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Clinical Value of Intravenous Fosfomycin Combinations

İntravenöz Fosfomisin Kombinasyonlarının Klinik Değeri

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ABSTRACT

Aim: Due to the increasing number of Multi-Drug Resistance (MDR) and Extensively Drug Resistant (XDR) pathogens and the difficulties in developing new antibiotics, some combinations are being tried. Fosfomycin is a phosphonic acid derivative UDP-N-acetyl glucosamine (MurA) inhibitor. Fosfomycin inhibits bacteria cell wall synthesis in its first step. It acts against both gram-positive and gram-negative Multi-Drug Resistance (MDR) and Extensive Drug-Resistant (XDR) bacteria. It prevents bacterial invasion into the urinary system and respiratory tract epithelium. It was aimed to evaluate the clinical and microbiological response rates of intravenous fosfomycin treatment in gram-negative MDR and XDR bacterial infections in this study.

Methods: Total 77 patients from four different centers where used intravenous fosfomycin treatment were involved to the study. It was evaluated clinical and microbiological response in 72 hours after the beginning of treatment and at the end of treatment. Clinical and microbiological response have been evaluated in the study population.

Results: While 41 of the patients were female (53.2%), 36 were male (46.8%), it is found that their mean age was 60.5. Clinical response rates 72 hours after the initiation of treatment and at the end of treatment were 46 (59.7%) and 45 (58.4%), respectively. Microbiological eradication rate was achieved in 40 (51.9%) patients in the first 72 hours and in 39 (50.6%) patients at the end of the treatment.

Conclusions: As a result, fosfomycin may be an alternative in combination therapy due to its low side effect profile and lack of drug interaction in the treatment of MDR and XDR pathogens.

Key Words: Fosfomycin; pharmaceutical preparations, drug resistance.

ÖZET

Amaç: Multi-Drug Resistance (MDR) ve Extensively Drug Resistant (XDR) patojenlerin artması ve yeni antibiyotiklerin geliştirilmesindeki zorluklar nedeniyle, bazı kombinasyonlar denenmektedir. Fosfomisin, fosfonik asit derive UDP-N-asetil glukozamin (MurA) inhibitörüdür. Fosfomisin bakteriyel hücre duvarı sentezini ilk aşamada inhibe eder. Gram negatif ve gram pozitif Multi-Drug Resistant (MDR) ve Extensive Drug-Resistant (XDR) bakterilere etkilidir. Üriner sistem ve respiratuar sistem epiteline invazyonu engeller. Bu çalışmada, gram negatif MDR ve XDR bakteriyel enfeksiyonlarda intravenöz fosfomisin tedavisinin klinik ve mikrobiyolojik yanıt oranlarının değerlendirilmesi amaçlanmıştır.

Gereç ve yöntemler: Dört farklı merkezden intravenöz fosfomisin kullanılan toplam 77 hasta çalışmaya alındı.

Bulgular: Hastaların 38'i (%52,1) kadın, 35'i (%47,9) erkekti. Yaş ortalamaları 60,1 idi. Tedavi başlangıcından 72 saat sonra ve tedavi bitiminde klinik yanıt oranları sırasıyla 46 (%59,7) ve 45 (%58,4) olarak gözlendi. Mikrobiyal eradikasyon oranı ilk 72 saatte 40 (%51,9) hastada ulaşılmışken, 39 (%50,6) hastada tedavi sonunda ulaşılmıştır.

Sonuç: Sonuç olarak, MDR ve XDR patojenlerin tedavisinde düşük yan etki profili ve ilaç etkileşimi olmaması nedeniyle, kombinasyon tedavisinde bir alternatif olabilir.

Anahtar kelimeler: Fosfomisin; ilaç kombinasyonları, ilaç direnci.

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Fosfomycin, which is in use in Europe, was first found in Spain in 1969. It was manufactured from type of Streptomyces but can be produced synthetically today (1, 2). For many years, the fosfomycin has been used in the treatment of urinary tract infections (UTI) which its oral form is uncomplicated. Nowadays, high doses of fosfomycin by combining with other antibiotics can be used in fosfomycin resistant bacterias related infections, in patients who do not respond to treatment or who are intolerant to antibiotics, especially in the treatment of severe infections of intensive care patients (1).

Due to the increasing number of Multi-Drug Resistance (MDR) and Extensive Drug-Resistant (XDR) pathogens and the difficulties in developing new antibiotic combinations, old antibiotics have resurfaced. In this study, we want to determine the responses to fosfomycin in the treatment of MDR and XDR pathogens. So that, we can contribute to literature about high doses fosfomycin (1).

The alternative treatment options have been come into use all over the world due to the increasing antibiotic resistance. Due to the increasing number of MDR and XDR pathogens and the difficulties in developing new antibiotics combinations with tigecycline, sulbactam, aminoglycosides, rifampicin, fosfomycin and/or carbapenems are being tried (1). Fosfomycin is a phosphonic acid derivative. UDP-N-acetyl glucosamine (MurA) inhibitor (2,3). Thus, it inhibits bacteria cell wall synthesis in its first step. It acts against both gram-positive and gram-negative MDR and XDR bacteria. It prevents bacterial invasion into the urinary system and respiratory tract epithelium. Immunodilator effect, effective on biofilm structure, increases neutrophilic phagocytosis even in chronic renal failure (CRF) and transplant patients (2).

It is used in frequent intervals and high doses in cases caused by fosfomycin resistant bacteria, in patients who do not respond to treatment or who are intolerant to antibiotics, especially in the treatment of severe infections of intensive care patients, by combining with other antibiotics (2–4). It was aimed to evaluate the clinical and microbiological response rates of intravenous fosfomycin treatment in gram-negative MDR and XDR bacterial infections in this study.

Materials and Methods

In this study, the findings of total 77 patients from four different centers where used intravenous fosfomycin treatment between October 2018 and September 2019 were retrospectively evaluated. The study was conducted in accordance with the Declaration of Helsinki. Research Ethics committee approval was received from Pamukkale University Faculty of Medicine Ethics Committee. Demographic characteristics, medical history and treatment indication, fosfomycin dose and duration, isolated pathogens, resistance profiles, laboratory parameters, clinical improvement at baseline and after fosfomycin treatment, regression in laboratory parameters, negative control cultures, concomitant antimicrobial agents, and duration of hospital stay were evaluated. It was evaluated clinical and microbiological response in 72 hours after the beginning of treatment and at the end of treatment. Clinical response has been defined as improvement at clinical symptoms (fever, vitals signs, regression at symptoms) and findings. Microbiological response has been defined as the eradication of the underlying pathogen. While evaluating drug side effects, laboratory parameters were also evaluated. All analyzes were performed using SPSS version 23.0 (IBM, USA). Mean, standard deviation and percentage distributions were used as descriptive criteria. An independent-sample T-test was used for the analysis of variables showing non-categorical normal distribution, and the results were given as mean ± standard deviation. Mann Whitney U test was used in groups that did not show normal distribution and it was specified as the median (minimum-maximum).

Results

The data of total 77 patients who applied intravenous fosfomycin treatment were included in the study. While 41 of the patients were female (53.2%), 36 were male (46.8%), it is found that their mean age was 60.5 ± 15.5 (19-95). The response to treatment and complication rates with the demographic and clinical characteristics of the patients are presented in Table 1.

Table 1: Demographic, clinical, microbiological and treatment response characteristics of our patients who used intravenous fosfomycin for treatment in 2018-2019

DEMOGRAPHIC FEATURES	n (%)
GENDER (F/M)	38/35 (52.1 -47.9)
AGE	60.1 ± 15.6 (19-95)
TYPE OF INFECTION	
• Bacteremia	12 (16.4)
• Soft tissue infections	7 (9.6)
• Pneumonia	7 (9.6)
• Urinary tract infections	29 (39.7)
• VIP + catheter related infections	4 (5.5)
• Urosepsis	4 (5.5)
• VIP + sepsis	6 (8.2)
• Soft tissue infection + pneumonia	3 (4.1)
• Intraabdominal infection	1 (1.3)
PATHOGEN MICROORGANISM	
• ESBL (+) *Klebsiella spp.*	28 (38.4)
• *A.baumannii*	20 (27.4)
• ESBL (+) *E.coli*	11 (15.1)
• *A.baumannii.+ P. aeruginosa*	6 (8.2)
• *P.aeruginosa*	5 (6.8)
• MR- CNS	1 (1.4)
• *Citrobacter spp.*	2 (2.7)
ANTIBIOTIC COMBINATION	
• Carbapenem	35 (48)
• Carbapenem + colistin	14 (19.2)
• Colistin	7 (9.5)
• Quinolone	6 (8.2)
• Carbapenem + tigecycline	5 (6.9)
• Tigecycline	3 (4.1)
• Other	3 (4.1)
CLINICAL RESPONSE	
• First 72 hours	46 (59,7)
• End of treatment	45 (58,4)
MICROBIOLOGICAL ERADICATION	
First 72 hours	40 (51,9)
End of treatment	39 (50,6)
SIDE EFFECTS	
Hypernatremia	26 (33,8)
Hypokalaemia	34 (44,2)

MR- CNS: Methicillin Resistant Coagulase Negative Stphylococci

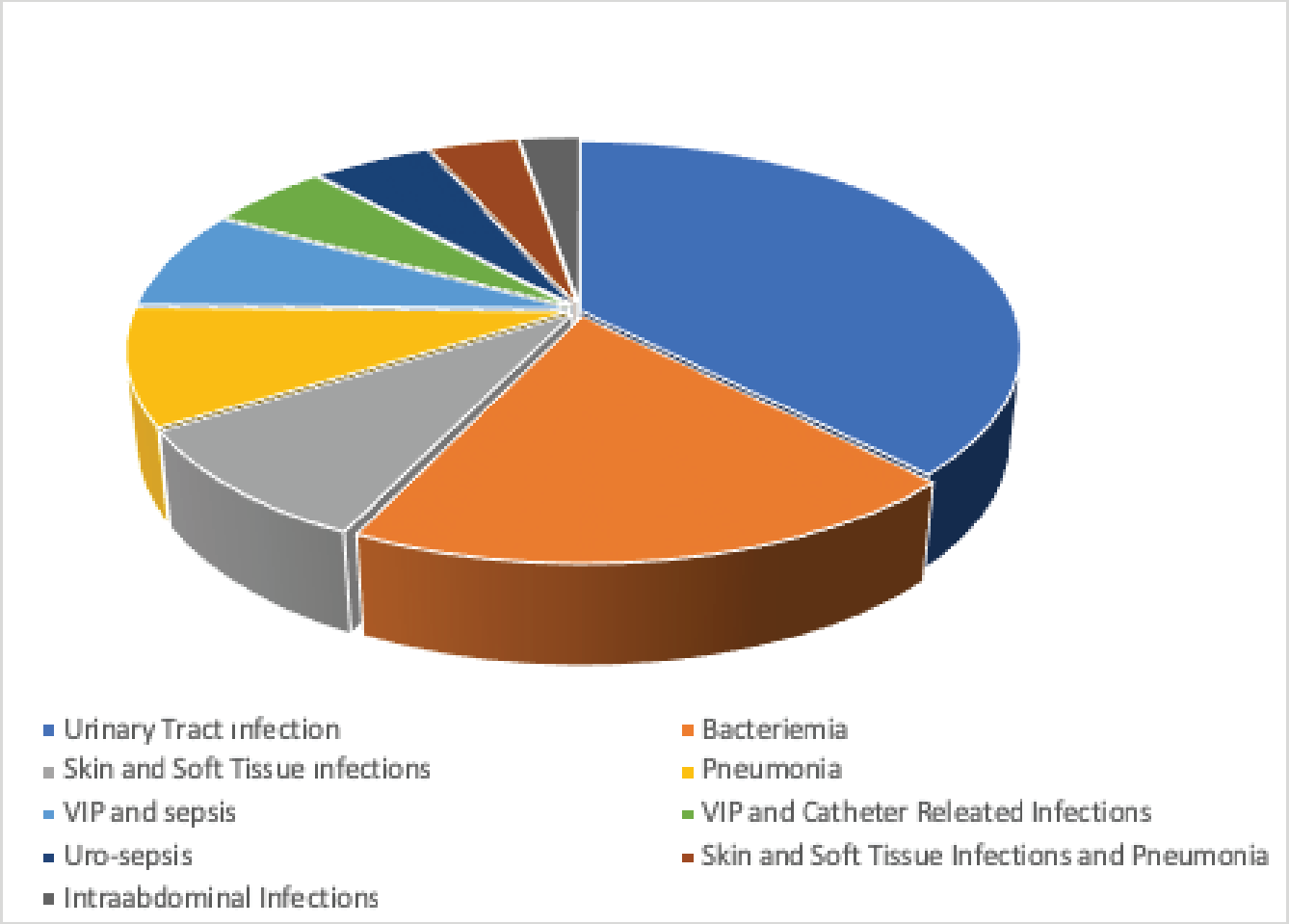

Figure 1: Infections which fosfomycin therapy is used.

The standart dose of fosfomycin was administered as 3x4 g (IV) in patients with normal creatinine levels (adjusted for creatinine clearance in patients with chronic renal failure) and fosfomycin susceptible pathogen related infections. The mean duration of treatment was 11±4.01 days. 29 (39.7%) of the patients who received fosfomycin treatment were followed up with the diagnosis of urinary tract infection and 12 (16.4%) of them with the diagnosis of bacteremia. Other indications were presented in Figure 1.

The bacteria most commonly used in fosfomycin treatment was ESBL (+) Klebsiella spp. (38.4%), A.baumannii (27.4%). Other causative microorganisms were presented in Figure 2. Fosfomycin treatment was combined with most frequent carbapenem 48% and carbapenem+colistin 19.2%. Other combined treatments were presented in Figure 3. It has been found that fosfomycin was mostly used in the treatment of infections grew with Extended Spectrum Beta Lactamase (ESBL) (+) Klebsiella spp. (38.4%), A.baumannii (27.4%) and ESBL (+) E.coli types (15.1%) and combined with carbapenems.

Clinical response rates 72 hours after the initiation of treatment and at the end of treatment were 46 (59.7%) and 45 (58.4%), respectively. Microbiological eradication rate was achieved in 40 (51.9%) patients in the first 72 hours and in 39 (50.6%) patients at the end of the treatment (Table 1). The 28-day all-cause mortality rate was found as 22 (28.6%). When the side effects were evaluated, hypernatremia was found in 26 (33.8%) patients and hypokalemia in 34 (44.2%) patients (Table 1).

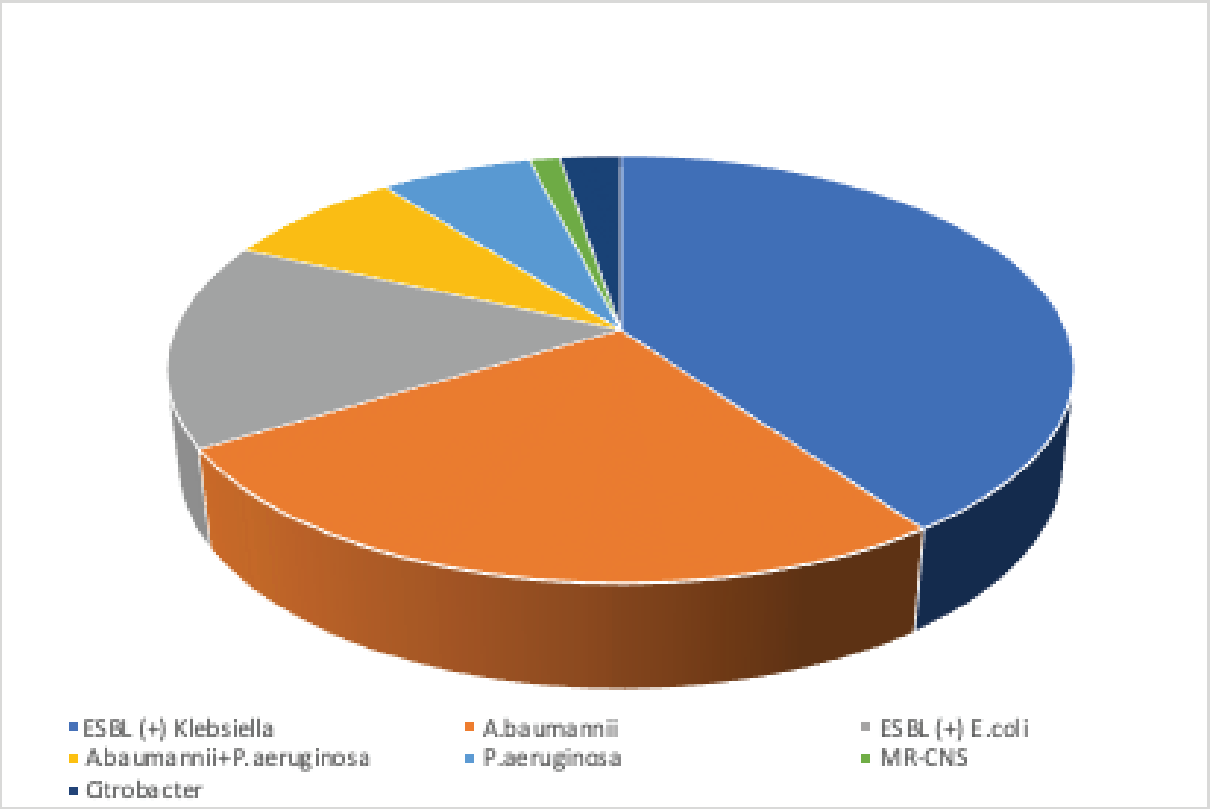

Figure 2: Bacteria which fosfomycin therapy is used.

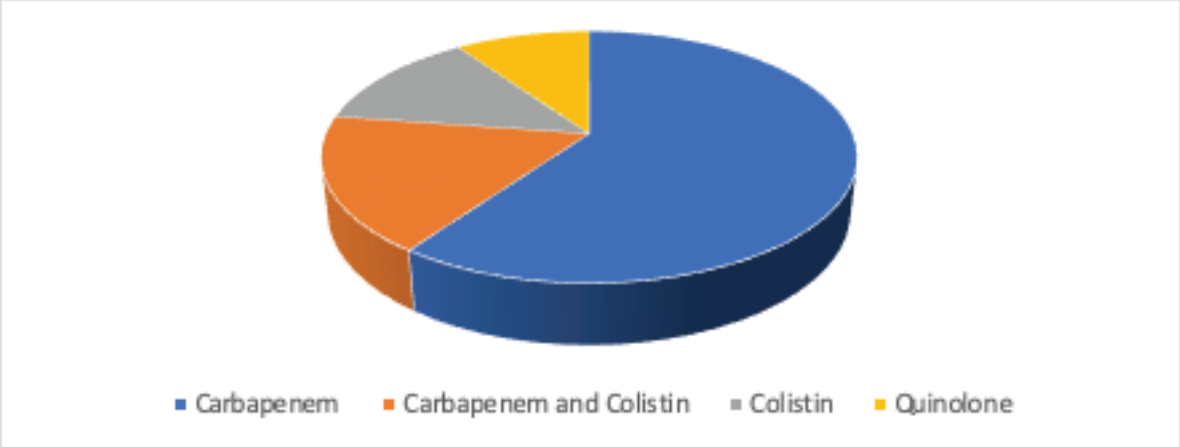

Figure 3: Fosfomycin combinations

Discussion

Intravenous fosfomycin treatment has been applied in combination with other antibiotics at frequent intervals and high doses in the treatment of bacteremia progressed with severe gram negative MDR and XDR bacteria, soft tissue infection, pneumonia, urinary system infection, catheter infection, urosepsis, sepsis and intraabdominal infections, especially in intensive care patients in this study. In the literature, it has been reported that it was most frequently used in sepsis, pneumonia, UTI, bone infections, central nervous system (CNS) infections and most urinary system infections caused by the P. aeruginosa, P. mirabilis, E.coli, K. pneumoniae in the meta-analysis of 128 clinical studies in which 5527 patients using fosfomycin were evaluated, and was not found difference in clinical and microbiological effectiveness by comparison with other antibiotic (5). Compared to this study, where the factors and foci of infection were similar, the sample was smaller in our study and no comparison was made with other antibiotics. The microbiological and clinical response rates of the patients receiving fosfomycin were evaluated, and the response rates at the 72nd hour of treatment and at the end of treatment were found to be 50.6-59.7%.

Total 209 patients who administered fosfomycin due to bacteremia /sepsis, CNS infections, pneumonia, ventilator-associated pneumonia (VAP), bone / joint infections and abdominal infections from a total of 20 centers in Germany and Austria were evaluated. In this study, 24.4% of pathogens were found as MDR pathogens. It was reported that 81.3% clinical success was observed with fosfomycin combination in this study (6). We found clinical response

rate (59.7 %) lower than this study. The reason for this may be the different number and the proportional difference of microorganisms that included the study, the time of initiation of treatment, and differences in underlying comorbid factors.

In our study; fosfomycin was mostly used in the treatment of infections grew with ESBL (+) Klebsiella spp., A.baumannii and ESBL (+) E.coli. It was found that in vitro activity of fosfomycin was good on ESBL (+) Enterobacteriaceae strains in many studies. In a study; 16,000 ESBL (+) E.coli was examined and the fosfomycin activity was found to be >80% in 2005-2011. It has been reported that ciprofloxacin resistance was 78.2%, co-trimaxazole resistance was 62.3%, and amoxicillin clavulonate resistance (AMC) resistance was 55.3% in this study (7). In another study; it has been reported that fosfomycin resistance was 2.6-10% in ESBL (+) E.coli (8). The sensitivity of fosfomycin was found to be 39-100% in the study in which Carbapenemase-producing Enterobacteriaceae (Carbapenemase-producing - KPC (+) K.pneumoniae) strains were evaluated (9). In the study in which 390 Enterobacteriaceae strain which has colistin resistance was evaluated, it was found that the sensitivity of fosfomycin was 100% (10).

It should not be used alone in the treatment of infections caused by MDR or XDR strains that make carbapenemes or panresistant strains. When it is used as monotherapy, resistant populations increase within 24 hours. Resistance development in fosfomycin monotherapy is 3.4%. Monotherapy is only recommended for urinary tract infections (4,11). It is thought that the development of resistance to fosfomycin may decrease with combination therapies (4,12). In our study, IV fosfomycin treatment was administered as combination therapies. Antibiotic combination which fosfomycin was used most commonly, was the combination of carbapenem and carbapenem + colistin. In the INCREMENT study, it was reported that mortality decreased with early combination in sepsis due to carbapenemase producing bacteria (85% KPC (+) Klebsiella) (13).

In the ZEUS study, data from 465 patients, most of whom had gram-negative bacterial infections, from 16 countries were evaluated. Fosfomycin (72.3%) and Piperacillin-Tazobactam (74.7%) were used for the treatment of E.coli strains causing complicated UTIs, and the results were compared. In this study; it was found that clinical success with piperacillin-tazobactam was 91.6% and microbiological eradication was 56.2% while clinical success with fosfomycin was 90.8%, and microbiological eradication rate was 65.8% (14). In our study, the clinical response rate and the microbiological eradication rate at the end of treatment were 58.4% and 50.6%, respectively. Response rates were found to be lower in our study when compared to this study. This is because the response rates for UTI caused by E.coli strains were evaluated in the ZEUS study. In our study; Klebsiella spp and Acinetobacter spp strains are more common than E.coli.

In vitro studies; it was found that bacteria such as ESBL, E. coli and Klebsiella that does not produce carbapenemase, has 100% sensitivity to fosfomycin. In some studies, in vitro fosfomycin combinations of MDR gram negatives have been investigated, and in OXA-48 positive Klebsiella pneumoniae strains; it was found that fosfomycin + imipenem was 42% synergistic, fosfomycin+meropenem was 33% synergistic, fosfomycin+tigecycline was 33% synergistic, colistin+ fosfomycin was antagonistic (15). In invitro studies investigated KPC-2 Klebsiella strains, the combination of imipenem, meropenem, doripenem, colistin, netilmicin was found to be 30-74% synergistic. Generally, it has been reported that good results are obtained with combinations containing carbapenem, antagonism of tigecycline and fosfomycin may be (16). Colistin + fosfomycin and colistin + tigecycline were found to be less synergistic for NDM-1 (+) Enterobacteriaceae strains (16). In invitro studies performed with XDR A. baumannii producing OXA-23, aminoglycoside, sulbactam or colistin and fosfomycin was found to be synergistic (4,12).

In our study, Klebsiella spp strains were the most frequently detected strains, and the most frequently used combination was; fosfomycin + carbapenem (48%), and the second most common combination was fosfomycin+colistin+carbapenem (14%). In invitro fosfomycin combination studies evaluating MDR gram-negative bacteria, it was found that fosfomycin+ amikacin was most effective combination in Klebsiella spp strains which has colistin resistant. The fosfomyci+colistin combination was also found to be superior according to monotherapy It was found that fosfomycin in Pseudomonas aeruginosa strains was 13-73% synergism in combination with carbapenem, colistin, netilmicin and tigecycline (11).

In 94 patients infected with Acinetobacter baumannii which has carbapenem resistant; Colistin and colistin + fosfomycin treatment (7-14 days) were compared and a significantly better microbiological response and clinical outcome was observed with combination therapy compared to monotherapy (18). In a meta-analysis, the results of 128 studies were evaluated and the clinical studies of 5527 patients in which fosfomycin was used and included in the study were analysed. In this meta-analysis, it has been reported that it is more effective than colistin therapy alone for A.baumannii of fosfomycin + colistin which has carbapenem-resistant (19).

In a meta-analysis of 23 studies investigated pneumonia due to resistant acinetobacter; clinical cure rate in inhaler colistin + intravenous colistin+sulbactam combination, and microbiological eradication rate in fosfomycin+intravenous colistin+sulbactam combination were found to be more effective compared to only colistin therapy (20). In our study, combination therapy was frequently used in the treatment of infections with resistant microorganisms, similar to the studies in the literature.

In another study; 104 cases which were found sepsis due to K. pneumoniae with carbapenem resistant were evaluated. Although ten of the treated strains were resistant to fosfomycin, the mortality rate was 7.7% in patients administered with fosfomycin combination therapy and 24.6% when fosfomycin combination was not used (21). In our study, the 28-day mortality rate was found to be 28.8% in the treatment of all agents and foci of infection included in the study. However, no sub-analysis was performed for agents and foci of infection. In our study, fosfomycin and linezolid treatment was used for gram (+) bacteria (MRSA) in only one

patient with blood clinical response was received. In the literature; it was reported that it was synergistic with beta lactam or glycopeptides in studies evaluated the effectiveness of fosfomycin in gram-positive bacterial infections (5,22). For MRSA strains; it was reported that combinations of fosfomycin+linezolid, fosfomycin+ vancomycin, fosfomycin+daptomycin and fosfomycin+ fusidic acid was synergistically effective (2) .

The sensitivity of MRSA to fosfomycin was found between >90% in twelve of 22 studies investigated fosfomycin resistant in stems of MRSA, Vancomycin resistant enterococci (VRE) and S.pneumoniae (PSP) with penicillin resistant, and 50-90% in seven of them, cumulative sensitivity rate was (87.9%). It was reported that there was a sensitivity of 30.3% in VRE strains and 87.2% in PRSP strains (23,24).

Adverse events of fosfomycin are i) gastrointestinal side effects reported in the literature; diarrhea, nausea, vomiting, abdominal pain, pseudomembranous colitis, hepatitis, cholestasis, jaundice, ii) skin side effects; rash, pruritus, urticaria, angioneurotic edema, anaphylactoid shock, iii) general side effects; edema, phlebitis, tachycardia, weakness, anorexia, dyspnea, iv) neurological side effects; headache, confusion, dizziness, visual impairment, v) hematological side effects; leukopenia, agranulocytosis, neutropenia, thrombocytopenia, pancytopenia, aplastic anemia, eosinophilia, vi) metabolic side effects; hypernatremia, hypokalemia, ALT, AST, ALP going up (25). In our study; hypernatremia was observed at a rate of 32.9% and hypokalemia at a rate of 43.8%.

Conclusion

The treatment decision should be made according to the location of the infection, the type of carbapenemase, liver and kidney function values of the patient, comorbidities and the resistance profile of the strains in our country. Synergy test should be done for the isolated strain. We think that fosfomycin may be an alternative in combination therapy due to its low side effect profile and lack of drug interaction in the treatment of MDR and XDR pathogens.

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