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Intravenous Fosfomycin Therapy Induced Hypernatremia and Hypokalemia in Critically Ill Patients: A Cross-Sectional Study

Kritik Hastalarda İntravenöz Fosfomisinin İndüklediği Hipernatremi ve Hipokalemi: Kesitsel Bir Çalışma

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ABSTRACT

Introduction: *This study aimed to evaluate the incidence of hypernatremia and hypokalemia and predisposing factors during IV fosfomycin treatment.*

Materials and Methods: *In this retrospective and cross-sectional study conducted at a university hospital, patients who received intravenous fosfomycin therapy between September 2021 and August 2022 were included. Demographic characteristics, comorbidities, and clinical and laboratory data of the included patients during their stay in the intensive care unit were extracted from the hospital information management system. The analyses were conducted using the SPSS 20.0 software.*

Results: *The mean age of the 62 patients included in the study, 24 of whom were women, was 58.8 ± 19.5 years. Following IV fosfomycin treatment, it was observed that 26 (41.9%) patients developed hypernatremia, with an average onset time of 4.81 ± 1.7 days. There was a statistically significant difference between patients with and without hypernatremia in terms of APACHE II scores ($t= 2.246$; $p< 0.05$), the presence of enteral nutrition ($p= 0.020$), and albumin replacement ($p= 0.007$). In all patients who developed hypernatremia, fosfomycin was diluted with 0.9% NaCl solution. After IV fosfomycin treatment, 21 (33.9%) patients developed hypokalemia, with an average onset time of 3.90 ± 1.14 days. There was a statistically significant difference between the patients with and without hypokalemia in terms of the presence of albumin replacement ($p= 0.004$).*

Conclusion: *The incidence of hypernatremia observed in this study was higher than the rates reported in previous studies. The APACHE II score, enteral nutrition, and albumin replacement appear to be significant predisposing factors in hypernatremic patients. Fosfomycin is recognized for its stability not only in 0.9% NaCl solution but also in 5% glucose solution. In patients susceptible to hypernatremia, the use of a 5% glucose solution to dilute fosfomycin could be considered as a preferable option, unless contraindicated.*

Key Words: *Fosfomycin; Hypernatremia; Hypokalemia*

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ÖZ

Kritik Hastalarda İntravenöz Fosfomisinin İndüklediği Hipernatremi ve Hipokalemi: Kesitsel Bir Çalışma

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Giriş: *Bu çalışmada IV fosfomisin tedavisi sırasında hipernatremi ve hipokalemi insidansının ve predispozan faktörlerin değerlendirilmesi amaçlanmıştır.*

Materyal ve Metod: *Bir üniversite hastanesinde gerçekleştirilen bu retrospektif ve kesitsel çalışmaya Eylül 2021-Ağustos 2022 tarihleri arasında IV fosfomisin tedavisi alan hastalar dahil edilmiştir. Çalışmaya dahil edilen hastaların yoğun bakımda tedavi gördükleri süre boyunca demografik özellikleri, komorbiditeleri, klinik ve laboratuvar verileri hastane bilgi yönetim sisteminden taranmıştır. Analizler SPSS 20.0 programı kullanılarak gerçekleştirilmiştir.*

Bulgular: *Çalışmaya alınan 24'ü kadın 62 hastanın yaş ortalaması 58.8 ± 19.5 yıl olarak hesaplandı. IV fosfomisin tedavisi sonrası 26 (%41.9) hastada ortalama 4.81 ± 1.7 gün sonra hipernatremi geliştiği belirlendi. APACHE II skorları (t= 2.246; p< 0.05), enteral beslenme varlığı (p= 0.020) ve albümin replasmanı (p= 0.007) açısından hipernatremisi olan ve olmayan hastalar arasında istatistiksel olarak anlamlı fark vardı. Hipernatremi gelişen tüm hastalarda fosfomisin %0.9'luk NaCl solüsyonu ile seyreltildi. IV fosfomisin tedavisi sonrası 21 (%33.9) hastada ortalama 3.90 ± 1.14 gün içinde hipokalemi gelişti. Hipokalemisi olan ve olmayan hastalar arasında albümin replasmanı varlığı açısından istatistiksel olarak anlamlı fark vardı (p= 0.004).*

Sonuç: *Bu çalışmada saptanan hipernatremi ve hipokalemi sıklığı önceki çalışmalara göre daha yüksek bulunmuştur. Hipernatremik hastalarda APACHE II skorunun yüksekliği, enteral beslenme ve albümin replasmanının varlığı, önemli bir predispozan faktör gibi görünmektedir. Fosfomisinin sadece %0.9 NaCl solüsyonunda değil, %5 glukoz solüsyonunda da stabil olduğu bilinmektedir. Hipernatremi riski olan hastalarda kontrendike değilse fosfomisini seyreltmek için %5 glukoz solüsyonu tercih edilebilir.*

Anahtar Kelimeler: *Fosfomisin; Hipernatremi; Hipokalemi*

INTRODUCTION

Fosfomycin was originally discovered in 1969, but it has regained significant attention in recent years due to its potential for treating multidrug-resistant bacterial infections. It has a unique mechanism of action, bactericidal activity, broad spectrum of activity, and relatively safe and tolerable adverse effect profile[1]. There are two formulations of fosfomycin available: oral and intravenous (IV). The 2022 Guidelines of the Infectious Diseases Society of America recommends the use of oral fosfomycin for the treatment of cystitis caused by extended spectrum-lactamase-producing *Escherichia coli*[2]. The utilization of oral fosfomycin was confined to cystitis due to its limited ability to attain effective concentrations in other infection sites. In cases where improved penetration is necessary, intravenous (IV) fosfomycin would be more appropriate. The IV administration of fosfomycin was widely approved by the European Medicines Agency. The use of IV fosfomycin is a good candidate for a combination of community- and hospital-acquired pneumonia/ventilator-associated pneumonia in critically ill patients[3]. However, IV formulations can be associated with different adverse drug reactions that include angioedema, aplastic anemia, cholestatic jaundice, and hepatic necrosis. The most common side effects of fosfomycin are hypernatremia and hypokalemia[4]. Hypernatremia and hypokalemia are associated with poor outcomes in critically ill patients[5]. The IV formulation of fosfomycin is associated with a high sodium intake which represents a life-threatening clinical condition and is a limitation, especially for patients with heart failure or those on hemodialysis[4]. The studies have reported different rates of IV fosfomycin-induced hypernatremia and hypokalemia[6].

The primary objective of this study was to assess the occurrence of hypernatremia and hypokalemia caused by intravenous (IV) fosfomycin. Additionally, the secondary aim was to identify the predisposing factors associated

with IV fosfomycin-induced hypernatremia and hypokalemia.

MATERIALS and METHODS

This retrospective and cross-sectional study was conducted at Çukurova Universtiy Balcalı Hospital. As part of the study, medical records were reviewed for patients who received intravenous fosfomycin treatment (FOSİT 4 g IV, Koçak Farma) in the Internal Medicine Intensive Care Unit (13 beds) and Reanimation Unit (9 beds) between September 2021 and August 2022. The study protocol was approved by the Clinical Trial Ethics Committee of Çukurova University (Date: 16.09.2022; Approval number: 125-39).

Patients

The study included patients aged 18 years and older who were admitted to the internal medicine intensive care unit or reanimation unit of the university hospital. Patients who received intravenous fosfomycin therapy for a minimum of three days between September 2021 and August 2022 were included in the study. Patients who had hypernatremia and hypokalemia prior to fosfomycin treatment were excluded. Fosfomycin was administered as one-hour infusions.

Data collection and analysis

Demographic and clinical data of the patients included in the study were recorded starting from the day before fosfomycin treatment. This allowed for the identification of patients who had hypernatremia or hypokalemia before the administration of fosfomycin. Hypokalemia was defined as serum potassium levels below 3.5 mEq/L, while hypernatremia was defined as serum sodium levels exceeding 145 mEq/L, serving as reference values. The drugs and crystalloid/colloid treatments that each patient received concurrently with fosfomycin treatment, as well as electrolyte levels and biochemistry findings were recorded and analyzed. The demographic characteristics, comorbidities, and clinical and laboratory data of the enrolled patients during their stay in the intensive care unit were extracted from the hospital information management system. To facilitate the comparison of study data based on specific parameters, normality assumptions were examined, and the Chi-square statistics and t-test for independent groups were employed. A value of $p< 0.05$ was considered statistically significant. The analyses were carried out using the SPSS 20.0 software.

RESULTS

A total of 62 patients, including 24 (38.7%) women, who fulfilled the relevant criteria, were enrolled in the study. The mean age was 58.8 ± 19.5 years and the mean APACHE II score was 22.8 ± 10.3. Following IV fosfomycin treatment, 26 (41.9%) patients developed hypernatremia after an average of 4.81 ± 1.7 days, and 21 (33.9%) patients developed hypokalemia in an average of 3.90 ± 1.14 days (Table 1). In all patients who developed hypernatremia, fosfomycin was diluted with 0.9% Sodium chloride (NaCl) solution.

Other concurrent treatments involving intravenous fosfomycin in patients with hypernatremia have been evaluated (Table 2). There was a statistically significant difference between patients with and without hypernatremia in terms of APACHE II scores ($t= 2.246$; $p< 0.05$), presence of enteral nutrition ($p= 0.020$) and albumin replacement ($p= 0.007$) (Table 2). There was a statistically significant difference between the patients with and without hypokalemia in terms of the presence of albumin replacement ($p= 0.004$).

DISCUSSION

In critically ill patients, hypernatremia can have an iatrogenic origin. Fosfomycin is one of the sodium-rich antibiotics and each gram of IV fosfomycin contains 14.5 mEq of sodium. Therefore, hypernatremia is observed as one of the side effects of fosfomycin, especially when given in high doses or for prolonged periods[7].

In our study, the rate of hypernatremia following IV fosfomycin was 41.9% and the rate of hypokalemia was 33.9%. This rate seems to be higher compared to the results of other studies. In a study by Putensen et al. in 2019, the rates of IV fosfomycin-induced hypernatremia and hypokalemia were 10.5% vs. 4.3%, respectively[1]. In the study by Chen et al., these rates were reported as 33.33% and 28.57%, respectively[3]. In the study by Scavare

Table 1. Demographic and clinical characteristics of the patients (n= 62)

Variable	
Age, years (Mean ± SD)	58.8 ± 19.5
Female, n (%)	24 (38.7%)
Comorbidities and concomitant therapies, n (%)	
Diabetes mellitus	18 (29)
Hypertension	24 (38.7)
Hypothyroidism	10 (16.1)
Cardiovascular disease	20 (32.2)
Enteral nutrition	29 (46.8)
Antineoplastic drugs	16 (25.8)
Corticosteroids	31 (50)
Albumin	15 (24.2)
Empirical fosfomycin therapy, n (%)	23 (37.1)
Targeted therapy with fosfomycin, n (%)	39 (62.9)
Blood culture, n (%)	7 (11.3)
Tracheal aspirate culture, n (%)	22 (35.9)
Urine culture, n (%)	8 (12.9)
Wound culture, n (%)	3 (4.8)
Pleura, n (%)	1 (1.6)

Table 2. Variables affecting the development of hypernatremia following IV fosfomycin

	Patients with hypernatremia	Patients without hypernatremia	p	t
Female, n (%)	11	13		
Hypertension, n (%)	12 (19.4)	12 (19.4)	0.224	-
Hypothyroidism, n (%)	1 (1.6)	4 (6.5)	0.295	-
GFR <60 mL/min, n (%)				
30-60 mL/min	11 (17.7)	10 (16.1)	0.343	-
<30 mL/min	6 (9.7)	7 (11.3)		
Enteral nutrition, n (%)	17 (27.4)	12 (19.4)	**0.020***	-
Corticosteroid use, n (%)	15 (24.2)	16 (25.8)	0.198	-
Albumin replacement, n (%)	4 (6.5)	11 (17.7)	**0.007***	-
Age (years), mean ± SD	57.885 ± 18.9533	59.472 ± 20.2393	0.753	-0.313
APACHE II, mean ± SD	26.231 ± 10.7603	20.444 ± 9.4368	**0.028***	2.246

GFR: Glomerular filtration rate.

et al., only the incidence of hypernatremia was reported as 17.7%[4]. Scavere's study also stated that a total of 63.7% of hypernatremia events were related to incorrect reconstitution of the drug. In our study, all fosfomycin solutions were prepared with 0.9% NaCl. The administration of 0.9% NaCl to all critically ill patients, regardless of their individual variations, is believed to be a contributing factor to the elevated incidence of fosfomycin-induced hypernatremia. Fosfomycin exhibits stability not only in a 0.9% NaCl solution but also in a 5% dextrose solution. Thus, it can be chosen as a preferred option for eligible patients.

In our study, the mean onset of hypernatremia following IV fosfomycin administration was 4.81 ± 1.7 days, while it was 3.90 ± 1.14 days for hypokalemia. Hypokalemia had occurred before hypernatremia. The mechanism is believed to be related to an increase in urinary potassium excretion within the distal tubules. Some authors associate the hypokalemia events with the short infusion time (30-60 min) and reported no hypokalemia events when the infusion was

extended to four hours. The role of potassium supplementation while receiving fosfomycin therapy remains unclear at this time[1].

In our study, we identified high APACHE II scores, enteral nutrition, and the presence of albumin replacement as variables associated with an increased predisposition to IV fosfomycin-induced hypernatremia. It is recognized that hypernatremia is one of the most prevalent complications associated with enteral nutrition and albumin replacement[8,9]. It is crucial to be vigilant about the heightened risk, particularly in patients undergoing enteral nutrition and receiving intravenous fosfomycin therapy. In our study, the incidence of hypernatremia was higher in patients with high APACHE II scores. The inability to compensate for the impaired sodium-potassium mechanism is expected in patients with multiple organ dysfunctions.

CONCLUSION

The incidence of hypernatremia observed in this study was higher than the rates reported in previous studies. The APACHE II score, enteral nutrition, and albumin replacement appear to be significant predisposing factors in hypernatremic patients. Fosfomycin is recognized for its stability not only in 0.9% NaCl solution but also in 5% glucose solution. In patients susceptible to hypernatremia, the use of a 5% glucose solution to dilute fosfomycin could be considered as a preferable option, unless contraindicated.

ETHICS COMMITTEE APPROVAL

This study wass approved by the Çukurova University Non-Invasive Clinical Research Ethics Committee (Decision no: 125, Date: 16.09.2022).

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: All of authors

Analysis/Interpretation: NS, FÇ, MGG

Data Collection or Processing: FA, MGG

Writing: NS, FÇ

Review and Correction: KA, DÖ

Final Approval: KA, DÖ

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