ORIGINAL ARTICLE

Amphotericin B associated nephrotoxicity – A single center retrospective study

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Abstract

Objectives
To analyze frequency of acute kidney injury (AKI) and electrolyte derangements associated with the use of amphotericin B deoxycholate (conventional amphotericin B) and comparison of these adverse effects between children and adults.

Materials & Methods
This is a retrospective study. Medical records of patients who received amphotericin B deoxycholate during 12 months from 1st May 2016 to 30th April 2017 were reviewed to determine patient's baseline characteristics, and to identify use of amphotericin B and calculate incidence of associated nephrotoxicity.

Results
A total of 228 patients received amphotericin B deoxycholate in the study duration. Most of our patients were males (65.8%). 51.75% were adults (=18 years of age). Most patients had cancer and acute lymphoblastic leukemia was the most common primary diagnosis (34.2%). 6.6% patients had co morbid conditions at baseline.

Most of our patients developed amphotericin B related adverse effects. Out of 228 patients who received amphotericin B deoxycholate, 80% developed hypokalemia. Hypokalemia was observed more commonly amongst the pediatric population (86.4%) as compared to adults (74.6%). Similarly, 61% children and 45% adults developed hypomagnesemia. Moreover, 59.2% patients developed acute kidney injury (AKI) with amphotericin B therapy, 9 of which required renal replacement therapy. Development of acute kidney injury was seen more frequently among adults (63.6%), as compared to children (54.5%).

30 days survival among children was 70% as compared to 60% for adults.

Conclusions
The results of the present study allow documentation of adverse effects associated with the use of conventional amphotericin B. This data shows that conventional amphotericin B is commonly associated with electrolyte abnormalities and acute kidney injury. This highlights the need for availability of liposomal or lipid-based formulations of amphotericin B in our country.

Key Words
Amphotericin B; AKI; Electrolyte Imbalance

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Introduction

Invasive fungal infections carry high mortality and morbidity in immunocompromised patients.[1] Amphotericin B is used to treat such fungal infections. However, the use of conventional amphotericin B is associated with serious adverse effects like nephrotoxicity which occurs early during treatment.[2] Other adverse effects of amphotericin B include infusion reactions and electrolyte abnormalities like hypokalemia and hypomagnesemia.[3]

The nephrotoxicity is thought to be caused by the direct toxic effect of amphotericin B on renal tubular cells, resulting in acute tubular necrosis and vasoconstriction.[4-5] Both these processes reduce glomerular filtration.[4-5] This nephrotoxic effect of conventional amphotericin B has been observed to be dose dependent and duration dependent. Other risk factors for amphotericin B associated nephrotoxicity include patient weight, diuretic use during amphotericin therapy, abnormal baseline creatinine and concomitant use of nephrotoxins especially cyclosporine. [6-7]

Relatively limited data is available in Pakistan regarding the incidence of nephrotoxicity associated with the use of conventional amphotericin B. Previous international studies have reported a variable frequency of amphotericin B associated acute renal failure ranging from 15% to 80%.[3,8] This high incidence of nephrotoxicity can be reduced by using lipid based or liposomal formulations of amphotericin B instead of conventional amphotericin B.[9]

Evaluation of the incidence of nephrotoxicity (acute kidney injury, electrolyte derangements) associated with use of

amphotericin could help us inform decisions about the need for newer, more costly but less nephrotoxic agents. Therefore, we performed a retrospective cross-sectional study that investigated the frequency of acute kidney injury and electrolyte derangements among patients who received conventional amphotericin B. In our study we also compared the incidence of these adverse effects between pediatric and adult populations.

Patients and Methods

Study setting

This study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC), a specialist charitable cancer hospital in Lahore, Pakistan. The hospital provides a full complement of cancer treatment to patients from all over the country.

Study Population

A total of 228 patients who received amphotericin B deoxycholate during the study period of 1 year from 1st May 2016 to 30th April 2017 were included in the study. This study was approved by the institutional review board of SKMCH&RC.

Data Extraction & Methods

The hospital's information system database was used to identify all patients who had received amphotericin B during the study period. The medical records were reviewed and retrospectively evaluated to collect the data. Baseline renal functions including baseline serum potassium, magnesium, creatinine, creatinine clearance and GFR were the last values before the start of amphotericin B & were noted. Following this, the peak value of serum creatinine in next 7 days & lowest values of serum potassium & magnesium during amphotericin B therapy were recorded. Incidence of acute kidney injury, hypokalemia & hypomagnesemia was recorded. Determinants including primary diagnosis, age, gender, indications for the use of amphotericin B, the dose of amphotericin B therapy, baseline absolute neutrophil count, days of neutropenia, co morbidities (Diabetes, Hypertension), need for renal replacement therapy, need for K & Mg replacement, hospital admission outcome, readmission, mortality & 30 days survival were also noted. Comparison of nephrotoxicity was made between children and adults.

Outcome Measures & Operational definitions

- AKI was defined according **Criteria (KDIGO) of acute kidney injury** i.e., Increase in serum creatinine to =1.5 times baseline, which is known or presumed to have occurred within the prior seven days after the start of amphotericin B.
- Hypokalemia was defined as serum potassium level of < 3.3 mmol/L. (Reference range 3.3-5.1 mmol/L)
- Hypomagnesemia was defined as serum magnesium level < 1.5 mg/dl. (Reference range 1.5-2.5 mg/dl)

Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software (version 20.0; SPSS, Chicago, IL, USA). Continuous variables were stated as Mean ± SD and categorical variables were computed as frequencies and percentages. Categorical variables were compared using chi square test or fisher's exact test (where necessary). Statistical significance was defined as a two-tailed p-value 0.05.

Results

Descriptive statistics

Altogether, there were 228 patients who received amphotericin B deoxycholate during the study period. Patients had a mean age of 21.03±19.30 years and most of the patients were male (65%). Patients were approximately equally distributed in adult and pediatric age groups (51% Vs 49%). Most of our study population comprised of cancer patients (97%) and acute lymphoblastic leukemia was the most common primary diagnosis (34.2%). Patients received a mean dose of 0.97 mg/kg of amphotericin B deoxycholate. (Table 1)

On assessment of patient's baseline status, we found that relatively few patients had co morbid conditions like diabetes mellitus, hypertension, and ischemic heart disease at baseline (6.6%). Similarly, only 5% patients had chronic kidney disease (CKD) and acute kidney injury (AKI) at baseline (Table 1).

We observed that most of our patients received amphotericin B empirically (78.5%) while 15% had positive fungal cultures and 6.5% had a positive fungal histopathology. Among the patients who had a positive fungal identification (either culture or histopathology), *Aspergillus* species were most common (42%) followed by *Candida* species (34%) and *Mucor* (14%). (Table 2)

On calculation of the incidence of adverse effects, we observed that a high percentage of our patients developed adverse effects with hypokalemia being the most common (80%). We also observed that the incidence of hypokalemia was higher in pediatric population (86%), as compared to adults (74.6%) (a statistically significant difference, p-value 0.02).

Furthermore, there was a statistically significant drop in mean serum potassium levels in both age groups as compared to baseline values with amphotericin B therapy. (1.22 mmol/L children, 0.82 mmol/L adults).

On analysis of hypomagnesemia, the incidence was found to be comparatively low as compared to hypokalemia (53.7% Vs 80%). Hypomagnesemia was also more common in pediatric population (61%) as compared to adults (45%) with a borderline statistical significance (p- value 0.09). Furthermore, a statistically significant drop in mean baseline Mg level was observed in both age groups with amphotericin B therapy (0.57 mmol/L children, 0.18 mmol/L adults). Table 2

Among our study population, 59% patients developed acute

Table 1: Description of study population.

Variables	Characteristics	Frequency N (%)
Age (years)	Mean ± standard deviation	21.03 ± 19.30
Age Groups	Pediatric	110 (48.2%)
	Adults	118 (51.8%)
Sex	Male	150 (65.8%)
	Female	78 (34.2%)
Comorbidity	None	213 (93.4%)
	Diabetes Mellitus (DM)	5 (2.2%)
	Hypertension (HTN)	3 (1.3%)
	Ischemic heart disease (IHD)	1 (0.4%)
	Multiple co-morbidities	6 (2.6%)
Chronic Kidney Disease (Baseline)	Yes	14 (6.1%)
Acute Kidney Injury (Baseline)	Yes	12 (5.3%)
Primary Diagnosis (Cancer patients)	Acute lymphoblastic leukemia	78 (34.2%)
	Non-Hodgkin's Lymphoma	59 (25.9%)
	Hodgkin's Lymphoma	16 (7.0%)
	Sarcoma	15 (6.5%)
	Breast Cancer	9 (3.9%)
	Others	45 (19.7%)
Infection as Primary Diagnosis (Non-Cancer patients)	Mucormycosis	3 (1.3%)
	Aspergillosis	3 (1.3%)
Baseline Absolute Neutrophil Count	Mean ± standard deviation	1.42 ± 3.64
Dose of Amphotericin B (mg/Kg*)	Mean ± standard deviation	0.97 ± 0.12

Table 2: Values of potassium, magnesium, and creatinine before and after therapy (Amphotericin B).

Variables	Before Therapy	With Therapy	Mean Difference	p-value
Pediatric Group				
Mean Potassium (mmol/L*)	4.06 ± 0.64	2.84 ± 0.67	1.22 ± 0.83	0.001
Mean Magnesium (mg/dl**)	1.98 ± 0.35	1.42 ± 0.40	0.57 ± 0.38	0.001
Mean Creatinine (mg/dl**)	0.19 ± 0.19	0.38 ± 0.33	0.18 ± 0.30	0.001
Adult Group				
Mean Potassium (mmol/L*)	3.84 ± 0.64	3.02 ± 0.70	0.82 ± 0.68	0.001
Mean Magnesium (mg/dl**)	1.71 ± 0.49	1.53 ± 0.50	0.18 ± 0.36	0.002
Mean Creatinine (mg/dl**)	0.70 ± 0.53	1.51 ± 1.09	0.81 ± 0.99	0.001

***millimole/liter, **milligram/deciliter**

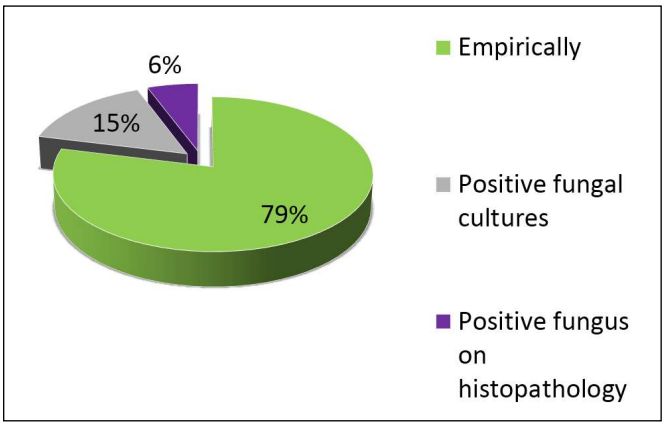

Fig 1. Indications to start amphotericin B

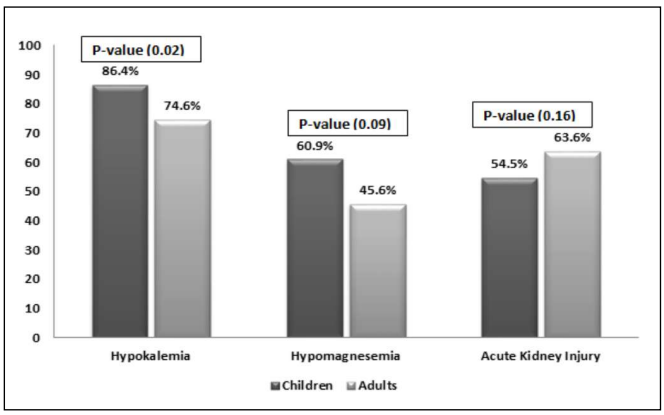

Fig 2. Incidence of side effects and comparison between children and adults

kidney injury with amphotericin B therapy. In contrast to electrolyte abnormalities, incidence of AKI was higher among adults (63.55%) as compared to children (54%), although this difference between age groups was not found to be statistically significant (p-value 0.16) Table 3. Furthermore, there was a statistically significant increase in mean serum creatinine levels in both age groups as compared to mean baseline values with amphotericin B therapy. (Increase of 0.18 mg/dl for children, 0.81 mg/dl for adults)

Evaluating mortality, we calculated that 30 days survival among children was 70% as compared to 60% for adults.

Discussion

Conventional amphotericin B has remained a cornerstone of therapy for systemic fungal infections for a long time, however its use has always been hampered by adverse effects like hypokalemia, hypomagnesemia and acute kidney injury.[10] Therefore, a balance between toxicity and efficacy has to be maintained while prescribing amphotericin B.[11]

The incidence of these undesirable effects can be reduced at the expense of cost with the use of newer forms of amphotericin B. [12] Lipid based formulations or liposomal amphotericin B have replaced conventional amphotericin B in developed countries however conventional amphotericin B is still the main antifungal agent that is being used in resource limited countries.

Our data suggests that most of our patients who received amphotericin B developed adverse effects. Hypokalemia was most observed adverse effect (80%) followed by acute kidney injury (59%) and hypomagnesemia (53.7%) respectively. Prior work on this topic has reported a variable frequency of amphotericin B associated acute kidney injury and other adverse effects. [3,13] The incidence of these adverse effects depends on many factors including dose of amphotericin B, baseline renal function status of patient and co morbidities. [6-7]

Gandhi et al. in 2005 reported incidence of renal adverse effects in up to 80% of the patients.[13] This is like results of our study. Bates et al. and Harbarth et al. reported a frequency of 27% and 28% respectively. [4-5]

Pathak et al. conducted their study in a community hospital and reported a frequency of just 15% however they used a broader definition of acute kidney injury than the current definition. [3] Additionally that study was conducted in a community hospital, and, therefore, the patients may have been less ill than the patients in the current study.

Our study documented a high incidence of amphotericin B associated nephrotoxicity with 59% of our patients developing acute kidney injury. In addition to the estimation of incidence of adverse effects our study also analyzed the quantitative difference in values of serum potassium, magnesium, and creatinine with amphotericin B therapy. We observed significant drops in mean baseline values of potassium and magnesium and a significant increase in mean baseline value of creatinine with amphotericin B therapy.

There has been no prior work on comparison of adverse effects between age groups. So, we also compared the incidence of adverse effects between the age groups. Our data suggests that the incidence of hypokalemia and hypomagnesemia was more common in pediatric population, though for hypomagnesemia the difference between age groups was found to have only borderline statistical significance (p- value 0.09). On analysis of acute kidney injury, the incidence was found to be higher in adult groups, though this difference between age groups was found to be statistically insignificant (p-value 0.16).

Our study has reported an alarming frequency of adverse effects related to conventional amphotericin B; however, this study has several limitations. This study is conducted in a specialized cancer-care institution, and the results may not be generalizable to other institutions. In addition, confounding by indication for initiating amphotericin therapy may exist. Most of the patients in current study received amphotericin B empirically (78.5%),

usually in the setting of fever and neutropenia, while only 21.5% received amphotericin B because of documented fungal infection. Also, confounding by severity of illness may exist. Similarly, we did not collect data about cyclosporine or hydration status at the time of acute kidney injury development, which might have been correlated with the presence of acute kidney injury.

Conclusions:

The results of the present study allow documentation of adverse effects associated with the use of conventional amphotericin B. This data shows that conventional amphotericin B is commonly associated with electrolyte abnormalities and acute kidney injury. This highlights the need for availability of liposomal or lipid-based formulations of amphotericin B in our country.

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