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RESEARCH ARTICLE

Factors Affecting Mortality in Resistant Gram-negative Infections Developed in Patients Followed in the Intensive Care Unit and Treated with Fosfomycin

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ABSTRACT

Objective: Our study aimed to investigate the survival rates and factors affecting mortality in Gram-negative infections treated with intravenous (IV) fosfomycin.

Materials and Methods: Patients with microbiologically proven infections in our hospital's intensive care unit (ICU) and who were treated with IV fosfomycin between 2019 and 2021 were included in our study. Demographic characteristics of the patients and initiation of treatment sequential organ failure assessment (SOFA) score, indications for fosfomycin usage, microbiological and clinical response to treatment, and outcome status of the patients were screened.

Results: Of the 96 patients included in the study, 58% (n=56) were male. The survival rate of the patients who received fosfomycin treatment was 27% (n=26). There was no statistically significant difference between the patient's age, gender, and comorbidities according to the outcome. The disease in which fosfomycin treatment was used the most was *pneumonia* (87%), and the most treated bacteria were *Klebsiella pneumoniae* (84%). No statistically significant correlation was found between the outcome status of the patients and the site of infection. However, there was a statistically significant relationship regarding initiation of the treatment SOFA score, type of concomitant antibiotic, clinical response after 72 h, microbiological response at the end of treatment, development of acute renal failure, and development of thrombocytopenia.

Conclusion: Care should be taken when administering combined treatments with fosfomycin to patients followed in the ICU and infected with multi-drug resistant Gram-negative infections. Treatment options are limited in this patient group, which has high mortality rates despite treatment. Our study investigated the parameters that can be used to predict treatment response to fosfomycin. It was thought that it would be beneficial to start the treatment according to these parameters when treating this patient group.

Keywords: Antibacterial drug resistance, fosfomycin, gram-negative bacteria, intensive care unit

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INTRODUCTION

Fosfomycin is a bactericidal antibiotic that inhibits bacterial cell wall synthesis. Due to its different mechanisms of action, it creates a synergistic effect with other antibiotic groups. There are three forms of fosfomycin, two oral and one intravenous (IV). The fosfomycin disodium can be administered with other antibiotics to treat nosocomial infections associated with multi-drug resistant (MDR) Gram-negative bacteria.[1–3]

In recent years, the rate of IV fosfomycin usage has increased in critically ill patients with sepsis or hospital-acquired infections due to MDR Gram-negative bacteria, especially carbapenem-resistant *Klebsiella pneumoniae*.[4–6] Our study aimed to investigate the factors affecting the survival rate and mortality of IV fosfomycin, which is increasingly used in our hospital due to carbapenem-resistant gram-negative bacterial infections.

MATERIALS and METHODS

Study Population and Design

Our study was a retrospective cohort study. Patients hospitalized in the intensive care unit (ICU) of Sultan 2. Abdulhamid

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Han Training and Research Hospital and treated with IV fosfomycin for longer than 72 h between May 2019 and March 2021 were retrospectively screened. Ninety-six patients over 18 years of age with microbiologically proven infections were included in the study. Patients who received fosfomycin treatment for <72 h, did not have a positive culture result, were not followed up in the ICU, and were under 18 were excluded from the study.

Data Collection

Demographic characteristics of the patients such as age, gender, comorbid diseases, initiation of fosfomycin therapy sequential organ failure assessment (SOFA) risk score, indications for use, fosfomycin dose and duration, side effects and combined antibiotic information, as well as microbiological and clinical response to the treatment, outcome, and cause of the patients on the 28th day, were screened. The obtained data were saved in Microsoft Excel.

Microbiology and Culture Procedures

Blood cultures were performed with a BacT/ALERT® 3D system (bioMérieux, Marcy-l'Étoile, France). Bronchial secretion cultures were performed quantitatively and were considered positive when the colony count was ≥10^6 CFU/mL. In addition, all patients followed in the ICU were followed up with a Foley catheter. Therefore, those with bacteria over ≥10^3 CFU/mL in the urine culture were considered positive.

Clinical Response

The regression of signs and symptoms of infection was defined as no need for additional antibiotic therapy.

Microbiological Response

It was determined that the same bacteria did not grow in the control cultures of the treated patients.

Cause of Mortality

The reason stated by the relevant clinic physician in the epicrisis was accepted and recorded.

Side Effects

The effects in the IV fosfomycin undesirable effects section stated by the Turkish Medicines and Medical Devices Agency of the Ministry of Health were examined.[7] In our retrospective study, information on hypernatremia, hypopotassemia, leukopenia, thrombocytopenia, neutropenia, (acute renal failure [ARF]: Increase in serum creatinine concentration of 0.5 mg/dL or more from baseline or 50% decrease from the calculated creatinine clearance value) and increase in liver enzymes above the expected value, which can be determined objectively, were scanned.[8,9]

Statistical Method

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage were given for categorical data and median, minimum, and maximum descriptive values for continuous data. In addition, "Mann Whitney-U Test" was used for the comparisons between groups, "Fisher's Exact Test or Chi-square test" was used for the comparison of categorical variables and "Logistic Regression Analysis" was used to examine the risk factors affecting survival. The results were considered statistically significant when the $p<0.05$.

For our study, approval was obtained from the Hamidiye Ethics Committee with the decision number 18/3 at the meeting dated July 27, 2022 and numbered 2022/18.

RESULTS

A total of 96 patients, 56 (58%) male and 40 (41%) female were included in the study. The 28th-day mortality rate of patients receiving fosfomycin treatment was 72% (n=70). It was determined that 41% (n=29) of the patients died due to the lack of response to treatment, 45% (n=32) of other infectious agents, and 12% (n=9) of comorbid diseases. The distribution of demographic findings according to the outcome of the patients included in the evaluation is given in Table 1. When the table was examined, there was no statistically significant difference between the groups according to the age and gender of the patients ($p>0.05$). At least one other disease was present in 72% (n=69) of the patients and the rate of additional disease in patients who died was higher than in patients who survived. However, the two groups had no statistically significant relationship according to different disease states ($p>0.05$). The mean SOFA score of the patients at the start of fosfomycin was 8.8±3.8, and the SOFA score was significantly lower in the surviving patient group ($p<0.05$).

The most common fosfomycin treatment was *pneumonia* (86%). It was determined that secondary bacteremia developed in 53% of the patients with *pneumonia*. Of the bacteria treated with fosfomycin, 52.1% (50) were MDR and 47.9% (46) were hyper resistant (XDR). The most commonly treated bacteria were *K. pneumoniae* in 84% (n=81), while the others were 8% (n=8) *Acinetobacter* spp. and 7% (n=7) *Pseudomonas aeruginosa*. The distribution by outcome status is given in Table 2. When the table was examined, no statistically significant relationship was found between the outcome status of the patients and the site of infection ($p>0.05$). There was no statistically significant relationship in general

Table 1. Distribution of demographic findings

Demographic and clinical findings	Total (n=96)		Survived (n=26)		Died (n=70)		p
	n	%	n	%	n	%	
Age, mean (years)	72 (30–99)		71 (37–95)		73 (30–99)		0.183
Gender							0.877
Male	56	58	16	62	40	57	
Female	40	42	10	38	30	43	
Treatment initiation SOFA score	9 (0–18)		6 (0–14)		10 (2–18)		0.002
Comorbidities	69	72	16	62	53	76	0.264
CRF	16	17	2	8	14	20	0.221
CHF	12	13	3	12	9	13	1.000
HT	52	54	12	46	40	57	0.466
DM	29	30	5	19	24	34	0.239
COPD	17	18	5	19	12	17	0.772
CAD	14	15	2	8	12	17	0.338

Data are given as n, % or median (min-max). SOFA: Sequential organ failure assessment; CRF: Chronic renal failure; CHF: Congestive heart failure; HT: Hypertension; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; CAD: coronary artery disease

Table 2. Bacteria isolated in patients using fosfomycin and its effect on mortality

Culture	Isolated bacteria	Total		Survived		Died		p
		n	%	n	%	n	%	
Bronchial secretion cultures	*Klebsiella pneumoniae*	28	72	7	64	21	75	0.754
	Pseudomonas aeruginosa	5	13	2	18	3	11	
	Acinetobacter spp.	6	15	2	18	4	14	
Bronchial secretion cultures total		39	40	11	42	28	40	1.000
Bronchial secretion and blood cultures	*Klebsiella pneumoniae*	40	91	10	83	30	94	0.045
	Pseudomonas aeruginosa	2	5	2	17	0	0	
	Acinetobacter spp.	2	5	0	0	2	6	
Bronchial secretion and blood cultures total		44	46	12	46	32	46	1.000
Urine culture	*Klebsiella pneumonia*	3	3	2	8	1	1	0.177
Wound culture	*Klebsiella pneumonia*	2	2	0	0	2	3	1.000
Abscess culture	*Klebsiella pneumonia*	2	2	0	0	2	3	1.000
Secondary bacteremia	*Klebsiella pneumonia*	4	4	1	4	3	4	1.000
Blood culture	*Klebsiella pneumonia*	2	2	0	0	2	3	1.000

in the group with growth in both bronchial secretion and blood culture (bacteremia secondary to *pneumonia*). However, there was a statistically significant correlation between the bacteria isolated in this group and the outcome status of the patients ($p<0.05$). While the rates of *K. pneumoniae* and *Acinetobacter* spp. were higher in the patients who died, the rate of *P. aeruginosa* was lower in those who survived.

The change in clinical findings according to the outcome status of the patients is examined in Table 3. The survival rate was high ($p<0.05$) in the patient groups that received a clinical and microbiological response in which fosfomycin was used only with carbapenems. However, the development of ARF and thrombocytopenia was more common in patients who died ($p<0.05$).

Table 3. The change in clinical findings according to the outcome status of the patients

Clinical and laboratory findings	Total (n=96)		Survived (n=26)		Died (n=70)		p
	n	%	n	%	n	%	
Dose of fosfomycin (gr)	18 (2–24)		24 (6–24)		16 (2–24)		0.269
Combined antibiotic							0.060
Carbapenem	**61**	**64**	**21**	**81**	**40**	**57**	**0.015**
Carbapenem+Tigecycline	**23**	**24**	**2**	**8**	**21**	**30**	**<0.001**
Carbapenem+Colistin	12	13	3	12	9	13	0.083
Clinical response after 72 h	**17**	**18**	**12**	**46**	**5**	**7**	**<0.001**
Microbiological response after 72–96 h	12	13	6	23	6	9	0.081
Post-treatment microbiological response	**38**	**40**	**23**	**89**	**15**	**21**	**<0.001**
Side effects							
Development of acute renal failure	**37**	**39**	**1**	**4**	**36**	**51**	**<0.001**
Hypernatremia	69	72	15	58	54	77	0.103
Hypokalemia	54	56	17	65	37	53	0.385
Hypertension	22	23	7	27	15	21	0.767
Cardiac effect	8	8	2	8	6	9	1.000
Leukopenia	14	15	2	8	12	17	0.338
Thrombocytopenia	**61**	**64**	**10**	**39**	**51**	**73**	**0.004**
Eosinopenia	40	42	7	27	33	47	0.120
High hepatic enzyme	53	55	11	42	42	60	0.187

Data are given as mean (min-max) and n, %

Table 4. Examination of risk factors affecting mortality. Data are given as odds ratio (95% confidence interval)

Clinical and laboratory findings	Univariate analysis		Multivariate analysis	
	OR (%95 CI)	p	OR (%95 CI)	p
SOFA score	**1.23 (1.07–1.40)**	**0.003**	**1.11 (0.89–1.37)**	**0.359**
Clinical response after 72 h	**0.10 (0.03–0.30)**	**<0.001**	0.16 (0.03–1.02)	0.052
Post-treatment microbiological response	**0.04 (0.01–0.14)**	**<0.001**	**0.09 (0.02–0.40)**	**0.002**
Development of acute renal failure	**26.47 (3.40–206.24)**	**0.002**	**28.62 (2.42–337.84)**	**0.008**
Thrombocytopenia	**4.30 (1.66–11.10)**	**0.003**	1.49 (0.36–6.10)	0.580

OR: Odds ratio; CI: Confidence interval; SOFA: Sequential organ failure assessment

Factors affecting survival were analyzed by logistic regression analysis. As a result of univariate analysis, the effects of SOFA score, clinical response after 72 h, a microbiological response at the end of treatment, and development of ARF and thrombocytopenia on survival were statistically significant (p<0.05). When these variables, which were influential in the univariate model, were evaluated in the multivariate model, SOFA score, end-of-treatment microbiological response, and ARF were found to be statistically significant (p<0.05) (Table 4).

DISCUSSION

As in the whole world, the incidence of MDR Gram-negative bacteria is increasing in our country. Therefore, despite being an old agent, IV fosfomycin has become a powerful alternative due to its different mechanisms of action.[3,4] However, the number of studies examining the effect of fosfomycin, which has been increasingly used in recent years, on mortality is limited. The mortality rate was 37.5% in the study of Pontikis et al.,[10] in which they examined patients followed in the

ICU and used IV fosfomycin. Dinh et al.[11] conducted a cohort study of 116 adult and pediatric patients with staphylococcal and pseudomonal MDR infections. This study determined the clinical success rate as 76.8%. In our study, the mortality rate was higher than in other studies and was 73%. However, the mortality rate that developed due to the lack of treatment response was similar 30%. When these two studies were examined, the SOFA score used to predict ICU mortality was identical to ours. However, due to susceptibility analysis, it was determined that fosfomycin treatment was applied to patients infected with susceptible microorganisms. This suggested that the high mortality rates in our study may be related to the inability to perform sensitivity analysis.

In another study examining the current clinical use of IV fosfomycin in ICU patients in Germany and France, clinical success was achieved in 82.1% of patients with single-organ infections.[12] In comparison, clinical success was slightly lower (75%) in infections of two or more organ systems. The highest clinical success rate was found in patients with signs of infection or bacteremia, but of unknown focus, with 90%. In our study, however, no significant relationship was found between the outcome of the patients and the infected organ. However, the effect of isolated bacteria on mortality in patients with bacteremia secondary to *pneumonia* was significant.

Due to its different mechanisms of action, fosfomycin has a synergistic effect with other antibiotic groups. Therefore, combination treatments should be preferred in resistant infections.[1,2] In the study of Pontikis et al.,[10] fosfomycin was combined with 66.7% colistin, 39.6% tigecycline, 31.3% gentamicin, 25% meropenem, and 8.3% piperacillin/tazobactam. In another study conducted in Germany and France, combination treatments were preferred in almost all (99%) patients. The combined antibiotics were predominantly β-lactam (48%), although glycopeptide, metronidazole, and quinolones were other preferred antibiotic groups.[12] Our study found that fosfomycin was combined with other antibiotics in all patients (100%). While fosfomycin was combined with carbapenems in all patients, tigecycline or colistin was added to carbapenem and fosfomycin in 37%. In our study, the clinical response was higher in the group combined with carbapenem alone than in the other groups. This may be attributed to adding other antibiotic groups besides fosfomycin and carbapenem in patients with more severe clinical conditions.

128 studies were evaluated in a meta-analysis examining adverse events associated with IV fosfomycin. Seventy-two (56%) of these studies reported 480 adverse events in 2.672 treated patients.[13] When the side effects were examined, hypokalemia was the highest at 2.92%. Others were listed as hepatic enzyme increase (2.2%), hypernatremia (0.68%), cardiac side effects (0.34%), leukopenia (0.22%), thrombocytopenia (0.15%), hypertension (0.07%), and ARF (0.04%).[13] In our study, when the side effects developed in the patients were examined, the most common side effect was found to be hypernatremia (72%). Other side effects were hypokalemia (56%), ARF (39%), hypertension (23%), cardiac side effects (8%), leukopenia (15%), thrombocytopenia (64%), and increased hepatic enzymes (55%). The average dose of fosfomycin in the meta-analysis differed significantly between studies and countries. The mean daily dose of fosfomycin was 12.7 g for France, Germany, and Australia and 15.7 g for Spain. In contrast, it was much lower in Japan at 3.9 g. However, in the meta-analysis, there were few studies on high-dose treatment >20 g.[13] Our study's average daily dose was 18 g, higher than the studies mentioned. According to the meta-analysis, it was thought that one of the reasons for the high rate of side effects might be the use of high doses.

Although fosfomycin was administered as a combined treatment regimen in most of the studies included in the meta-analysis, the number of patients receiving monotherapy was also at a level that could not be neglected (combination: 73 studies, 2675 patients, monotherapy: 44 studies, 1757 patients).[13] In our study, all patients were receiving combination therapy. Another reason for our study's high rate of side effects is the combination treatment regimens. In addition, most studies included in the meta-analysis did not adequately explain the randomization methods or reason for treatment and were not planned as observational studies. The population to which most studies were applied consisted of patients followed outside the ICU.[13]

The lack of a control group is one of the most important limitations of our study, which examined the factors affecting survival in patients treated with fosfomycin. In addition, the inability to perform fosfomycin susceptibility analyses in our laboratory can be another limitation of our study.

CONCLUSION

Caution should be exercised when administering combined treatments with fosfomycin to patients followed in the ICU and infected with MDR Gram-negative infections. Treatment options are limited in this patient group, which has high mortality rates despite treatment. Our study investigated parameters that can be used to predict treatment response to fosfomycin. It was thought that starting the treatment according to these parameters would be beneficial when treating this patient group.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences Hamidiye Scientific Research Ethics Committee (No: 18/3, Date: 27/07/2022).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

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