BRIEF RESEARCH COMMUNICATION

A Real-world Study on Prescription Pattern of Fosfomycin in Critical Care Patients

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Abstract

Background: This study presents a real-world scenario for prescription pattern, efficacy, and safety data on the current clinical use of intravenous fosfomycin in critically ill patients in Indian settings.

Patients and methods: This was a retrospective cohort study conducted for a period of 10 months among critically ill patients admitted to hospital's critical care unit. The primary objective of the study was to analyze the prescription pattern of intravenous fosfomycin, and the secondary objective was to evaluate the safety profile and patient outcomes.

Results: A total of 309 patients were enrolled, and they were diagnosed with bacteremia (45.3%), pneumonia (15.85%), septic shock (14.24%), and urinary tract infections (UTI) (13.91%). The average dose of fosfomycin given was 11.7 $\pm$ 4.06 gm/day. The average duration of the therapy was 4.85 $\pm$ 3.59 days with a median duration of 4 days. Fosfomycin was given at 8 hourly dosing frequency to maximum (45.6%) cases. Hypokalemia was the most observed adverse event. The overall survival was seen in 55% of patients.

Conclusion: Our data suggest that UTI, infection caused by *Escherichia coli,* and a daily dose of >12 g were associated with better clinical outcomes. The overall survival of critically ill patients receiving fosfomycin was 55%.

Keywords: Critically ill adults, Fosfomycin, Retrospective study.

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Introduction

Fosfomycin is a broad-spectrum, reemerging bactericidal antibiotic active against various gram-positive and gram-negative pathogens.[1] Due to its unique chemical structure and the mechanism of action, fosfomycin does not exhibit cross-resistance with other antibiotics.[2] Intravenous fosfomycin has been prescribed for various serious systemic infections, such as acute osteomyelitis, nosocomial lower respiratory tract infections, complicated urinary tract infections (UTI), bacterial meningitis, and bacteremia, in various countries.[3,4] Standardization of fosfomycin dose for serious infections is needed, as in cases of severe infections, comparatively higher doses may be needed for the prevention of heteroresistant mutant selection. The daily dose used in clinical practice is anywhere between 12 and 24 g as two to four divided doses.[5] A prospective, randomized, controlled clinical trial with fosfomycin in mono- and combination therapy, though having been initiated recently, is still ongoing.

Currently, data on the prescription pattern and safety of intravenous fosfomycin in the daily clinical practice, specifically in critically ill patients, with high bacterial load are still limited. Herein, we present a real-world scenario for prescription pattern and safety data on the current clinical use of intravenous fosfomycin (fosfomycin disodium inj) in critically ill patients in Indian clinical settings.

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Materials and Methods

Study Objective

The primary objective of the study was to analyze the prescription pattern of intravenous fosfomycin in critically ill patients having positive bacterial cultures. The secondary objective was to evaluate the safety profile of fosfomycin and patient outcomes by means of assessing adverse events and all-cause mortality till day 30, respectively.

Study Design and Recruitment

A retrospective cohort study was conducted for period of 10 months (March to December) among critically ill patients admitted to hospital critical care unit suffering from various serious infections and receiving at least 24 hours therapy of fosfomycin disodium injection. Patient's medical records were sought at each site by review of microbiology reports and bacteremia databases. Patients

who had missing key data and death sooner than 24 hours after the index date were excluded from the study. Patients undergoing therapy with an active antibiotic for at least 2 days when blood cultures (BCs) were taken and having subsequent episodes of infection were also excluded.

Key data tracked for enrolled patients included demographics, medical, and surgical history, prior and concomitant medications, physical examination, weight, vital signs, Charlson comorbidity index, Pitts score, BC and aspartate aminotransferase test report, serum electrolytes, hematology, serum chemistry, urinalysis, assessment of adverse events or serious adverse events, and fosfomycin sodium inj. administration details.

Study Endpoints

Primary outcomes included analysis of indication, dose, frequency, and duration of fosfomycin among critically ill patients. Secondary outcomes included analysis of frequencies of adverse events in patients dosed fosfomycin. Further outcomes also comprise comparison of disease severity based upon various scores between survivors and nonsurvivors who were given fosfomycin.

Safety

Tracking of serum electrolytes, serum creatinine, and liver function tests for the 30-days' time period or until discharge/death (whichever occurred first) from patients' medical records was done to capture any significant finding. In cases of fosfomycin discontinuation due to adverse events, the timing and reason were recorded. Renal toxicity was defined as at least a doubling of the baseline creatinine value or a glomerular filtration rate decrease by at least 50%, whereas severe hypokalemia was arbitrarily defined as any serum level <3.0 mEq/L.

Table 1: Baseline characteristics of enrolled patients

Overall average age (years)	60.59 ± 15.90	
Male:Female	193:116	
	Diagnosis	
Diagnosis	*No. of patients*	*Percentage*
Bacteremia	140	45.30
Septic shock	44	14.24
Pneumonia	49	15.85
IAI	3	0.97
Infective endocarditis	4	1.29
Osteomyelitis	2	0.65
SSTI	10	3.24
UTI	53	13.91
Meningitis	2	0.65
Gynecological infection	1	0.32
Suspected CRE infection	1	0.32
Organism		
Enterobacter aerogenes	3	0.9
Escherichia coli	49	15.85
Klebsiella pneumoniae	149	48.22
Proteus mirabilis	3	0.9
Pseudomonas aeruginosa	27	8.73
Serratia marcescens	2	0.64
Staphylococcus spp.	12	3.88
Mixed	47	15.21
No growth	17	5.50

Results

A total of 309 patients' dataset was found valid to be considered for the full analysis set (FAS). The average age of the population in FAS was 60.59 ± 15.90 years. The cohort consisted of 193 (62.45%) males and 116 (37.54%) females (Table 1).

Bacteremia with 45.3% of incidence was the most common diagnosis. The second most common diagnosis was pneumonia (15.85%) followed by septic shock (14.24%) and UTI (13.91%). Cases diagnosed to be UTI had a significantly lower mortality proportion (11 out of 53) (p <0.01) (Table 1). Other cases were skin and soft tissue infections (SSTI) (3.24%) and infective endocarditis, osteomyelitis, meningitis, gynecological infection, and suspected carbapenem-resistant Enterobacteriaceae (CRE) infection (<2% each). The proportion of the various diagnoses among survivors and nonsurvivors was not significantly different except in cases of UTI.

Immunocompromised patients consisted of 21.6% of the mortality group, which was significantly higher than survivors of 12.9% (p = 0.042).

Among the organisms isolated from various culture sources collected from the cohort of critically ill patients, *Klebsiella pneumoniae* with 149 cases (48.22%) was the most common bacterial isolate. With 49 cases (15.9%) of occurrence, *Escherichia coli* emerged as the second most cultured bacteria with significantly lower mortality (21.76% survivor vs 8.63% nonsurvivors) (p = 0.001). No association was observed between the isolated organism and the survival status of the patients.

The average duration of the fosfomycin therapy was 4.85 ± 3.59 days with a median duration of 4 days. Fosfomycin was given at 8 hourly dosing frequency to maximum (45.6%) cases. It was given at 6 hourly and 12 hourly frequencies to 20.1 and 13.3% of cases, respectively. Dosing frequency of more than 12 hours, 3 hours, and stat dose was practiced sparingly (Table 2).

The average dose of fosfomycin given was 11.7 g/day. The average frequency of fosfomycin prescription was 9.13 ± 4.45 hours (3–24 hours). It was noted that 27.4% of cases given a daily dose of ≥12 gm showed clinical resolution as compared to only 4.6% of cases receiving an average daily dose of <12 g (p <0.001).

Hypokalemia was the most observed adverse event with the occurrence seen in a total of 62.1% of cases. However, its incidence was not significantly different between survivors and nonsurvivors. Surprisingly, higher average daily doses, that is, ≥12 g, were associated with a lower incidence of hypokalemia (48.4% in higher vs 75% in lower average doses) (p <0.001). Hypernatremia was observed in a total of 24.3% of cases. It was significantly higher among nonsurvivors (31.7%) as compared to survivors (18.2%) (p = 0.007). Hypernatremia was also recorded in a greater incidence among patients given higher average daily doses of ≥12 g (28.7 vs 19.7%) (p = 0.06) (Table 2). Overall, the survival rate was 55.01% among patients in our study, with the highest for UTI (79.24%) followed by bacteremia (52.14%), pneumonia (44.89%), and septic shock (43.18%). Survival was better with *E. coli* (75.51%) as a pathogen compared to *Klebsiella pneumoniae* (49.66%). The average dose was 11.88 ± 3.83 g/day for 4.71 ± 3.81 days.

Discussion

This retrospective study with 309 patients conducted by our group is among very few studies focused on understanding the

Table 2: Prescription pattern, outcomes, and safety of fosfomycin

Parameters	*Mean*	*SD*
Average dose of fosfomycin (gm)	11.76	4.06
Average duration of therapy (days)	4.66	3.68
Parameters	*No. of patients*	*Percentage*
Fosfomycin dosing (gm/day)		
3	3	1
4	4	1.3
6	62	20.1
8	141	45.6
12	41	13.3
24	18	5.8
>24	40	12.9
Outcomes		
Discharged with clinical cure	50	16.2
Died	139	45
Adverse events		
No adverse events	71	23
Hypokalemia	190	61.5
Hypernatremia	75	24.3

prescription pattern and the use of intravenous fosfomycin in a real-world scenario. The wider use of fosfomycin against various infections was observed in our study, which is in concordance with previous studies.[5]

In real-world practice, fosfomycin has been used not only against infections of various bacterial origins but also at different difficult-to-treat infections, such as those involving biofilm formation.[6] This justifies the prescription of fosfomycin at a higher rate in *Klebsiella pneumoniae* infection observed in this study.[7] The properties of fosfomycin, including its tiny size, good volume of distribution, and tissue penetration, explain the use of fosfomycin in our study cohort for bacteremia, septic shock, infective endocarditis, and meningitis.[8]

The highest percentage of patients in fosfomycin-treated cohort included bacteremia cases. This high percentage of bacteremia patients treated with fosfomycin corroborates with few earlier studies that have shown the use of fosfomycin in combination with other agents for the treatment of bacteremia infections.[9] Noticeably, the percentage of survivors in *E. coli*-infected group was significantly higher than nonsurvivors, suggesting the potential activity of fosfomycin against *E. coli,* which is in line with a previous study that reported 100% susceptibility of fosfomycin to *E. coli* isolates.[10] The average dose of fosfomycin given to the overall population was 11.76 ± 4.06 g/day, and the average duration of the therapy was 4.66 ± 3.68 days. Fosfomycin was given at 8 hourly dosing frequency to maximum (45.6%) cases. We compared the prescription pattern of fosfomycin in our study with various other studies and their outcomes in two contexts, viz. dose and duration. The dose in our study was comparable to a study carried out in two European countries where an average dose of 13.7 g/day was given. Various other studies have also reported the dose of fosfomycin between 12 and 24 g/day.[11,12] We noted that 27.4% of cases receiving an average daily dose of ≥12 g recovered completely compared to only 4.6% of cases given an average daily dose of <12 g (p <0.001). Experts recommend that the dose of fosfomycin could be optimized in case of systemic infections.[13] A multicentric ZEUS study recruiting patients for UTI suggested 18 g daily dose of fosfomycin with 6 g fosfomycin every 8 hours.[14] Based on the observations from various studies, it has been found that on an average in the case of patients with normal renal function, the dose of fosfomycin could be in the range of 12–16 g of total daily dose administered in two to three doses.[15–17]

The maximum number of patients received fosfomycin at 8 hourly frequency that was supported by an *in vivo* study of intravenous fosfomycin disodium showing that effective plasma concentration for susceptible pathogens could be achieved up to 8 hours after intravenous administration.[18] Eight-hour interval has been observed in various other studies also, such as ZEUS study as discussed above.

After intravenous administration of fosfomycin, sodium overload and hypokalemia are the most common adverse events observed. Every gram of intravenous fosfomycin contains 0.32 g of sodium. It has been postulated that fosfomycin leads to increased urinary excretion of potassium in the distal part of the renal tubules. In a French study, hypokalemia was reported in 19 of the 76 subjects, that is, 26% of patients.[19] The authors reported that while potassium was administered in all patients, hypokalemia was found only when fosfomycin was administered in 30–60-minute infusions, while it did not occur when fosfomycin was administered for 4 hours. Similar to the above-reported studies, we also found hypokalemia as the most observed adverse event with the occurrence seen in a total of 62.1% of cases. Incidentally, the higher average daily dose (>12 g) subgroup had a significantly lower incidence of hypokalemia that could not be explained. Hypokalemia is a common manifestation seen in intensive care unit patients, and medications used in the management of various critical conditions are commonly associated with it.[20] Therefore, clinicians should be aware of disturbances in sodium and potassium homeostasis and initiate adequate measures early to avoid further complications.

Conclusion

Our results indicate that bacteremia and pneumonia were the most common indication for fosfomycin prescription. *Klebsiella pneumoniae* was the most common pathogen. UTI and infection caused by *E. coli* were found to be associated with better clinical outcomes.

The overall survival in critically ill patients receiving fosfomycin was 55%. The daily dose of >12 g was associated with better clinical outcomes. Hypokalemia was the most frequent side effect reported.

Limitations and Future Aspects

The retrospective nature of the study posed few challenges like the availability of limited data on culture and sensitivity and resistance pattern to fosfomycin and other combination antibiotics presenting the usage pattern as empirical and less specific. Nonavailability of microbial curve data limited the efficacy outcome measures.

Future studies with double arms in Indian settings can throw more light on the use of fosfomycin in critical infections as targeted monotherapy and in combination with other antibiotics.

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