Proteinuria lowers the risk of amphotericin B-associated hypokalaemia

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Objectives: Amphotericin B-induced nephrotoxicity is frequent, severe and associated with an increased risk of death. Patients with underlying renal disease are considered to be at high risk for amphotericin B nephrotoxicity. Amphotericin B is a molecule that is highly protein bound over a wide range of protein and drug concentrations, including those seen in patients with ≥3+ proteinuria. We hypothesized that amphotericin B treatment in patients with proteinuria will be associated with less hypokalaemia than patients with non-proteinuric renal disease.

Methods: Thirty-six subjects who received amphotericin B deoxycholate were studied retrospectively. Twenty-five patients with proteinuria <3 g/L and 11 with proteinuria ≥3 g/L were compared.

Results: Hypokalaemia (K+ <3.5 mmol/L) developed in 47.2% (17/36) of our cohort of patients. There was a 64% (16/25) incidence of hypokalaemia in the group with <3 g/L of proteinuria in contrast to an incidence of 9.1% (1/11) in the other group.

Conclusions: In our study, heavy proteinuria appears to protect the tubular luminal membrane by decreasing the luminal concentration of free drug available to bind with the membrane. Our findings redefine the patient population deemed to be at risk of developing amphotericin B nephrotoxicity. This ensures the benefit of this important antifungal treatment option to patients with heavy proteinuria who might otherwise not be administered this drug due to the presence of pre-existing kidney disease.

Keywords: nephrotoxicity, tubular toxicity, protein binding, drug–protein interaction, antifungal therapy, electrolyte abnormalities

Introduction

Amphotericin B deoxycholate has been available for more than four decades and it continues to play a major role in the treatment of systemic mycoses.1,2 Unfortunately, amphotericin B is associated with acute and chronic adverse effects, especially nephrotoxicity. Amphotericin B-induced nephrotoxicity is frequent, severe and associated with an increased risk of death. Reported renal adverse effects associated with the administration of amphotericin B include hypokalaemia,3,4 hypomagnesaemia5,6 and renal tubular acidosis,4,7 decreased glomerular filtration rate (GFR)8 and acute tubular necrosis.8 As a result, early detection of renal toxicity can be accomplished by looking for evidence of tubular dysfunction such as hypokalaemia.9 Patients with underlying renal disease are considered to be at high risk for amphotericin B nephrotoxicity. A lower tubular luminal concentration of filtered free drug may lower the incidence of amphotericin B tubular toxicity. The presence of urinary protein may lower the concentration of free drug through protein binding. We hypothesized that amphotericin B treatment in patients with proteinuria will be associated with less hypokalaemia than in patients with non-proteinuric renal disease.

Mechanisms of amphotericin B nephrotoxicity

The adverse effect of amphotericin B on the kidneys is mediated by two independent mechanisms: an increase in the afferent arteriolar resistance and an increase in the tubular permeability.10 The acute increase in afferent arteriolar resistance caused by amphotericin B lowers renal blood flow6,11 and GFR.10 Studies in toad and turtle bladders (surrogates for human
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distal nephron) suggest that the mucosal surface (luminal side) is the major site of action of amphotericin B, with no detectable effect on the basolateral surface of the cells. The increase in tubular luminal membrane permeability to monovalent cations results from the formation of intramembranous pores after binding with sterol molecules in the membranes. The increased permeability causes an increased movement of K⁺ and H⁺ ions across the luminal membrane along their respective electrochemical gradients. This movement leads to the increased potassium loss in the urine and impaired urine acidification often seen with amphotericin B administration.

Methodology

We reviewed the medical records of patients admitted to the Harlem Hospital Center who received conventional amphotericin B deoxycholate therapy between 1 January 2002 and 31 December 2004. We excluded patients who were treated for fewer than 7 days or who received a cumulative dose of <200 mg of amphotericin B. Thirty-six subjects were at risk for developing amphotericin B-related hypokalaemia: patients were divided into two groups. Patients in group 1 had proteinuria <3 g/L (<3+) on a semi-quantitative urinalysis (Table 1) and patients in group 2 had proteinuria ≥3 g/L (≥3+). The urine protein was estimated using urine dipsticks (Multistix, Bayer), which is a semi-quantitative colorimetric test that uses tetrabromophenol blue indicator and is based on the protein-error-of-indicators principle.

All patients received the same formulation of conventional amphotericin B, using a standardized administration protocol recommended by our hospital pharmacy. Patients received oral diphenhydramine 25 mg and acetaminophen 1000 mg with 500 mL of 0.9% sodium chloride intravenous infusion an hour prior to the administration of amphotericin B. Patients received another 500 mL sodium chloride infusion following administration of amphotericin B.

We collected patient weight, indication for therapy, daily drug dosage and duration of amphotericin B therapy, concurrent medications, duration of therapy, cumulative dose of amphotericin, serum electrolytes, renal function, blood pH, serum albumin, urine specific gravity and pH of the two groups (Table 2). Hypokalaemia (K⁺ <3.5 mmol/L) developed in 47.2% (17/36) of patients. There was a 64% (16/25) incidence of hypokalaemia in the group with <3 g/L of proteinuria (group 1). This contrasted sharply with the single case (9.1%) of hypokalaemia among the patients with proteinuria ≥3 g/L (group 2). The difference in the incidence of hypokalaemia was statistically significant (Fisher’s exact test, \( P = 0.024 \)).

Statistical analyses

We used SPSS version 14.0 for our statistical analyses. We compared the baseline patient characteristics and laboratory data of the two groups using the \( t \)-test (for continuous data) and the \( \chi^2 \) or Fisher’s exact tests (for categorical data). The incidence of hypokalaemia in the two groups was compared using the Fisher’s exact test.

Results

Thirty-six subjects were studied. Twenty-five patients were in group 1 (proteinuria <3 g/L) and 11 in group 2 (proteinuria ≥3 g/L). At baseline, there was no significant difference in the age, gender, weight, prevalence of co-morbidities (diabetes mellitus, hypertension, HIV or hepatitis C infection), indication for amphotericin B therapy, concurrent medications, duration of therapy, cumulative dose of amphotericin, serum electrolytes, renal function, blood pH, serum albumin, urine specific gravity and pH of the two groups (Table 2). Hypokalaemia (K⁺ <3.5 mmol/L) developed in 47.2% (17/36) of patients. There was a 64% (16/25) incidence of hypokalaemia in the group with <3 g/L of proteinuria (group 1). This contrasted sharply with the single case (9.1%) of hypokalaemia among the patients with proteinuria ≥3 g/L (group 2). The difference in the incidence of hypokalaemia was statistically significant (Fisher’s exact test, \( P = 0.024 \)). This difference occurred despite the higher mean potassium supplementation (667.5 ± 1239 versus 312 ± 290 mEq, \( P = \) not significant) for patients in group 1 and the significantly greater number of patients who received potassium supplementation (64% versus 18.2%, \( P < 0.05 \)) in group 1. The lack of a statistical difference in the potassium supplementation requirements between the two groups probably reflects the limited power of our study.

Discussion

Depending on the type of assay used, it is estimated that between 3% and 20% of amphotericin B is excreted unchanged in the urine. Thus, patients receiving a dose of 70 mg/day (at 0.25–1 mg/kg) of amphotericin B excrete at least 1–2 mg/day and up to ~14 mg/day. This corresponds to a urinary excretion rate of at least 1–2 μmol/L (amphotericin B mol. wt of 924.09 Da). Urinary dipstick finding of ≥3+ corresponds to an approximate urinary albumin concentration of ≥40 μmol/L. Amphotericin B is a highly protein bound molecule over a wide range of protein and drug concentrations even at the lowest urinary drug concentrations.

Amphotericin B-related tubular toxicity results in increased luminal membrane permeability to monovalent cations such as H⁺ and K⁺. The high affinity binding of amphotericin B to albumin at the protein and drug concentrations seen in the tubular lumen decreases the free drug available to bind to the luminal surface of the epithelial cells. This hypothesis is supported by the significantly lower incidence of hypokalaemia among patients with heavy proteinuria.

Patients with pre-existing kidney disease (manifested by a reduced GFR) are predisposed to the development of amphotericin B nephrotoxicity and the resultant electrolyte abnormalities including hypokalaemia and metabolic acidosis. To the best of our knowledge, the effect of proteinuria on the likelihood of developing amphotericin B-associated hypokalaemia in patients

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Table 1. Frequency and degree of proteinuria in the cohort

<table>
<thead>
<tr>
<th>Proteinuria on dipstick</th>
<th>Amount of protein in urine (mg/L)</th>
<th>Number of patients in each category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Trace</td>
<td>&lt;300</td>
<td>1</td>
</tr>
<tr>
<td>1+</td>
<td>&gt;300</td>
<td>12</td>
</tr>
<tr>
<td>2+</td>
<td>&gt;1000</td>
<td>7</td>
</tr>
<tr>
<td>3+</td>
<td>&gt;3000</td>
<td>5</td>
</tr>
<tr>
<td>4+</td>
<td>&gt;20000</td>
<td>5</td>
</tr>
</tbody>
</table>
Prevalence of co-morbidities

In addition, we were unable to limit statistical analysis power and the retrospective design of the study could have biased our findings. Furthermore, we were unable to protect the tubular luminal membrane by decreasing the luminal concentration of free drug available to bind with the membrane. The protective effect of heavy proteinuria was reflected in a significantly lower incidence of amphotericin B-related nephrotoxicity in patients with heavy proteinuria compared with those with lower rates of protein excretion. Patients with HIV/AIDS often require systemic antifungal therapy and this subset of patients is also at risk of developing heavy proteinuria resulting from secondary glomerulonephritis such as HIV-associated nephropathy. Our findings may redefine the patient population deemed to be at risk of developing amphotericin B nephrotoxicity. This may provide the benefit of this important antifungal treatment option to patients with heavy proteinuria who might otherwise not be administered this drug due to the presence of pre-existing kidney disease. Further prospective studies are needed to confirm our findings.

Conclusions

Kidney disease associated with a decreased GFR is a well-known risk factor for the development of amphotericin B-related nephrotoxicity. In our study, heavy proteinuria appears to protect the tubular luminal membrane by decreasing the luminal concentration of free drug available to bind with the membrane. The protective effect of heavy proteinuria was reflected in a significantly lower incidence of amphotericin B-related nephrotoxicity in patients with heavy proteinuria compared with those with lower rates of protein excretion. Patients with HIV/AIDS often require systemic antifungal therapy and this subset of patients is also at risk of developing heavy proteinuria resulting from secondary glomerulonephritis such as HIV-associated nephropathy. Our findings may redefine the patient population deemed to be at risk of developing amphotericin B nephrotoxicity. This may provide the benefit of this important antifungal treatment option to patients with heavy proteinuria who might otherwise not be administered this drug due to the presence of pre-existing kidney disease. Further prospective studies are needed to confirm our findings.

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Transparency declarations

None to declare.

References

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