

Retrospective Evaluation of Intravenous Fosfomycin in Multi-drug Resistant Infections at A Tertiary Care Hospital in İstanbul

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ABSTRACT

Introduction: Fosfomycin has started to be used again as a possible therapeutic alternative in cases injected with resistant bacterial pathogens. Its primary mechanism of action is inhibition of the first step of cell wall synthesis; This mechanism is effective against both Gram-positive and Gram-negative bacterial groups. However, its clinical efficacy against bacteria that develop multidrug resistance is largely unknown. Therefore, we aimed to evaluate the clinical and microbiological efficacy of intravenous Fosfomycin in a tertiary care center.

Methods: The group of adult patients aged 18 years and over who applied to the hospital between January 2018 and December 2022 and were given intravenous fosfomycin therapy for at least 24 hours due to any infection were retrospectively analyzed.

Results: 71 patients were included in our study. The female/male ratio of these patients was 35/36, and the mean age was 61.5 ± 17.0 (18-84). The average time to treatment was 10.6 days ($11.3 - 11.4$). 22 patients (31%) from Intensive Care Unit and 49 (69%) patients from other clinics were included in the study. 18 bacteremia (26%), 15 pneumonia (21%), 14 wound infections (19%), 13 ventilator-associated pneumonia (18%), 5 urinary tract infections (UTI) (8%), 4 abdominal infections (6%) and 2 endocarditis (3%). Detected causative microorganisms were 18 Extensively Drug-Resistant (XDR) *Klebsiella pneumoniae*, pandrug resistant *Klebsiella pneumoniae* (17.5%), 5 MRSA (12.5%), 5 pandrug resistant *Pseudomonas aerinosa* (12%), 4 *Escherichia coli* (10%), 1 *Acinetobacterbaumannii* (2.5%) and 1 *Enterobacter spp.* (2.5%). Looking at the underlying diseases, one of our patients had diabetes mellitus and another patient had chronic renal failure. Mean procalcitonin (PCT) and C reactive protein (CRP) (cutoff value 0.5 ng/mL) values were 2.53 ± 1.2 ng/ml and 89.7 ± 21.9 mg/dl, respectively. Median sodium (Na), potassium (K), AST, ALT, and creatinine values of the patients before and after fosfomycin IV treatment were calculated and there was no statistically significant difference.

Clinics combined with fosfomycin IV were as follows: 31 meropenem (44%), 15 colistin (26%), 18 tigecycline (26%), 3 vancomycin (4%), 3 amikacin (4%) and 1 daptomycin (1%).

Conclusions: According to the results of our study, it was seen that Fosfomycin is a safe and effective option in the treatment of multidrug-resistant infections. Accordingly, our results are compatible with the literature.

Keywords: Fosfomycin, multidrug-resistant bacteria.

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I. INTRODUCTION

Fosfomycin, derived from *Streptomyces fradiae* in 1969, is a phosphoenolpyruvate (PEP) analog and broad-spectrum antibiotic. It has the smallest molecular mass among the antibiotics available, with a weight of 138 Da. It is a strong polar molecule that can dissolve in water. Fosfomycin has been used for a long time in the treatment of various

infections in many European countries and in our country. The Food and Drug Administration (FDA) approves the use of the oral form of fosfomycin only for the treatment of uncomplicated cystitis [1].

Fosfomycin is one of the bactericidal antibiotics known to be effective against a variety of Gram-positive and Gram-negative bacteria [3], [4].

With the recommendation of Fosfomycin as a first-line

agent in the treatment of acute and uncomplicated urinary tract infections and pyelonephritis in women by the American Society of Infectious Diseases (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the clinical use of this agent has increased significantly [2].

Antibiotic resistance is an important public health problem worldwide and threatens our ability to prevent and treat infections [5].

Reusing old antibiotics such as Fosfomycin is a new strategy for treating resistant bacteria, as few antimicrobials are available [6].

Due to the difficulties encountered in the treatment of infections caused by both Multi-drug resistant (MDR) and extensively drug-resistant (XDR) bacteria, the use of both oral and intravenous (IV) forms of Fosfomycin in the treatment of infections with these bacteria have become very popular. Fosfomycin has important advantages such as low resistance rates in vitro, pharmacokinetic/pharmacodynamic advantages, in vivo activity and clinical efficacy, and high tolerability and safety [1].

Specifically, Fosfomycin is highly active against *Staphylococcus aureus* and *Enterococcus* spp., with significant activity against Gram-negative bacteria such as *Escherichia coli* and *Klebsiella pneumoniae*, including Extended-spectrum beta-lactamases (ESBL) and carbapenemase-producing bacteria [7].

It is usually used in combination with another agent when first-line agents are not effective. Some clinical studies have examined the activity of IV Fosfomycin [8].

Here, we aim to present the clinical and laboratory findings of patients treated with IV fosfomycin.

II. MATERIALS AND METHODS

Demographic and clinical characteristics and laboratory values of patients aged 18 years and older who were treated with IV Fosfomycin for at least 24 hours for any infection between January 2018 and December 2022 were obtained retrospectively from the hospital health information system. Written informed consent and approval of the Research Hospital Ethics Committee were obtained (number 2020.2/09-294, dated January 20, 2021).

Fosfomycin treatment dose and duration were determined by a doctor specialized in infectious diseases according to the type and severity of the infection in line with international

guidelines.

EUCAST has determined the gold standard method for susceptibility determination for fosfomycin as the agar dilution method. Standardized methods for antimicrobial susceptibility testing of fosfomycin have been published by the Clinical and Laboratory Standards Institute (CLSI) [9] and the European Committee for Antimicrobial Susceptibility Testing (EUCAST) [10].

A. Statistical Methods

Descriptive statistics of the data included the mean, standard deviation, median, minimum, maximum, frequency, and ratio values. Kolmogorov-Smirnov test was used for the variable distribution measurement. The dependent quantitative data was analyzed by utilizing the Wilcoxon test. The SPSS 28.0 version was used in the statistical analysis.

III. RESULTS

71 patients were included in our study. The female-male ratio was 35/36, and the mean age of the patients was 61.5 ± 17.0 (18-84). The median duration of treatment was 10.6 days (11.3 +11.4). 22 patients (31%) from the Intensive Care Unit (ICU) and 49 (69%) patients from other clinics were included in the study. Patients were diagnosed with 18 bacteremia (26%), 15 pneumonia (21%), 14 wound infections (19%), 13 ventilator-associated pneumonia (18%), 5 UTIs (8%), 4 abdominal infections (6%), and 2 endocarditis (3%). 41 causative microorganisms were detected: 18 Extensively Drug-Resistant (XDR) *Klebsiella pneumoniae*, 7 pandrug-resistant (PDR) *Klebsiella pneumoniae* (17.5%), 5 MRSA (12%), 5 PDR-*Pseudomonas aeruginosa* (12%), 4 *Escherichia coli* (*E. Coli*) (10%), 1 *Acinetobacter baumannii* (*A. baumannii*) (2.5%) and 1 *Enterobacter* sp. (2.5%) were detected (Table I). Comorbidities were diabetes mellitus (DM) in 1 patient and chronic renal failure (CRF) in 1 patient.

The mean procalcitonin (PCT) and C reactive protein (CRP) (cutoff value 0.5 ng/mL) values were 2.53 ± 1.2 ng/ml and 89.7 ± 21.9 mg/dl, respectively. Median sodium (Na), potassium (K), AST, ALT, and creatinine values of the patients before and after fosfomycin IV treatment were calculated, and there was no statistically significant difference (Table II).

When the antibiotics combined with fosfomycin IV were examined, it was found that 31 meropenem (44%), 15 colistin (26%), 18 tigecycline (26%), 3 vancomycin (4%), 3 amikacin (4%), 1 daptomycin (1%) seen (Table III).

TABLE I: DISTRIBUTION OF ISOLATED MICROORGANISMS N (%)

Microorganism name	Types of clinical samples				Total (n=41) %
	Blood	Wound	Urine	Sputum/ Bronchial lavage	
<i>Klebsiellapneumoniae</i> PDR	2	2	1	2	7 (17)
<i>Klebsiellapneumoniae</i> XDR	5	7	3	3	18(44)
MRSA	5	0	0	0	5(12)
<i>E. coli</i> PDR	2	0	2	0	4(10)
<i>Acinetobacter baumannii</i>	1	0	0	0	1(2,5)
PDR	1	0	0	0	1(2,5)
<i>Enterobacterspp.</i> PDR	1	0	0	0	1(2,5)
<i>Pseudomonas aeruginosa</i> PDR	1	3	0	1	5(12)

PDR: Pandrug resistant.

TABLE II: LABORATORY VALUES BEFORE AND AFTER USING FOSFOMYCIN

	Before antibiotic		After antibiotic		P
	Mean±SD	Median	Mean±SD	Median	
K	3.95±0.62	3.87	3.94±0.71	3.90	0.66
Creatinine	1.36±1.33	0.87	1.24±1.22	0.76	0.05
Na	140.6±8.2	138.5	141.0±8.3	139.0	0.87
AST	182.8±1152.5	31.0	62.4±106.1	26.7	0.87
ALT	30.2±43.6	19.0	42.9±89.5	15.9	0.77

K: Potassium, Na: Sodium, AST: Aspartate transaminase, ALT: Alanine transaminase.

TABLE III: ANTIBIOTICS COMBINED WITH INTRAVENOUS FOSFOMYCIN

Antibiotics	Patient number n (%) (n=71)
Meropenem	31 (44)
Tygecycline	18 (26)
Colistin	15 (21)
Vancomycin	3 (4)
Amikacin	3 (4)
Daptomycin	1 (1)

IV. DISCUSSION

In carbapenem-resistant *K. pneumonia* isolates, it showed a synergistic activity of 70% with carbapenems, 36% with colistin, 42% with netilmicin, and 30% with tigecycline. In *K. pneumoniae* isolates producing *Klebsiella pneumoniae* carbapenemase-2 (KPC-2), it showed a synergistic activity of 65% with meropenem and 12% with fosfomycin and 12% with colistin, while it showed no difference with gentamicin. Similarly, combinations of fosfomycin and colistin and fosfomycin and colistin and meropenem showed synergistic effects in *K. pneumoniae* isolates producing VIM (Verona integron-encoded metallo-lactamase) and New Delhi metallo-beta lactamase (NDM). In addition, the combination of fosfomycin-colistin showed an antagonistic effect in OXA-48 producing *K. pneumoniae* isolates [11].

Some studies have examined the effectiveness of Fosfomycin against MDR, XDR and PDR strains of various Gram-negative bacteria. According to these studies, it has been observed that Fosfomycin has an in vitro and in vivo effect against various MDR and XDR Enterobacteriaceae species, including those expressing extended spectrum lactamase (ESBL) and Metallo-beta lactamase (MBL) [12]. Due to the wide range of MIC values and changes in the methods used to determine sensitivity (e.g., agar dilution, microdilution, E-test), it is difficult to compare the results of different studies. In addition, considering that more than 90% of MDR and XDR isolates of some studies are susceptible to Fosfomycin, and in vivo results support in vitro data, Fosfomycin seems to be a promising candidate to treat infections with these pathogens [13].

MDR *P. aeruginosa* and *A. baumannii* are Gram-negative pathogens that are primarily responsible for nosocomial (i.e., hospital-acquired) infections, especially in intensive care units [14].

When microbiological, animal, and clinical studies with non-fermented Gram-negative bacilli are evaluated systematically; It has been concluded that the use of Fosfomycin in the combined treatment of infections caused by MDR *P. aeruginosa* may be a safe and effective treatment option [15]. Fosfomycin, in addition to cystic fibrosis cases with infective pulmonary attacks; It is effective against MDR bacteria, including *P. aeruginosa*, in patients with serious

illnesses and critical conditions [17]. For this reason, additional evaluations are needed in clinical trials, ideally for the use of Fosfomycin in *P. aeruginosa* infections. It should be known that the combination therapy does not prevent the emergence of fosfomycin resistance, even though it has a higher rate of bacterial killing [19].

In a study Kaye *et al.* [20], it has been reported that Fosfomycin is not less effective than piperacillin-tazobactam in the treatment of complicated urinary tract infections, considering its high cure rates and tolerability values.

In laboratory findings, transient and clinically insignificant changes such as increase in eosinophil count, changes in leukocyte and platelet counts, decreases in hematocrit and hemoglobin, and increases in bilirubin, ALT, AST, and alkaline phosphatase (ALP) can be observed [21]. Asymptomatic and mild liver enzyme abnormalities have been reported as a liver side effect of fosfomycin use. Liver function may need to be monitored in patients receiving IV fosfomycin therapy. It has been stated that using fosfomycin in patients with liver failure causes no harm [22].

It can be used in all age groups. However, due to the high sodium load (1 g of fosfomycin contains 14 mmol (320 mg) of sodium), electrolyte imbalances such as hypernatremia or hypokalemia may occur [23].

Hypokalemia and hypernatremia are one of the frequently expected side effects associated with intravenous fosfomycin use. In our study, none of the patients developed complications [22].

V. CONCLUSIONS

According to our findings, Fosfomycin is a safe and effective option for the treatment of multidrug-resistant infections. This is also compatible with literature.

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