Original Article

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Electrolyte Disorders: Insights from a Prospective, Multicenter, Observational Cohort Study on Fosfomycin's Impact

Elektrolit Bozuklukları: Fosfomisinin Etkisi Üzerine Prospektif, Çok Merkezli, Gözlemsel Bir Kohort Çalışmasından Elde Edilen Veriler

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ABSTRACT

Objective: Intravenous (IV) fosfomycin is widely used in combination therapies for resistant pathogens. This study aims to investigate the frequency and risk factors of electrolyte disorders (EDs) associated with IV fosfomycin in hospitalized patients.

Methods: This was a prospective, multicenter, observational cohort study, conducted in six centers from February 2023 to February 2024. The Naranjo adverse drug reaction probability scale (NADRPS) was used to evaluate the relationship between IV fosfomycin use and EDs.

Results: A total of 54 patients with a median age [interquartile range (IQR)] of 60 (35-73) years were included in the study. Most patients (38.8%) were admitted to the intensive care unit (ICU). The median IV fosfomycin dose was 12 g (IQR: 12-18), and the mean treatment duration was 13.2±7.2 days. Hypokalemia occurred in 28 patients (51.8%), and hypernatremia in 10 patients (18.5%). NADRPS scores were consistent with a probable

ÖZ

Amaç: İntravenöz (IV) fosfomisin, dirençli patojenler için kombinasyon tedavilerinde yaygın olarak kullanılmaktadır. Bu çalışma, hastaneye yatırılmış hastalarda IV fosfomisin'in neden olduğu elektrolit bozuklukları (EB) sıklığını ve risk faktörlerini araştırmayı amaçlamaktadır.

Yöntemler: Bu çalışma, 2023 Şubat ile 2024 Şubat tarihleri arasında altı farklı merkezde gerçekleştirilen prospektif, çok merkezli, gözlemsel bir kohort çalışmasıdır. Naranjo advers ilaç reaksiyonu olasılık ölçeği (NADRPS), EB ile IV fosfomisin kullanımı arasındaki ilişkiyi değerlendirmiştir.

Bulgular: Çalışmaya toplamda yaş ortalaması [çeyrekler arası aralık (ÇAA)] 60 (35-73) yıl olan 54 hasta dahil edilmiştir. Hastaların çoğu (%38,8) yoğun bakım ünitesinde (YBÜ) yatırılmıştır. IV fosfomisin medyan (ÇAA) dozu 12 g (ÇAA: 12-18) olup tedavi süresi ortalama 13,2±7,2 gündür. Hipokalemi 28 hastada (%51,8) ve hipernatremi 10 hastada (%18,5) görülmüştür. NADRPS

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ABSTRACT

association between fosfomycin use and EDs. The incidence of hypokalemia was significantly higher in ESBL-positive patients (63.4% vs. 30.7%, p=0.04). The incidence of hypernatremia was significantly higher among patients with hypokalemia than among those without hypokalemia (90% vs. 46.1%, p=0.013). Mortality was significantly higher in patients with EDs than in those without, with an odds ratio (OR) of 6.25 [95% confidence interval (CI): 1.82-20, p=0.002]. Furthermore, the presence of ESBL and positive fluid balance were associated with increased ED risk, with ORs of 3.77 (95% CI: 1.09-13.10, p=0.032) and 5.40 (95% CI: 1.12-26.04, p=0.03), respectively.

Conclusion: The correlation between IV fosfomycin and electrolyte abnormalities requires careful consideration, especially in ICU patients. Clinicians must regularly monitor electrolyte levels while administering IV fosfomycin to minimize potential risks while ensuring patient safety.

Keywords: Fosfomycin, electrolyte disorders, hypernatremia, hypokalemia, intensive care unit

ÖZ

skorları, hastaların EB'leri ile uyumlu bulunmuştur. ESBL pozitif hastalarda hipokalemi insidansı daha yüksekti (%63,4 vs. %30,7, p=0,04). Hipokalemik hastalarda hipernatremi insidansı, hipokalemisi olmayanlardan anlamlı derecede yüksekti (%90 vs. %46,1, p=0,013). EB'li hastalarda mortalite oranı, EB'siz hastalara göre anlamlı derecede yüksekti ve odds oranı (OR) 6,25 [%95 güven aralığı (GA): 1,82-20, p=0,002] olarak bulunmuştur. Ayrıca, ESBL (+) varlığı ve pozitif sıvı dengesi, sırasıyla OR'leri 3,77 (%95 GA: 1,09-13,10, p=0,032) ve 5,40 (%95 GA: 1,12-26,04, p=0,03) ile artmış EB riski ile ilişkilendirilmiştir.

Sonuç: IV fosfomisin ile elektrolit anormallikleri arasındaki ilişki, özellikle YBÜ hastalarında dikkatle değerlendirilmelidir. Klinik uzmanlar, IV fosfomisin tedavisi sırasında elektrolit düzeylerini düzenli olarak izlemeli, potansiyel riskleri en aza indirirken hasta güvenliğini sağlamalıdır.

Anahtar Kelimeler: Fosfomisin, elektrolit bozukluğu, hipernatremi, hipokalemi, yoğun bakım ünitesi

Introduction

Electrolyte homeostasis is maintained through a complex system involving the coordinated action of various hormones and organs (1). Moreover, several medications used in clinical practice can lead to electrolyte disorders (EDs) (1-3).

Fosfomycin is a bactericidal antibiotic with broad-spectrum activity against both gram-positive and gram-negative pathogens. Notably, it is effective against challenging strains such as carbapenemase- and extended-spectrum beta-lactamases (ESBL) producing *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus*, glycopeptide-resistant enterococci, and multidrug-resistant *Pseudomonas aeruginosa* (4-7). However, intravenous (IV) fosfomycin administration may lead to hypernatremia, particularly when high doses or prolonged treatment regimens are used, due to its high sodium content (8-11). In addition, IV fosfomycin has been frequently associated with hypokalemia, as reported in multiple studies (8-11).

Based on several clinical studies, including the multicenter ZEUS study, a daily dose of 12-18 g of fosfomycin has been recommended for the treatment of urinary tract infections (UTIs) (6,8,12,13). Notably, higher daily doses (>12 g) have been associated with a greater incidence of hypernatremia compared to lower doses (28.7% vs. 19.7%, p=0.06) (10). A European study reported that IV fosfomycin, commonly used to treat challenging infections, caused hypernatremia in 10.5% of patients (11). Furthermore, treatment was discontinued in six cases due to hypernatremia attributed to the high sodium content of fosfomycin (14 mmol sodium per gram) (11,14,15). Across multiple studies, the incidence of hypernatremia associated with IV fosfomycin has ranged from 6% to 24.3% (4,9,10,16,17). Review of medical records revealed that most cases were classified as severe (68%), although subsequent evaluations showed improvement or resolution in 44% of cases. Notably, in 72% of these cases, fosfomycin was the sole suspected causative agent (18).

In addition to hypernatremia, hypokalemia has also been documented as an adverse effect of IV fosfomycin, with reported frequencies ranging from 2.4% to 62.1% (8-11). The underlying mechanism is thought to involve increased potassium excretion in the distal renal tubules (4). Notably, hypokalemia may occur following short IV infusion durations (30-60 minutes), whereas extending infusion times to four hours has been shown to reduce its incidence (8,9). Interestingly, hypokalemia appeared to be less frequent among patients receiving higher daily doses (≥12 g) compared to those receiving lower doses (<12 g) (48.4% vs. 75%, p<0.001) (10). Importantly, no patients in these studies required treatment discontinuation due to hypokalemia (11).

IV fosfomycin has been used in Türkiye for specific clinical indications for approximately six years (17,19,20). Due to the limited data on its adverse effects, further research is needed to better understand the spectrum of potential complications, particularly EDs. This study aims to investigate the incidence and associated factors of EDs among hospitalized patients receiving IV fosfomycin.

Methods

Study Design and Participants

This study was a prospective, multicenter, observational cohort conducted across six centers involving patients who received IV fosfomycin between February 2023 and February 2024. The inclusion criteria consisted of individuals aged 18 years or older who had been hospitalized for more than 24 hours for any reason and received IV fosfomycin for more than 48 hours. Written informed consent was obtained from each patient or their legal guardian prior to study inclusion. Patients with missing key clinical or laboratory data were excluded from the

analysis. Thus, no imputation was performed, and all statistical analyses were conducted on complete cases. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Guidelines (21).

Ethics Approval and Consent to Participate

The study received ethical approval from the Clinical Research Ethics Committee of Marmara University (decision no: 09.2023.22, date: 03.02.2023). Written informed consent was obtained from all participants. All procedures adhered to the ethical standards and the principles of the 1964 Helsinki Declaration and its later amendments.

Sample Size

To assess the adequacy of our sample size, we conducted a post-hoc calculation based on the findings of a previous study by Sürmelioğlu et al. (22), which reported a 33.9% incidence of hypokalemia in critically ill patients receiving IV fosfomycin. Assuming a 90% confidence level and an acceptable absolute margin of error of ±12%, the minimum required sample size was calculated as 43 patients. Since our study included 54 patients, it met this requirement, and the sample size could be considered sufficient under these parameters.

Data Collection

Fosfomycin treatment and the course of infection were monitored for clinical and microbiological outcomes and safety until discharge or death, when applicable. All data were (pseudo)-anonymized by the investigators at each study center and verified by a double-entry procedure. Recorded data included demographic characteristics, admission and definite diagnosis, body mass index, medical history and treatment indication, fosfomycin dose, duration and dosing schedule, pathogens isolated, susceptibility pattern and resistant status, diagnostic methods concerning infection, relevant concomitant diseases and risk factors, laboratory parameters, concomitant antimicrobial agents and duration of hospital stay. No intervention was performed.

Evaluation of the Relationship of EDs to IV Fosfomycin

The process for evaluating EDs was as follows:

- EDs were defined as the presence of at least two consecutive readings outside the usual range. In this study, the detection of hypernatremia and/or hypokalemia was also defined as ED.
- The resolution of EDs was ascertained when two consecutive normal values were observed.
- Information resources such as the drug package insert UpToDate® (Wolters Kluwer Health Inc., 2023), Micromedex® Drug Information (Merative™), and Sanford Guide to Antimicrobial Therapy were utilized to evaluate the appropriateness of IV fosfomycin infusion solutions, dosage, and potential side effects.
- The study utilized the Naranjo adverse drug reaction probability scale (NADRPS) to assess the correlation between EDs and patients receiving IV fosfomycin. NADRPS consists of 10 questions answered as "yes", "no" or "I don't know". Each answer is assigned different point values (-1,0, +1 or +2). Total scores range from -4 to +13: if the score is nine or higher, the reaction is considered definite; if it is 5 to 8, it is considered probable; if it is 1 to 4, it is possible; and if it is 0 or less, it is considered doubtful (23). While NADRPS provides a structured causality assessment tool, it is not fully optimized for multifactorial adverse effects like EDs in critically ill patients. Results should therefore be interpreted with this limitation in mind.

Hypernatremia is classified as mild (146-149 mmol/L), moderate (150-169 mmol/L) and severe (≥170 mmol/L) (24). Hypokalemia is classified as mild (3-3.4 mmol/L), moderate (2.5-3 mmol/L), and severe (<2.5 mmol/L) (25). Laboratory reference ranges of electrolytes were the same in all places where the study was conducted.

Definitions

Clinical success was defined as either clinical cure or clinical improvement. Microbiological success was defined as the eradication of the underlying pathogen. Clinical cure was defined as the resolution of signs and symptoms of infection and/or no additional antibiotic therapy necessary. Clinical improvement was defined as improvement of signs and symptoms of infection and/or administration of additional antibiotic therapy.

Statistical Analysis

Descriptive statistics, including mean, median, standard deviation, interquartile range (IQR), count, and percentages, were used to summarize continuous variables. For categorical variables, frequencies and percentages were given. The Kolmogorov-Smirnov test examined continuous variable normality and identified a non-parametric distribution. Mann-Whitney U tests were used for continuous variables to compare groups, whereas chi-square tests were used for categorical data. Statistical significance was determined using a 95% confidence interval (CI) and p-value <0.05. ED risk variables were evaluated, and odds ratios (OR) (95% CI, p-value) were provided. The full dataset was processed using IBM SPSS Statistics for Windows, Version 29.0 (Armonk, New York: IBM Corp.).

Results

A total of 60 patients were initially followed during the study period. However, 6 patients were excluded due to incomplete follow-up data or missing clinical information. Consequently, 54 patients who met the inclusion criteria and had complete data were enrolled in the final analysis (Figure 1). The median age (IQR) was 60 (35-73) years, and 68.5% of the patients were male. Most were admitted to the intensive care unit (ICU) (38.8%) or the infectious diseases department (25.9%). Demographic characteristics are summarized in Table 1.

Most culture samples were obtained from wound sites (40.7%). The predominant pathogens identified were *Acinetobacter baumannii (A. baumannii)* (38.9%) and *Klebsiella pneumoniae*

(*K. pneumoniae)* (27.8%). A total of 92.6% of patients received at least one additional antibiotic alongside IV fosfomycin. Common combinations included meropenem (25.9%) and meropenem with polymyxin E (16.7%). Culture results and antibiotic use are presented in Table 2. In 18 patients, the cultured pathogens could not be eradicated. These included *A. baumannii* (n=8), *K. pneumoniae* (n=3), *Proteus* species (n=3), and other organisms (n=4). Among these, ESBL plus carbapenem-resistant (CR) was identified in *A. baumannii* (7/8 patients) and *Proteus* spp. (2/3 patients). No resistance was found in 2 out of 3 non-eradicated *K. pneumoniae* isolates.

The median (IQR) IV fosfomycin dose was 12 g (12-18), with a mean treatment period of 13.2±7.2 days. The average daily dose in ICU patients (11.9±4.3 g) was higher than the dose used in other ward patients (10.3±4.5 g) (p=0.209). Hypernatremia developed in 10 patients (18.5%), while hypokalemia occurred in 28 patients (51.8%). After IV fosfomycin treatment, hypernatremia occurred in 2.8±2.4 days and hypokalemia at 2.7±2.0 days. Hypernatremia was observed at mild (6,60%) and moderate (4,40%) levels. Hypokalemia was observed at mild (20,71.4%), moderate (6,21.4%) and severe (2,7.1%) levels. While no patients were terminated IV fosfomycin treatment due to hypernatremia, two patients (7.1%) were stopped it due to hypokalemia, as seen in Table 3. For hypernatremia, the median Naranjo score was 4 (IQR: 3-4.5), indicating a possible relationship. For hypokalemia, the median Naranjo score was 4 (IQR: 4-5), corresponding to a possible-probable association.

Hypokalemia was considerably lower in those discharged versus those who died (38.4% vs. 69.4%, respectively, p=0.016). Patients with ESBL-positive infections had a greater risk of hypokalemia than those with negative (63.4% vs. 30.7%, respectively, p=0.04). The incidence of hypernatremia was significantly higher among patients with hypokalemia than among those without hypokalemia (90% vs. 46.1%, p=0.013). The rate of hypernatremia development in patients admitted to the ICU was substantially greater than in patients admitted to other wards (90% vs. 45.2%, respectively, p=0.002) (Table 4).

The incidence of EDs was found to be statistically significantly greater in patients who died (76% vs. 34.4%, p=0.002), patients with ESBL-positive infections (63% vs. 31.2%, p=0.032), and patients with positive fluid balance at the start of IV fosfomycin treatment (70.5% vs. 30.7%, p=0.03) than in other patients. The mortality rate was significantly higher among patients with EDs, with an OR of 6.25 (95% CI: 1.82-20, p=0.002), compared to those without EDs. Furthermore, the presence of ESBL (+) and positive fluid balance were associated with an increased risk of EDs, with respective OR of 3.77 (95% CI: 1.09-

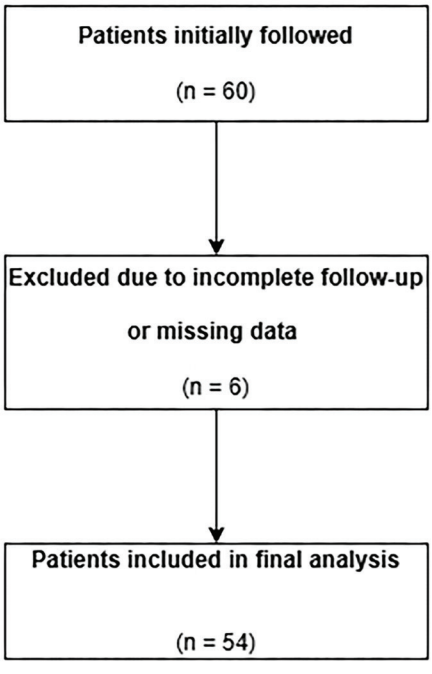

Figure 1. Study flowchart

Table 1. Socio-demographic characteristics of the patients

Variable	n=54
Age, median (IQR)	60 (35-73)
Sex, n (%)	
Male	37 (68.5)
Female	17 (31.5)
Body mass index, median (IQR)	25.37 (23.12-26.66)
Patient's hospitalization service, n (%)	
Intensive care unit	21 (38.8)
Infection diseases	14 (25.9)
Internal medicine service	6 (11.1)
Orthopedics	4 (7.4)
Other	9 (16.8)
Comorbidities*, n (%)	
Diabetes mellitus	19 (23.4)
Hypertension	12 (14.8)
Coronary artery disease	4 (4.9)
Dementia	4 (4.9)
Cerebrovascular accident	4 (4.9)
Chronic kidney disease	3 (3.7)
Atrial fibrillation	3 (3.7)
Heart failure	2 (2.4)
Other	30 (37)
Total length of stay (days), median (IQR)	29.5 (14.75 -49.25)
Discharge status, n (%)	
Discharged	29 (53.7)
Death	25 (46.3)
Renal status, n (%)	
Normal (eGFR >60 mL/min/m^2)	33 (61.1)
Decreased eGFR (eGFR <60 mL/min/m^2)	18 (33.3)
Hemodialysis	3 (5.6)

*: The patients had more than one comorbidity, eGFR: Estimated glomerular filtration rate, IQR: Interquartile range

Table 2. Distribution of clinical and microbiological characteristics of the patients

Variable	n=54
Culture sample location/site of infection, n (%)	
Deep tracheal aspirate	16 (29.6)
Urine	11 (20.4)
Blood	2 (3.7)
Wound	23 (40.7)
Catheter	3 (5.8)
Pathogens, n (%)	
Acinetobacter baumanii	21 (38.9)
Klebsiella pneumoniae	15 (27.8)
Pseudomonas aeruginosa	3 (5.6)
Acinetobacter baumanii + Klebsiella pneumoniae	3 (5.6)
Klebsiella pneumoniae + Pseudomonas aeruginosa	3 (5.6)
Proteus sp.	5 (9.3)
Proteus sp.*+ Klebsiella pneumoniae*	2 (3.7)
Corynebacterium striatum	1 (1.9)
Escherichia coli + Proteus sp.	1 (1.9)
Resistance status of pathogens*, n (%)	
ESBL, yes	38 (70.4)
CR, yes	35 (64.8)
ESBL + CR	30 (55.5)
None	11 (20.3)
Antibiotics used in combination with fosfomycin, n (%)	
Meropenem	14 (25.9)
Polymyxin E	5 (9.3)
Meropenem + polymyxin E	9 (16.7)
Tigecycline	3 (5.6)
Meropenem + tigecycline	2 (3.7)
Amikacin	1 (1.9)
Meropenem + amikacin	1 (1.9)
Tigecycline + polymyxin E	4 (7.4)
Piperacillin-tazobactam	1 (1.9)
Imipenem	2 (3.7)
Ceftazidime-avibactam	3 (3.7)
None	4 (7.4)
Other	5 (9.5)
Eradication status (microbiological success), n (%)	
Yes	36 (66.6)
Clinical efficacy status, n (%)	
Clinical cure	23 (42.5)
Clinical improvement	18 (33.3)
Failure	13 (24.2)

*: Patients have more than one pathogen and resistance mechanism, CR: Carbapenem-resistant enterobacterales, ESBL: Extended-spectrum beta-lactamases

13.10, p=0.032) and 5.40 (95% CI: 1.12-26.04, p=0.03) (Table 5). There is no significant difference in EDs between patients hospitalized in the ICU and those treated elsewhere (62.5% and 46.6%, respectively, p=0.246).

Although the IV fosfomycin dose and treatment time did not show any notable variation in the treatment of ESBL-positive bacteria, a significant disparity was observed in the usage of additional antibiotics. The rate of administering at least one

Table 3. Distribution of information regarding intravenous fosfomycin treatment

Variable	n=54
IV fosfomycin dose (g), median (IQR)	12 (12-18)
IV administration time (minute), median (IQR)	120 (60-120)
Total treatment time (days), mean ± SD	13.2±7.2
Has hypernatremia occurred? n (%)	
Yes	10 (18.5)
No	44 (41.5)
On what day after treatment did hypernatremia occur? mean (± SD)	2.8±2.4
Has hypernatremia been treated? n=10, (%)	
Yes	3 (30)
No	7 (70)
Has fosfomycin treatment been stopped due to hypernatremia? n=10, (%)	
Yes	0 (0)
No	10 (100)
Naranjo score for hypernatremia-fosfomycin, n=10, (%)	
Doubtful	1 (10)
Possible	7 (70)
Probable	2 (20)
Has hypokalemia occurred? n (%)	
Yes	28 (51.8)
No	26 (48.2)
On what day after treatment did hypokalemia occur? mean (± SD)	2.7±2.0
Has hypokalemia been treated? n=28, (%)	
Yes	13 (46.4)
No	15 (53.6)
Has fosfomycin treatment been stopped due to hypokalemia? n=28, (%)	
Yes	2 (7.1)
No	26 (92.9)
Naranjo score for hypokalemia- fosfomycin, n=28, (%)	
Doubtful	2 (7.2)
Possible	13 (46.5)
Probable	13 (46.4)

IQR: Interquartile range, IV: Intravenous, SD: Standard deviation

additional antibiotic was (64.8% vs. 27.7%, p=0.032) in ESBL-positive and ESBL-negative individuals, respectively.

There were no differences between patients' EDs and variables such as IV fosfomycin doses, administration time, treatment duration, hospital stay length, number of additional antibiotics, or baseline sodium and potassium levels (p>0.05). Furthermore, the daily sodium and potassium meq loads estimated across all treatments received by the patients did not alter their ED status (p>0.05).

Table 4. Statistical analysis of parameters associated with electrolyte disorders

Variable		p-value
	Hypokalemia (%)	
Discharge status		0.016
Discharged	38.4	
Death	69.4	
ESBL-positive		0.04
Yes	63.4	
No	30.7	
	Hypernatremia (%)	
Patient's hospitalization service		0.002
Intensive care unit	90	
Other	45.2	
Hypokalemia		0.013
Yes	90	
No	46.1	
	Total electrolyte disorders (%)	
Discharge status		0.002
Discharged	34.4	
Death	76	
ESBL-positive		0.03
Yes	63	
No	31.2	
Fluid balance at the start of IV fosfomycin		0.03
Positive	70.5	
Other	30.7	
Patients' hospitalization service		0.246
Intensive care unit	62.5	
Other	46.6	

ESBL: Extended-spectrum beta-lactamases, IV: Intravenous

Table 5. Factors associated with electrolyte disorders (odds ratios from logistic regression)

Risk factors	OR (95% CI)	p-value
Death	6.25 (1.82-20)	0.002
ESBL (+)	3.77 (1.09-13.10)	0.032
Positive fluid balance at the beginning of fosfomycin treatment	5.40 (1.12-26.04)	0.03

CI: Confidence interval, ESBL: Extended-spectrum beta-lactamases, OR: Odds ratio

Discussion

In this study, we addressed the prevalence and risk factors for EDs in patients receiving IV fosfomycin in a variety of medical settings, with a focus on ICUs. Additionally, we evaluated pathogen resistance profiles, the usage of additional antibiotics concomitantly with IV fosfomycin, and the efficiency of targeted organism eradication.

Resistance and Eradication Status of Targeted Organisms

Fosfomycin exhibits a notable attribute in its efficacy against ESBL-producing *Escherichia coli (E. coli)* and ESBL + CR *K. pneumoniae*, as demonstrated in numerous recent studies (26). Conversely, including IV fosfomycin as part of the combination regimen for treating *A. baumannii* showed a trend toward a more favorable microbiological response and reduced mortality (19,27,28). A study evaluating the efficacy and safety of IV fosfomycin in treating difficult-to-treat resistant Gram-negative infections, particularly UTIs (56.7%), identified *K. pneumoniae* (56.7%) and *E. coli* (23.3%) as the most prevalent target organisms. In most cases (76%), IV fosfomycin was used in combination with other antimicrobial agents. Clinical improvement was achieved in 73.3% of patients, and eradication of the initial infections occurred in 66.7% (29). In another study focusing on cases of CR *K. pneumoniae* and *E. coli*, a 91% success rate was attained in eradicating the bacteria (30). As observed in this study, the situation was similar to previous studies, suggesting that the effectiveness of fosfomycin in combination with other antimicrobial agents could be increased (4,11,14).

The current study used IV fosfomycin in conjunction with other antibiotics to treat wound infections, deep tracheal aspirates, and UTIs caused by *A. baumannii* and *K. pneumoniae*. Furthermore, roughly 80% of these pathogens possess at least one resistance mechanism, such as ESBL or CR. Therefore, more than 90% of patients received IV fosfomycin in addition to another antibiotic. This study supports previous studies on the effectiveness and safety of IV fosfomycin in combined regimens for treating antibiotic-resistant infections (11,17,19,28,29,31). Compared to other studies, this one found a somewhat lower eradication rate of *A. baumannii* when using a fosfomycin combination

regimen (19,27,28). This finding may reflect the inherent treatment challenges associated with multidrug-resistant *A. baumannii* infections. However, no microbiological resistance profiling was conducted to confirm specific mechanisms in this study. IV fosfomycin appeared to provide more successful results, especially in *E. coli* and *K. pneumoniae* cases. Meanwhile, variations in the target organisms, treatment dosages, hospitalization status (ICUs or other services), and existence of infections with various resistance mechanisms could account for differences in eradication and microbiological cure rates across studies (11,17,19,28,29,31).

IV Fosfomycin Dose and Duration of Administration

Studies recommend a daily dose of 12-24 g of IV fosfomycin, administered in 2 to 4 divided doses (6,10,13,32). It can also be administered via continuous infusion at daily doses ranging from 8 to 32 g (26,33). In a study focusing on CR *K. pneumoniae* and *E. coli* cases, daily IV fosfomycin doses of 16-24 g were used (30). Temoçin et al. (17) reported that the average daily IV fosfomycin dose was 13.11±4.4 g. The total daily dose was observed to be higher in ICU patients compared to those in general wards. Studies using IV fosfomycin in combination regimens for resistant pathogens employed doses similar to those in the current study (11,17). However, average IV fosfomycin doses varied across studies—either lower or higher than in this study—depending on factors such as pathogen resistance profile, infection site and severity, treatment duration, and whether patients were hospitalized in the ICU or other wards (6,10,14,19,29,30).

Similar to dosing, treatment durations with IV fosfomycin in this study are consistent with those reported in the literature (11,19). In a similar ICU-based study, Zirpe et al. (10) reported an average treatment duration as short as four days, which contrasts with established durations. However, the resistance mechanisms of the pathogens were not specified, as noted in the study's limitations. Likewise, Temoçin et al. (17) reported an average treatment duration of eight days. In their study, which included a population primarily with *K. pneumoniae* UTIs, the resistance status of the target organisms was not specified. This lack of data limits the ability to compare the impact of resistance mechanisms on treatment duration. Although the targeted pathogens were appropriate for IV fosfomycin treatment, resistance mechanisms may have contributed to shorter treatment durations. In the present study, the presence of resistant pathogens in most patients necessitated prolonged and high-dose IV fosfomycin regimens.

IV Fosfomycin-induced Hypernatremia-hypokalemia and Risk Factors

In previous studies investigating IV fosfomycin use, the incidence rates of hypernatremia (23.3-41.9%) and hypokalemia (28.57-43.3%) have varied, though they remain common findings (17,22,29,34). However, Michalopoulos et al. (6) reported no fosfomycin-associated side effects in their study. Despite potential side effects, IV fosfomycin has generally been considered a safe treatment option. Most studies have described its adverse effects as mild to moderate, non-serious, and reversible (35). These side effects rarely lead to discontinuation of therapy (29,31,36). Nevertheless, some cases have reported treatment cessation due to hypernatremia (11,15,18,37). In the present study, IV fosfomycin was discontinued in two patients due to non-severe hypokalemia. The variability in adverse event rates across studies may be due to differences in laboratory reference ranges, electrolyte monitoring frequency, and ICU patient populations (38).

Importantly, most previous studies did not use a formal causality assessment scale to evaluate the association between IV fosfomycin and adverse effects (6,10,11,17,22,29,34). For example, Putensen et al. (11) suspected a link between fosfomycin and adverse events in 22 patients (10.5%) and documented hypokalemia in five cases (2.4%). In contrast, our study used NADRPS, which revealed a strong association between EDs and IV fosfomycin. Although the Naranjo scale added structure to our assessment, it is important to acknowledge that EDs in ICU patients are often multifactorial. As such, the limitations of NADRPS in this complex setting should be considered. Moreover, although we recorded the timing of ED onset, we did not correlate this with pharmacokinetic variables such as drug serum levels or dosing intervals. Future studies using time-to-event analyses and dose-response models are warranted.

Multiple studies have identified dysnatremia as the most common ED among ICU patients (39-43). In our study, hypernatremia frequently co-occurred with hypokalemia. Putensen et al. (11) found this co-occurrence in only four patients. We also observed that hypernatremia was significantly more common among ICU patients than among those in general wards. EDs due to IV fosfomycin developed within approximately two days in our cohort, which was shorter than the four-day onset reported by Sürmelioğlu et al. (22). Stelfox et al. (40) reported a similar two-day onset in the ICU setting. These findings suggest that electrolyte monitoring should begin promptly after initiating IV fosfomycin therapy.

Most patients in our study were ICU patients, and mortality was 6.25 times higher among those who developed EDs. Multiple non-drug-related factors influence ED development in the ICU, many of which are highly prevalent (40-42). Previous studies have shown that EDs are independently associated with poor prognosis and increased mortality in critically ill patients (40,43). While the observed association between EDs and increased mortality (OR: 6.25) is clinically significant, this finding should be interpreted cautiously. The relationship may reflect underlying disease severity rather than a direct causal effect. Confounding by indication and severity of illness are likely contributing factors. In our cohort, the primary causes of death included septic shock, respiratory failure, and multiorgan dysfunction, consistent with severe underlying infections. While EDs were not the direct cause of death in any patient, they may have contributed to clinical deterioration in critically ill individuals. Given the multifactorial nature of EDs and mortality in ICU settings, distinguishing causality is challenging; however, the strong statistical association suggests that EDs may serve as markers of poor prognosis in this population (39,40,44).

Treatment of ESBL-producing pathogens with higher doses of IV fosfomycin, which contains significant sodium content, may further elevate the risk of hypokalemia and hypernatremia (11,20,22). Our data show that patients with ESBL-positive infections had significantly higher odds of developing hypokalemia (OR: 3.77; 95% CI: 1.09-13.10; p=0.032). This observation may reflect the increased severity of illness and higher antibiotic burden typically associated with ESBL-positive infections. Patients infected with ESBL-producing organisms are more likely to have prolonged hospital stays, receive combination antimicrobial therapies, and experience fluid-electrolyte imbalances due to their complex clinical course. Therefore, the observed association might be driven more by infection severity than by ESBL status alone. The rate of additional antibiotic utilization was seen to be markedly greater in the management of ESBL-positive pathogens as opposed to negative ones. Hypokalemia is thought to result primarily from increased renal potassium loss induced by IV fosfomycin, particularly when infused over less than four hours (9,11,22). Additionally, patients with positive fluid balance may be more prone to dilutional hypokalemia. A key finding of this study was that positive fluid balance increased the odds of EDs by 5.40. All patients in our cohort received fosfomycin via short-term infusions, which may explain the higher hypokalemia incidence compared to other studies (11,17,22,29,34). The underlying mechanism likely involves osmotic diuresis induced by high sodium content in fosfomycin formulations, leading to increased renal potassium excretion. Sodium-induced volume expansion may also enhance urinary potassium loss, especially with short-term infusions. Nevertheless, the exact pharmacokinetic dynamics remain to be clarified. Regardless of these mechanisms, EDs are consistently more prevalent in ICU patients than those in general wards. This can be attributed to multiple factors such as underlying organ dysfunction, use of nephrotoxic and diuretic medications, frequent fluid shifts, nutritional support, and the overall complexity of ICU care. In addition, polypharmacy and high-dose antimicrobial regimens—common in this setting—may further exacerbate EDs. These factors, combined with fosfomycin's sodium load and renal potassium excretion effects, likely contribute to the high baseline ED rates observed in ICU patients (39-41,43,45). A recent multicenter study from Türkiye also demonstrated the multifactorial nature of drug-induced EDs in ICUs and supports our findings (39). Furthermore, a significant association has been established between EDs and mortality in hospitalized patients (15,40-42).

Hypernatremia related to IV fosfomycin can often be managed by adjusting co-administered drugs, changing the diluent solution, and increasing maintenance fluids to improve fluid balance (17,18). Sürmelioğlu et al. (22) identified enteral nutrition and albumin supplementation as additional risk factors for fosfomycin-induced hypernatremia. While hypernatremia has been attributed to fosfomycin's high sodium content, the exact pathophysiological mechanism remains unclear (4,9-11,14-18,22). Shorr et al. (14) emphasized that prolonged or high-dose fosfomycin use may increase hypernatremia risk. Notably, our study found no direct association between the sodium load of IV fosfomycin and the development of hypernatremia. Neither the dose nor the duration of fosfomycin administration had a significant effect on ED incidence. This raises the possibility that factors other than sodium content may be involved in the development of hypernatremia associated with IV fosfomycin use. In our study, IV fosfomycin was administered as part of combination therapy in more than 90% of cases. The most common co-administered antibiotics were meropenem and polymyxin E. Although these agents are not typically associated with high rates of EDs, the cumulative effect of multiple nephrotoxic and electrolyte-altering agents—especially in critically ill patients—should not be underestimated. Clinicians should consider the overall risk profile of combination regimens when initiating fosfomycin-based therapies.

Based on our findings, we recommend initiating close electrolyte monitoring protocols during IV fosfomycin therapy, particularly within the first 48 hours. Prolonging infusion time and adjusting fluid composition may help mitigate EDs. Prospective studies comparing different infusion durations and evaluating multivariate risk prediction models would help refine clinical guidelines.

Study Limitations

This study has several limitations that should be acknowledged. First, the relatively limited clinical use of IV fosfomycin in Türkiye resulted in a modest sample size. Although the inclusion of 54 patients was deemed sufficient based on post-hoc calculations to estimate the prevalence of hypokalemia with acceptable confidence, the sample size was not adequate to support multivariable regression modeling. Therefore, all presented associations are unadjusted and potentially subject to residual confounding from factors such as age, comorbidities, renal function, and ICU admission.

Second, the study population was clinically heterogeneous, comprising patients from various departments including intensive care, internal medicine, infectious diseases, and orthopedics. Due to the limited sample size, stratified analyses by hospital ward or treatment indication could not be conducted, which restricts the generalizability of the findings across different patient subgroups. Furthermore, as this was not a randomized controlled trial, causal inferences should be made with caution.

Despite these limitations, the study has important strengths. It is one of the few prospective, multicenter investigations to evaluate EDs associated with IV fosfomycin. The use of NADRPS provided a structured approach to causality assessment, which is rarely implemented in studies of this nature. Additionally, by including patients from diverse clinical settings, the study offers a broad overview of fosfomycin use in real-world hospital practice, contributing meaningful data to the limited safety literature on this agent.

Conclusion

IV fosfomycin appears to be a generally safe and effective option for treating multidrug-resistant infections, particularly when

used in combination with other antibacterial agents. However, clinicians should be aware that EDs, especially hypokalemia and hypernatremia, are relatively common adverse effects. These disorders are more frequently observed in ICU patients and may be influenced by factors such as pathogen resistance profiles, positive fluid balance, and mortality-related complications. Awareness of these risks is critical to ensure safe prescribing practices. Close electrolyte monitoring and individualized fluid management strategies are recommended to minimize adverse outcomes during IV fosfomycin therapy.

Ethics

Ethics Committee Approval: The study received ethical approval from the Clinical Research Ethics Committee of Marmara University (decision no: 09.2023.22, date: 03.02.2023).

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

Footnotes

Authorship Contributions

Concept: Y.E.A., C.Ç., N.A., Ö.F.Ö., M.S., Design: Y.E.A., C.Ç., N.A., Data Collection or Processing: Y.E.A., C.Ç., Ö.F.Ö., B.D., R.Ş., Ö.A., B.E., Z.Ü.G., Analysis or Interpretation: Y.E.A., C.Ç., N.A., Literature Search: Y.E.A., C.Ç., N.A., Writing: Y.E.A., C.Ç., N.A., M.S.

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