Original Article

Pentoxifylline in Prevention of Amphotericin B-induced Nephrotoxicity and Electrolyte Abnormalities

Mahsa Panahi-Shokouh[1], Azadeh Moghaddas[1], Shirinsadat Badri[1,2], Saeedeh Jabalameli[1], Mahnaz Momenzadeh[1], Valiollah Mehrzad[3], Farzaneh Ashrafi[3]

[1]Department of Clinical Pharmacy and Pharmacy Practice, Isfahan University of Medical Sciences, Isfahan, Iran

[2]Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

[3]Department of Oncology/ Hematology, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Objective: Amphotericin B is an antifungal agent used to treat serious fungal infections mainly in critically ill patients. Despite its adverse effects including renal toxicity and electrolyte imbalances, amphotericin B remains one of the best choices for antifungal treatment. Information from animal studies has provided a strong scientific basis for the use of pentoxifylline as lowering nephroprotective agent. The present study was designed to evaluate the efficacy of pentoxifylline in preventing renal toxicity and electrolytes imbalances induced by amphotericin B. **Methods:** This study was conducted as a randomized controlled trial on 44 patients admitted to Sayyedoshohada Hospital, Isfahan, Iran, from October 2016 to August 2018. Patients were assigned to one of the two groups: Pentoxifylline, 400 mg twice a day, or matching placebo, from the 1st day of amphotericin B therapy till minimum of 7 days. All patients' information including lab data (serum and urine levels of Mg, Na, and K, serum creatinine level, blood urea nitrogen [BUN] and urinary creatinine excretion) were gathered at the time of drug initiation and during the study period. The results were analyzed by SPSS v. 20 software and Repeated measures test was used to assess the differences between groups **Findings:** This study did not show any significant differences between the two groups in terms of all the assessed variables, including serum and urinary levels of electrolytes, and creatinine, as well as the number of cases presented acute kidney injury during the study period. **Conclusion:** Despite the positive effects of pentoxifylline in preventing renal complications in previous studies, this study could not show a definitive result in salt wasting or renal damage induced by amphotericin B. So, Designing robust studies with more included samples would be valuable.

Keywords: *Amphotericin B, electrolytes imbalance, nephrotoxicity, Pentoxifylline*

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Introduction

Despite more than 50 years of its clinical use and the introduction of newer antifungal agents, amphotericin B has remained as a major antifungal medication for treatment of disseminated, serious, and life-threatening mycotic infections such as *Candida* spp., *Aspergillus* spp., and the Mucorales. This is due to the broad spectrum antifungal activity as well as low rates of resistance to amphotericin B.[1,2] Besides clinical effectiveness, amphotericin B treatment is associated with a range of acute and chronic adverse reactions.[2] Nephrotoxicity and consequent electrolyte imbalances have been demonstrated as the most clinically significant adverse reactions of amphotericin B which may restrict its clinical utility.[3] Electrolyte abnormalities including hypokalemia and hypomagnesemia also occur frequently during amphotericin B therapy in a dose-dependent pattern.[4,5] These electrolyte abnormalities can cause serious complications such as metabolic disorders, rhabdomyolysis, and life-threatening

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Address for correspondence:
Dr. Saeedeh Jabalameli, E-mail: saedeehjameli@yahoo.com

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arrhythmias.[4] Among many approaches studied so far, only saline loading and administering lipid formulations of amphotericin B (especially liposomal amphotericin B) have been clearly implicated to be clinically effective and safe in preventing or decreasing its nephrotoxicity.[6] However, these two modalities are not without disadvantages. For example, excess salt intake may exacerbate the condition of patients with pre-existing sodium or fluid overload such as congestive heart failure and cirrhosis.[7] Lipid formulations of amphotericin B are very expensive and still associated with some degrees of nephrotoxicity and electrolytes imbalances.[6]

Pentoxifylline is a non-specific phosphodiesterase inhibitor used to treat peripheral vascular diseases.[8] Pentoxifylline has several pharmacological effects, including improvement in microcirculation, decreasing blood viscosity, inhibition of platelet aggregation, endothelial-bearing vascular relaxation, immunosuppressive and antiproliferative effects.[9] Also, pentoxifylline inhibits several inflammatory cytokines including TNF-α, interleukin 1 and 6.[10] Pentoxifylline can inhibit the activity and proliferation of lymphocytes and renal fibroblasts, which play an important role in kidney fibrosis.[11] Many studies have demonstrated the positive effects of this drug in diabetic and chronic kidney diseases, chronic cerebrovascular disease and idiopathic infertility.[12-14] Some of the pharmacological mechanisms of this drug to improve acute renal failure include interfering with adenosine receptors, stimulating vasodilator prostaglandin synthesis, inhibiting vascular conjugation, inhibiting nitrate production and inflammatory factors, as well as inhibiting proteinuria and apoptosis.[15] Pentoxifylline reduces the oxidative activity of polymorphonuclear leukocytes that play a role in amphotericin B-induced nephropathy;[16] this mechanism may be considered as the logic for pentoxifylline implication in preventing amphotericin B-induced renal toxicity.

Nephrotoxicity risk can be reduced by using less doses of amphotericin B and by avoiding simultaneous treatment with other nephrotoxins.[17] The use of vasodilator drugs such as calcium channel antagonists in mice[18] and antioxidant drugs such as N-acetylcysteine in humans[19] were also prophylactic interventions to reduce amphotericin B-induced nephropathy.

Considering the pathological background of amphotericin B-induced renal toxicity, we designed a placebo-controlled trial to evaluate the nephroprotrctive effect of pentoxifylline addition to amphotericin B therapy in hospitalized patients. The objective is to answer the question of whether pentoxifylline further improves renal outcome in patients already receiving standard measurement for kidney protection.

Methods

This study was designed as a prospective, placebo-controlled, double-blinded trial, to evaluate the effect of pentoxifylline administration in prevention of amphotericin B-induced electrolytes imbalances and nephrotoxicity.

The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (No. 195013) and was carried out from October 2016 to August 2018. This study was registered in the Iranian Registry of Clinical Trials (No. IRCT2016071328901N1).

Samples were collected from patients admitted to the Sayyedoshohada Hospital, a center of Hematology and Oncology affiliated to Isfahan University of Medical Sciences. The intervention was conducted on 60 patients aged 18-65 years, who were identified to have fungal infection and were supposed to receive conventional amphotericin B for more than seven days. Patients were eligible for enrollment if their baseline creatinine clearance exceeded 60 mL/min.

Subjects entered a two-week study period during which background nephroprotective therapy to prevent amphotericin B nephropathy, which included administration of 0.9% sodium chloride fluid, was established before and left unchanged throughout the study period. Enrolled patients were randomly assigned to one of the two treatment groups, using blocked randomization method: pentoxifylline, 400 mg oral tablets [Amin Pharmaceutical Company, Isfahan, Iran] twice daily or matching placebo. In either groups, pentoxifylline or placebo were added to the standard therapy for the underlying pathology. The physician, patients, the main researcher, and also the analyst were blind for the type of treatment groups. All included patients signed informed consent form.

Baseline and follow-up laboratory assessments included serum creatinine concentration and urinary creatinine excretion, blood urea nitrogen (BUN), serum and urinary levels of Na, K, and Mg, and venous blood gas (VBG). The estimated glomerular filtration rate (eGFR) was calculated by the MDRD (Modification of Diet in Renal Disease) formula.[20]

In this study, NGAL (neutrophil gelatinase-associated lipocalin) was measured in blood samples by ELISA kit at days 0 and 7 from the start of treatment with amphotericin B, to identify acute renal damage due to amphotericin B administration.

Normal distribution of all extracted clinical parameters were investigated in both groups using Kolmogorov–Smirnov test. Furthermore, age, baseline eGFR, total dose and duration of amphotericin B administration, and the mean values of the electrolytes administered for the studied patients during hospitalization, were compared between two groups at the study beginning using Independent Samples T-test.

Differences in the assessed parameters were compared between two study groups at the end of the study, using Repeated measures ANOVA test. Also, the occurrence of acute kidney injury (AKI), defined as a minimum of 0.3 mg/dL increase in serum creatinine within 48 hours from amphotericin B initiation,[21] was evaluated and compared between two groups, using Pearson Chi-Square test.

All analyses were conducted using SPSS for windows (SPSS, Chicago, IL, USA) version 16.0. A level of $P < 0.05$ was considered statistically significant.

Results

Sixteen of the initially screened 60 patients dropped out because of changes in treatment center and loss to follow-up or changes in treatment regimen; thus, forty four patients finally finished the study. These were randomly assigned to pentoxifylline (19 patients) or placebo (25 patients) groups. All patients were administered by conventional amphotericin B for a minimum of seven days, for various fungal infections. The two groups were similar with respect to age ($P = 0.324$) and baseline clinical parameters including eGFR ($P = 0.305$), total dose ($P = 0.778$) and duration ($P = 0.766$) of amphotericin B administration, but not baseline urine potassium excretion ($P = 0.002$); so there were no statistically significant baseline differences between the two groups across all analyzed variables, except urinary potassium excretion. Table 1 shows demographic, clinical, and laboratory characteristics of both groups at baseline, and final (seventh day of treatment) analyses.

As shown in this table, concomitant treatment with pentoxifylline for 7 days besides amphotericin B, resulted in no significant changes in all the assessed variables compared to the placebo group. Nevertheless, according to the Pearson Chi-Square test, the number of AKI occurrence was not significantly different in either groups (2 cases in the pentoxifylline, and 3 cases in the placebo group). The baseline urine potassium excretion was different between groups, however, as demonstrated by ANCOVA sub-analysis, this baseline difference had no effect on the final assessment of this parameter in the two study groups.

The pentoxifylline therapy was well tolerated in this study.

Discussion

This study was the first placebo-controlled clinical trial to investigate the effects of adding pentoxifylline to the therapeutic regimen of patients receiving amphotericin B, to prevent its major side effects, namely electrolyte disturbances and nephrotoxicity.

Recent studies on the renoprotective effects of pentoxifylline is steadily increasing.[22-24]

In two animal studies, pentoxifylline could show beneficial results in reducing renal damage induced by amphotericin B administration.[25,26]

One study conducted on 11 patients with lupus nephritis, showed a decrease in proteinuria concentrations after use of pentoxifylline in all patients.[27] Also, proteinuria reduction has been demonstrated in the other study by administering pentoxifylline (800-1200 mg daily) for six month in patients with membranous glomerulonephritis.[28]

In one study on five patients receiving bone marrow transplantation, the positive effect of administering 1200 mg/day pentoxifylline for at least 2 weeks was shown in the treatment of secondary nephrotoxicity induced by amphotericin B and cyclosporine compared to the control group.[29]

In this placebo-controlled study, the preventive effects of electrolyte disturbances derived from pentoxifylline therapy were evaluated in patients with malignancy or reduced immune status who were treated with conventional amphotericin B for various fungal infections. Although the study attempted to address the limitations of previous studies, including the lack of placebo arm, and the differences in administered pentoxifylline dose, however, the addition of pentoxifylline (800 mg/day) did not show any significant changes in the studied variables compared to the control group, in the present study. Notably it should be considered that the small number of included patients may be a key point for observing the non-significant results of pentoxifylline administration compared to the control group.

Authors' Contribution

Azadeh Moghaddas and Shirinsadat Badri conceptualized the research protocol and interpreted data. Valiollah Mehrzad and Farzaneh Ashrafi helped in patients' recruitment and assisted in manuscript editing. Mahsa Panahi-Shokouh, Saeedeh Jabalameli, and Mahnaz Momenzadeh helped in data collection and analysis, and manuscript writing. All authors read and approved the final version of the manuscript for publication.

Table 1: Demographic, clinical, and laboratory characteristics of both groups at baseline, and final (seventh day of treatment) analyses

Clinical/Laboratory parameter	Study phase	Pentoxifylline group (*n*=19)	Placebo group (*n*=25)	*P*
Age (years)	-	49.40±15.84 (25-79)	44.79±13.79 (18-66)	0.324
eGFR (mL/min)	Baseline	111.31±25.92 (60.1-158.8)	122.53±37.34 (60.5-165.7)	0.305
Dose of Amphotericin B (mg/day)	-	55.27±13.63 (33.75-89.16)	53.99±14.48 (25-91.42)	0.778
Duration of Amphotericin B administration (days)	-	8.53±2.72 (7-14)	8.83±3.26 (7-15)	0.766
Mean values of the electrolytes administered for the studied patients during hospitalization				
K (oral, parenteral)	-	68.96±24.76 (40-120)	55.84±23.7 (40-140)	0.082
Mg (parenteral)	-	6.19±2.14 (3.2-12.8)	6.58±2.51 (3.2-16)	0.590
Na (parenteral)	-	17.68±7.91 (17-25.5)	18.78±8.85 (17-25.5)	0.671
Serum creatinine concentration (mg/dL)	Baseline	0.69±0.19 (0.3-1.1)	0.78±0.17 (0.5-1.1)	0.100
	Day 7	0.86±0.29 (0.5-1.4)	0.91±0.28 (0.5-1.5)	0.635
BUN concentration (mg/dL)	Baseline	11.01±4.65 (4-18)	4.51±8.74 (5-49)	0.052
	Day 7	20.78±11.11 (11-46)	19.91±8.12 (8-45)	0.813
eGFR (mL/min)	Baseline	111.31±25.92 (60.1-158.8)	122.53±37.34 (60.5-165.7)	0.305
	Day 7	85.95±34.99 (42.3-158.5)	100.63±40.24 (39.9-169.1)	0.348
Urine creatinine excretion (mg/dL)	Baseline	21.91±14.46 (9.0-61.0)	29.83±13.22 (6.2-53.1)	0.075
	Day 7	18.01±8.70 (8.5-31.0)	25.81±14.69 (8.9-74.0)	0.172
Serum NGAL concentration (ng/mL)	Baseline	0.568±0.341 (0.342-1.166)	0.659±0.638 (0.342-3.017)	0.360
	Day 7	1.355±1.155 (0.343-3.295)	1.126±0.886 (0.342-4.705)	0.462
VBG values				
Bicarbonate (HCO_3^-)	Baseline	22.47±3.24 (16.2-27.2)	22.40±4.14 (12.8-31.3)	0.964
	Day 7	23.32±1.58 (20.6-24.5)	23.46±4.41 (14.5-31.1)	0.946
$PaCO_2$	Baseline	34.48±4.72 (27-44)	34.86±5.18 (23-42)	0.812
	Day 7	34.43±4.19 (31-41)	34.56±6.09 (25-44)	0.960
pH	Baseline	7.43±0.05 (7.32-7.50)	7.43±0.09 (7.17-7.80)	0.935
	Day 7	7.42±0.06 (7.34-7.49)	7.44±0.04 (7.34-7.49)	0.460
Serum Na level (mEq/L)	Baseline	136.91±3.81 (131.0-144.0)	137.84±4.63 (127.3-148.7)	0.507
	Day 7	141.15±1.69 (138.4-144.0)	139.78±6.06 (128.7-159.0)	0.512
Serum K level (mEq/L)	Baseline	3.91±0.73 (2.90-5.90)	3.71±0.49 (2.90-4.57)	0.303
	Day 7	3.58±0.51 (2.94-4.40)	3.77±0.70 (2.64-5.64)	0.481
Serum Mg level (mEq/L)	Baseline	2.26±0.44 (1.30-3.19)	2.21±0.63 (1.34-3.04)	0.662
	Day 7	2.25±0.35 (1.41-2.60)	2.26±0.45 (1.71-3.49)	0.937
Urine Na excretion (mEq/L)	Baseline	99.19±44.86 (47.0-184.0)	96.63±42.80 (43.0-189.0)	0.855
	Day 7	102.31±33.88 (50.0-167.0)	92.59±42.11 (38.8-170.0)	0.071
Urine K excretion (mEq/L)	Baseline	31.53±14.05 (4.5-47.0)	21.17±6.93 (11.4-40.0)	0.002
	Day 7	28.82±10.40 (6.0-38.0)	22.33±13.86 (5.1-54.0)	0.244
Urine Mg excretion (mEq/L)	Baseline	3.79±2.15 (1.3-10.6)	2.95±1.38 (0.6-7.3)	0.123
	Day 7	4.64±1.94 (2.1-8.6)	3.24±1.69 (0.8-7.1)	0.081

Data presented as Mean±SD (range). SD: Standard deviation; eGFR: Estimated glomerular filtration rate; Na: Sodium; K: Potassium; Mg: Magnesium; BUN: Blood urea nitrogen; NGAL: Neutrophil gelatinase-associated lipocalin; VBG: Venous blood gas

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Conflicts of interest

There are no conflicts of interest.

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