of all the Gram-positive non-urinary isolates examined. The 1846 study isolates comprised 1380 *Staphylococcus* spp. (74.8%), 199

Streptococcus spp. (10.8%), 166 *Enterococcus* spp. (9.0%) and 101 other Gram-positive isolates (5.5%) (*Corynebacterium* spp., *Micrococcus* spp., *Aerococcus* spp., *Lactococcus* spp., *Gemella* spp., *Listeria* spp. and *Brevibacterium* spp.). Table 1 shows the origin of the patients who provided the culture specimens from which the isolates grew as well as the type of specimens.

Overall, 1275 (69.1%) of the 1846 studied isolates were found to be susceptible to fosfomycin. Among the antimicrobial agents evaluated, only linezolid, vancomycin, teicoplanin and rifampicin were more active than fosfomycin for all isolates studied, with rates of susceptibility to the above agents of 98.5%, 98.2%, 97.1% and 81.7%, respectively. Tetracycline (68.7% susceptible), trimethoprim/sulfamethoxazole (57.4%), amoxicillin/clavulanic acid (56.3%), gentamicin (52.9%), imipenem (45.0%), clindamycin (44.7%) and ciprofloxacin (44.4%) followed fosfomycin in terms of highest susceptibility rates.

Table 2 presents the susceptibility rates to fosfomycin and other selected antibacterial agents tested for the staphylococcal and streptococcal isolates studied. Specifically, 84.1% of the 1380 staphylococcal isolates studied were susceptible to fosfomycin, including 99.3% of the 419 *Staphylococcus aureus* isolates. The presence of meticillin resistance in *S. aureus* isolates did not affect susceptibility to fosfomycin. Additionally, 48.7% of all the 199 streptococcal isolates studied were susceptible to fosfomycin, including 61.9% of the 42 *S. pneumoniae*

isolates. The subset of 23 multidrug-resistant (MDR) *S. pneumoniae* isolates (defined as resistant to at least two of the following agents: penicillin, cefuroxime, erythromycin or trimethoprim/sulfamethoxazole) had lower susceptibility to fosfomycin. None of the 166 enterococcal isolates studied was found to be susceptible to fosfomycin. These comprised 115 *E. faecalis* and 51 *Enterococcus faecium* isolates; 7 (6.1%) and 19 (37.3%), respectively, were vancomycin-resistant. Finally, 5.5% of the 73 *Corynebacterium* spp. isolates studied were susceptible to fosfomycin.

4. Discussion

The main finding of this study, which evaluated recent Gram-positive non-urinary isolates collected at a university hospital in Greece, is that fosfomycin exhibits high in vitro antimicrobial activity against *S. aureus,* including meticillin-resistant *S. aureus* (MRSA). Fosfomycin also shows activity against a substantial proportion of coagulase-negative staphylococci. Fosfomycin may be active against some *S. pneumoniae* isolates (particularly those without a MDR phenotype) as well as other streptococcal isolates, including *Streptococcus pyogenes*. However, it appears to be inactive against enterococcal isolates.

Previous studies have also shown high in vitro susceptibility of MRSA to fosfomycin. A recent systematic review on this issue identified 22 relevant studies, the majority of which showed susceptibility of MRSA isolates to fosfomycin of

>90% [8]. Other studies have shown that fosfomycin can be active against penicillin-non-susceptible *S. pneumoniae* [8]. It should be mentioned, however, that the majority of the aforementioned studies referred to isolates collected in relatively distant periods in the past. It is also noteworthy that fosfomycin can modify the expression of altered penicillin-binding proteins in MRSA and penicillin-non-susceptible *S. pneumoniae*, resulting in synergy with β-lactams [9,10].

An important issue for the interpretation of data on antimicrobial susceptibility to fosfomycin refers to the choice of appropriate susceptibility breakpoints. The relevant breakpoints that have been issued by major pertinent organisations vary considerably. Moreover, the CLSI breakpoints used in this study refer to urinary isolates of *E. faecalis.* Recently, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) issued fosfomycin minimum inhibitory concentration (MIC) breakpoints for staphylococci that are not site-specific. The latter breakpoints are one dilution stricter than the CLSI MIC breakpoints for *E. faecalis* that correspond to the disk zone diameter breakpoints used in our study.

Fosfomycin has bactericidal antimicrobial activity through a unique mechanism of action that involves inhibition of MurA, an enzyme that catalyses the first committed step in bacterial cell wall synthesis [4]. This may partly explain the low levels of cross-resistance that have been noted between fosfomycin and other antibacterial agents [5]. However, mutational resistance to fosfomycin can arise rather rapidly in

vitro after exposure to this agent [11]. Moreover, resistance determinants encoding for fosfomycin resistance have been identified on plasmids [12]. In Greece, fosfomycin was off the market during the period of our study. Whether resistant strains will predominate if fosfomycin is used at large for the treatment of MRSA infections is thus a matter of concern.

Fosfomycin has been mainly used as single-dose oral therapy for acute uncomplicated cystitis, in the form of fosfomycin tromethamine [5]. The disodium salt of fosfomycin is also available in certain countries for intravenous (i.v.) administration. Although fosfomycin has not been formally evaluated for the treatment of infections other than those involving the urinary tract, cumulative experience from the use of i.v. fosfomycin for various types of systemic infections appears to be favourable [4]. The pharmacokinetic or pharmacodynamic properties of this drug do not limit its role to the treatment of urinary tract infections only [13]. Apart from urine, fosfomycin appears to achieve clinically relevant concentrations in tissues that MRSA infections can involve, such as skin and subcutaneous tissue, bone, lungs and serum. However, clinical evidence regarding the use of fosfomycin for the treatment of MRSA infections is scarce and consists only of a few reports that have generally showed effectiveness of fosfomycin therapy, commonly in combination with other active agents, in cases of serious staphylococcal infections [8].

A particular value of fosfomycin in the treatment of MRSA infections lies in the fact that it can be administered orally. Thus, it could prove to be a therapeutic option for patients with hospital-acquired MRSA who need to complete a course of treatment at home. Additionally, it could prove a useful option for the treatment of MRSA infections acquired in the community, as resistance of community-acquired MRSA to commonly used oral antibiotics is increasing [14]. Furthermore, some of the agents that are active against community-acquired MRSA may be the cause of worrisome toxicity in children, where a substantial proportion of these infections occur, whilst fosfomycin has generally proved safe when used in this population [15].

In conclusion, this study indicates that fosfomycin can have substantial antimicrobial activity against staphylococcal isolates, especially against *S. aureus* regardless of the presence of meticillin resistance. We suggest further microbiological and clinical evaluation of fosfomycin in this regard, particularly as the armamentarium of orally available anti-MRSA drugs is diminishing.

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Competing interests

None declared.

Ethical approval

Not required.

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Table 1

Main characteristics of the 1846 Gram-positive non-urinary isolates studied

Characteristic	*n* (%)
Origin of patient	
Surgical wards	441 (23.9)
Medical wards	409 (22.2)
Intensive Care Unit	386 (20.9)
Dialysis unit	46 (2.5)
Adult outpatient units	216 (11.7)
Paediatric units	294 (15.9)
Inpatients	283 (96.3)
Outpatients	11 (3.7)
Other hospital units	54 (2.9)
Culture specimen	
Blood	723 (39.2)
Purulent collections or surgical specimens	552 (29.9)
Upper respiratory tract	166 (9.0)
Lower respiratory tract	129 (7.0)
Normally sterile fluids	126 (6.8)
Obstetric and gynaecological specimens	51 (2.8)
Removed catheter tips	39 (2.1)
Other clinical sites	60 (3.3)

Table 2

Susceptibility to fosfomycin and other selected antibacterial agents of the staphylococcal and streptococcal isolates tested

Drug	Susceptible isolates [*n*/*N* (%)]						
	Staphylococcus aureus	MRSA [a]	CoNS [b]	*Streptococcus pneumoniae*	MDR *S. pneumoniae* [c]	*Streptococcus agalactiae*	Other streptococci [d]
AMC	ND	ND	ND	18/18 (100)	1/1 (100)	24/24 (100)	55/56 (98.2)
Ampicillin	40/314 (12.7)	ND	18/374 (4.8)	18/19 (94.7)	ND	24/24 (100)	51/52 (98.1)
SAM	198/314 (63.1)	ND	90/374 (24.1)	ND	ND	ND	ND
Cefoxitin	24/88 (27.3)	ND	ND	ND	ND	ND	ND
Cefuroxime	198/314 (63.1)	ND	68/351 (19.4)	25/42 (59.5)	6/23 (26.1)	ND	ND
Ceftriaxone	ND	ND	ND	41/42 (97.6)	22/23 (95.7)	ND	ND
Clindamycin	330/419 (78.8)	93/130 (71.5)	313/961 (32.6)	31/42 (73.8)	12/23 (52.2)	19/25 (76.0)	56/68 (82.4)
Ciprofloxacin	287/331 (86.7)	47/66 (71.2)	285/567 (50.3)	ND	ND	ND	ND
Erythromycin	304/419 (72.6)	85/130 (65.4)	243/961 (25.3)	22/42 (52.4)	3/23 (13.0)	19/25 (76.0)	41/67 (61.2)

Fosfomycin	416/419 (99.3)	129/130 (99.2)	745/961 (77.5)	26/42 (61.9)	10/23 (43.5)	14/25 (56.0)	31/68 (45.6)
Gentamicin	402/419 (95.9)	121/130 (93.1)	523/961 (54.4)	ND	ND	ND	ND
Imipenem	198/314 (63.1)	ND	106/390 (27.2)	ND	ND	ND	ND
Linezolid	417/417 (100)	128/128 (100)	915/933 (98.1)	41/41 (100)	23/23 (100)	25/25 (100)	67/67 (100)
Oxacillin	116/182 (63.7)	ND	83/300 (27.7)	ND	ND	ND	ND
Penicillin	53/419 (12.6)	ND	68/932 (7.3)	20/42 (47.6)	2/23 (8.7)	25/25 (100)	58/62 (93.5)
Rifampicin	400/419 (95.5)	119/130 (91.5)	837/961 (87.1)	39/42 (92.9)	20/23 (87.0)	24/25 (96.0)	64/68 (94.1)
Tetracycline	298/419 (71.1)	72/130 (55.4)	728/960 (75.8)	20/42 (47.6)	5/23 (21.7)	3/25 (12.0)	32/68 (47.1)
SXT	410/419 (97.9)	124/130 (95.4)	576/961 (59.9)	18/42 (42.9)	3/23 (13.0)	0/25 (0)	27/68 (39.7)
Vancomycin	419/419 (100)	130/130 (100)	954/961 (99.3)	42/42 (100)	23/23 (100)	25/25 (100)	68/68 (100)

MRSA, meticillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci; MDR, multidrug-resistant; AMC, amoxicillin/clavulanic acid; SAM, ampicillin/sulbactam; SXT, trimethoprim/sulfamethoxazole; ND, no data.

[a] The 130 MRSA isolates constitute a subset of the 419 *S. aureus* isolates.

[b] Includes *Staphylococcus epidermidis*, *Staphylococcus saprophyticus* and *Staphylococcus haemolyticus*.

[c] The 23 MDR *S. pneumoniae* isolates constitute a subset of the 42 *S. pneumoniae* isolates.

[d] Other streptococci include (i) α-haemolytic streptococci other than *S. pneumoniae* and (ii) β-haemolytic streptococci other than *S. agalactiae* or *S. pyogenes.*