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Amphotericin B nephrotoxicity

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The use of amphotericin B limited by dose-dependent nephrotoxicity. Elevated creatinine associated with amphotericin B is not only a marker for renal dysfunction, but is also linked to an increase in hospital costs and a substantial risk for the use of haemodialysis and a higher mortality rate. Therefore, amphotericin B nephrotoxicity is not a benign complication and its prevention is essential. Several manipulations have been proposed to minimize amphotericin B-induced nephrotoxicity. Mannitol and frusemide administration are reported to be protective based on anecdotal observational reports. Small prospective and randomized trials do not suggest a protective effect. Three new formulations have been developed in attempts to improve both efficacy and tolerability: amphotericin B in a lipid complex (ABLC; Abelcet); amphotericin B colloidal dispersion; and liposomal amphotericin B (AmBisome). Three prospective randomized studies have clearly shown that AmBisome is less nephrotoxic than amphotericin B. In a double-blind randomized trial significantly fewer patients receiving AmBisome had nephrotoxic effects. This significant reduction in azotaemia was also observed among subgroups of patients receiving concomitant therapy with nephrotoxic agents. Moreover, there were fewer patients with hypokalaemia in the group receiving AmBisome. A recent multicentre double-blind study has shown that AmBisome (3 or 5 mg/kg/day) has a better safety profile than Abelcet (5 mg/kg). Patients in both AmBisome treatment groups experienced less chills/rigors, less nephrotoxicity based on a doubling of serum creatinine, and fewer toxic reactions resulting in discontinuation of therapy. In conclusion, amphotericin B nephrotoxicity is observed frequently. It clearly increases patient mortality. Nephrotoxicity must be recognized early, based on tubular abnormalities and a mild increase in serum creatinine. Its prevention relies on the detection and suppression of risk factors and the use of AmBisome.

Introduction

Therapeutic regimens have advanced at an increasingly frenetic pace in recent years, and there are very few areas in which the first effective treatment is still the treatment of choice. Quinine is one example, amphotericin B another. If this drug were not effective against so many fungal pathogens, it would have been abandoned many years ago. Amphotericin B remains the most effective drug in treating systemic fungal infections. Nevertheless, it can produce a wide variety of acute and chronic side effects, the most important of which is nephrotoxicity.

There are three reasons why we must be aware of this complication: (i) incidence; (ii) severity; and (iii) clinical consequences.

Incidence and severity of amphotericin B nephrotoxicity

The incidence of amphotericin B nephrotoxicity is very high and there is reason to be cautious. Acute renal failure is common. Several papers report rates of acute renal failure for patients on amphotericin B between 49% and 65%.[1–4] In the study by Wingard *et al.*,[1] >50% of patients had a significant increase in serum creatinine compared with baseline. Specifically, serum creatinine doubled in 53% of patients and 29% had a serum creatinine of >250 mmol/L, representing a decrease in renal function of at least 70%. Furthermore, 15% of all patients in the study required dialysis. Amphotericin B nephrotoxicity is frequent and severe.

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In addition, this study looked retrospectively at the clinical significance of amphotericin B nephrotoxicity: the rate of nephrotoxicity, dialysis and fatality; factors associated with fatality were analysed using multivariate Cox's proportional hazards analysis. The use of other nephrotoxic therapies and dialysis were significantly associated with mortality. When a patient requires dialysis, he/she has a three-fold increase in the risk of mortality. The mortality rate of patients not dialysed as compared with patients that were dialysed, was 76% versus 57% ($P = 0.039$). Thus, every effort must be made to prevent renal failure.

Amphotericin B nephrotoxicity is frequent and severe, and clearly associated with the risk of death; therefore, we must understand the pathophysiology of this complication and if possible, prevent amphotericin B nephrotoxicity.

Pathophysiology of amphotericin B nephrotoxicity

The pathophysiology of nephrotoxicity involves vasoconstriction and direct interaction with epithelial cell membranes. These alterations are responsible for the decrease in glomerular filtration rate (GFR) and tubular dysfunction. It has been known for some years that amphotericin B, when given in animal models, will decrease renal blood flow. This can happen as quickly as 45 min after infusion of amphotericin B. The same effect has been reported in humans. In five patients who received amphotericin B, renal blood flow and GFR (based on inulin clearance) were assessed before, during and up to 6 months after cessation of treatment.[5] Mean renal blood flow decrease was 55% during drug administration. In four patients studied 4–6 months later, inulin clearance was only 85% of the initial control value. Thus, amphotericin B induced marked vasoconstriction without normalization of renal function occurring after the drug was stopped. To summarize the mechanisms of toxicity to the kidneys, amphotericin B forms pores in membranes that cause tubular dysfunction. Amphotericin B is also responsible for severe vasoconstriction that will decrease renal blood flow and GFR and ultimately cause ischaemic injury. Together these two mechanisms induce acute renal dysfunction.

Prevention of amphotericin B nephrotoxicity

Can amphotericin B nephrotoxicity be prevented? There are three possible ways: (i) Intralipid, or other pharmacological agents; (ii) infusion rate; and (iii) early detection of risk factors and renal toxicity and the use of new formulations.

Intralipid

When Intralipid and amphotericin B are mixed, the effect is similar to 'French mayonnaise'. The main ingredients are known, but we do not know the toxicity. There are five prospective trials comparing renal toxicity of amphotericin B in either glucose or Intralipid[6–10] (Table 1). In three of these, there was less nephrotoxicity, but the remaining (in the more critical patients) found no efficacy in mixing amphotericin B and Intralipid in lowering the renal toxicity. Therefore the beneficial effect is unknown. Furthermore, problems associated with the mixture include: lower antimycotic activity; thrombocytopenia; hepatic function abnormalities; cholestasis; and pulmonary toxicity. Intralipid mixed with amphotericin B cannot be recommended.

Other pharmacological agents

Diuretics have been used for the last 50 years for prevention of drug-induced nephrotoxicity.

Mannitol decreases renal medullary PO_2 and renal medullary blood flow. There are no experimental data to support the use of mannitol in the prevention of amphotericin B-induced nephrotoxicity. Only one randomized clinical trial has looked at the effect of mannitol on amphotericin B nephrotoxicity.[11] Eleven patients were randomized to receive amphotericin B in either 5% glucose alone (control), or 5% glucose with 1 g/kg mannitol. The study found that mannitol did not prevent either functional or histological manifestations of amphotericin B toxicity. Creatinine clearance was depressed in both groups and all but one patient needed potassium supplementation. I do not recommend the use of diuretics in an attempt to reduce amphotericin B-induced nephrotoxicity.

Infusion rates

Can the nephrotoxic effects of amphotericin B be reduced by altering infusion rates? One prospective study by Ellis *et al.*[12] concluded that infusion rates did not modify amphotericin B toxicity. However, in patients with renal insufficiency, rapid infusion may be responsible for severe hyperkalaemia and potentially fatal arrhythmia.[5,13] In patients with renal insufficiency, amphotericin B must be infused at a low rate.

Risk factors of amphotericin B nephrotoxicity

Potential risk factors that could affect the nephrotoxicity of amphotericin B include: the patient's average daily amphotericin B dose; dehydration; cumulative dose; abnormal baseline renal function; concomitant nephrotoxic drugs (e.g. cyclosporin); and patient's risk category.

Regarding risk category, the study by Wingard *et al.*[1] examined the rate of nephrotoxicity and haemodialysis in four separate patient groups (Table 2). The rate of nephrotoxicity in both allogeneic and autologous bone marrow transplant (BMT) patients was much higher than in solid organ transplant patients. Therefore, BMT patients should be considered at very high risk of acquiring nephrotoxicity from amphotericin B. To assist in the prevention of ampho-

Table 1. Prospective trials evaluating ability of Intralipid to reduce renal toxicity of amphotericin B

Publication	Patient population	Reduced nephrotoxicity
Moreau *et al*. (1992)[6]	haematology patients	yes
Caillot *et al*. (1994)[7]	haematology patients	yes
Sorkine *et al*. (1996)[8]	ICU critically ill patients	yes
Schoffshi *et al*. (1998)[9]	neutropenic patients	no
Nucci *et al*. (1999)[10]	oncology patients	no

ICU, intensive care unit.

Table 2. Nephrotoxicity and renal failure in different patient groups

Patient group	Nephrotoxicity (2× creatinine) (%)	Dialysis required (%)
Allogeneic BMT	61	20
Autologous BMT	80	19
Solid organ transplantation	35	18
Non-transplantation	54	7

From Wingard *et al.*[1]

tericin B nephrotoxicity, it is essential to identify and monitor the risk factors listed above. The early detection of renal toxicity can be accomplished by looking for clinical evidence of amphotericin B nephrotoxicity, such as tubular dysfunction and renal insufficiency. Amphotericin B will induce the following alterations in a high percentage of patients: hypokalaemia, 25–75% of patients; hypomagnesaemia, 30–75% of patients; renal tubular acidosis, 50–100% of patients; and polyuria, 50–100% of patients. Importantly, these abnormalities will occur before renal insufficiency and are dose dependent.

The other feature of amphotericin B nephrotoxicity is azotaemia. Azotaemia is characterized by an increase in serum creatinine and is preceded by tubular dysfunction. Azotaemia is considered reversible upon the discontinuation of drug but may be irreversible with large cumulative doses of amphotericin B (>4 g). Assessment of renal function with inulin clearance shows a significant reduction in GFR in many patients. Azotaemia is often underestimated by serum creatinine assessment. A 25% rise in serum creatinine level may appear small, but actually represents a substantial fall in GFR—perhaps as much as a 50% reduction. This is because of the exponential rise in serum creatinine level with declining renal function. In addition, overall renal function and muscle mass decline in parallel with advancing age or severe disease. Therefore, older and very sick patients with a normal serum creatinine have a GFR of only *c.* 30% of that of a young healthy adult. Therefore, patients in these categories are at higher risk for amphotericin B nephrotoxicity. A 25% rise in serum creatinine should be considered as evidence of drug toxicity.

Lipid formulations of amphotericin B

There are three lipid formulations of amphotericin B that are commercially available: AmBisome (Gilead Sciences), a true liposome structure; Abelcet [amphotericin B lipid complex (ABLC), Wyeth], with a ribbon-like structure; and Amphocil/Amphotec [amphotericin B colloid dispersion (ABCD), Sequus Pharmaceuticals], composed of disc-like structures. Are these formulations less nephrotoxic? If the answer is yes, which one is best?

Data from six different randomized clinical trials comparing renal toxicity of the various amphotericin B lipid formulations with conventional amphotericin B, or, in one case, with each other, are available. White *et al.*[2] performed a randomized, double-blind clinical trial of ABCD versus amphotericin B in the empirical treatment of fever and neutropenia in >200 patients. Treatment was either ABCD 4 mg/kg/day or amphotericin B 0.8 mg/kg/day. Renal toxicity was defined as a doubling of serum creatinine, an absolute serum creatinine increase of 100 mmol/L or a 50% decrease in creatinine clearance. In all evaluable patients, the incidence of ABCD nephrotoxicity was *c.* 40% in comparison with 60% with amphotericin B. Thus, in this study, ABCD was significantly less nephrotoxic than amphotericin B.

For Abelcet there is only one full publication by Sharkey *et al.*[14] which looked at the effects of Abelcet compared with amphotericin B for patients with cryptococcal meningitis. Treatments included amphotericin B, given at l mg/kg/day, and Abelcet given to separate cohorts at 1.2 mg/kg/day, 2.5 mg/kg/day, and 5 mg/kg/day. At the highest dose of Abelcet, the 6 week mean increase in serum creatinine was 49 mmol/L compared with an increase of 80 mmol/L for the amphotericin B group.[8] This difference was statistically significantly. However, the percentage of patients with a two-fold increase in serum creatinine level was virtually identical for these two groups (50% and 53% for Abelcet and amphotericin B, respectively). The authors also pointed out that potassium and magnesium levels were decreased in 24% of patients in both of these groups. There are no randomized studies to suggest that Abelcet is less nephrotoxic than amphotericin B.

There are three comparative studies showing that AmBisome is less nephrotoxic.[4,15,16] The study by Walsh *et al.*[4] was a randomized double-blind study of >600 patients that compared liposomal amphotericin B (AmBisome) with conventional amphotericin B for empirical treatment in patients with persistent fever and neutropenia. The treatments compared were amphotericin B given at 0.6 mg/kg/day and AmBisome given at 3 mg/kg/day. From an efficacy viewpoint, both treatments had identical success rates, although there were significantly fewer proven breakthrough fungal infections in patients receiving AmBisome. The safety results showed that patients in the AmBisome treatment group had remarkably lower incidence of renal insufficiency. The percentage of patients with a doubling in serum creatinine while being treated with amphotericin B was nearly double that of patients being treated with AmBisome (33.7% and 18.7% for amphotericin B and AmBisome, respectively). What is even more interesting is the analysis of nephrotoxicity in patients who, in addition to receiving amphotericin B or AmBisome, were also receiving at least two or three other nephrotoxic drugs. As shown in the Figure, AmBisome was significantly less nephrotoxic than amphotericin B, regardless of the number of concomitant nephrotoxic drugs being administered to these patients.

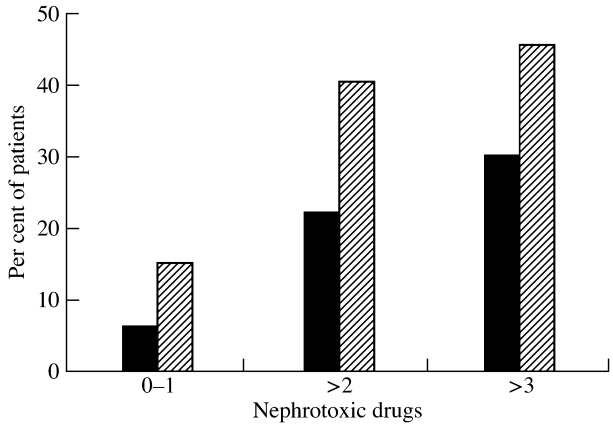

Figure. Comparative nephrotoxicity of AmBisome (■) and amphotericin B (▨) in patients taking concomitant nephrotoxic drugs (percentage of patients with at least a doubling in serum creatinine).

Another interesting point from this paper is hypokalaemia. In this study, hypokalaemia was defined as a serum potassium level ≤2.5 mmol/L. This represents a very low serum level, with a risk of potentially fatal arrhythmia. Once more, AmBisome treatment was less toxic to the kidneys, with only 6.7% hypokalaemia compared with 11.6% for amphotericin B ($P = 0.02$). AmBisome is an encouraging development, at least for a nephrologist.

Wingard *et al.*[17] performed a randomized double-blind trial evaluating the safety of AmBisome compared with Abelcet as empirical treatment in 250 patients with unresolved fever and neutropenia. AmBisome was given at 3 and 5 mg/kg/day, and Abelcet was given at 5 mg/kg/day. In patients who had at least a doubling in serum creatinine, the rate of nephrotoxicity for Abelcet was >40%, whereas for both AmBisome groups, it was <15%. The incidence of Abelcet nephrotoxicity is comparable to that associated with conventional amphotericin B. AmBisome is clearly a less nephrotoxic drug than Abelcet.

Indications for use of amphotericin B lipid formulations

Conventional amphotericin B should not be used if a patient has at least one of the following factors: renal insufficiency, hypokalaemia and/or hypomagnesaemia, tubular acidosis or polyuria. In these situations, AmBisome is indicated. If there are no risk factors, routine use of AmBisome is determined by resource availibilty. If one cannot afford AmBisome routinely, as is the case at the author's hospital, then start with amphotericin B. If there is at least a 25% increase of serum creatinine, *stop the drug*. If there is any kind of tubular abnormality, *stop the drug*. In these situations, begin treatment with AmBisome. If there are no renal abnormalities, amphotericin B may be continued.

Conclusions

Amphotericin B nephrotoxicity remains a frequent and severe impediment in the treatment of disseminated fungal infections. Amphotericin B-induced renal failure is *not* a benign complication. The recognition of risk factors and early intervention are much more effective than treating established acute renal failure in preventing mortality. The risk of death increases with relatively small increments in serum creatinine level. Any increase in serum creatinine level while a patient is on amphotericin B should be regarded as important, and should trigger review and possible intervention. The prevention of these serious com-

plications is straightforward if detection and suppression of risk are used in clinical practice.

I recommend the use of true liposomal formulations of amphotericin B AmBisome as first-line therapy in high-risk patients and patients with amphotericin B nephrotoxicity.

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