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Antifungals and renal safety—getting the balance right

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Abstract

Many patients who receive antifungal agents are immunocompromised or critically ill. This leaves many of these patients prone to renal failure, especially following transplantation. A wealth of clinical data have shown that older antifungal agents, particularly conventional amphotericin B deoxycholate (AmBd), are still highly efficacious, except that AmBd confers extensive nephrotoxicity. This paper examines the pharmacological alternatives that could provide a more suitable balance between clinical efficacy and renal safety.

Keywords: Invasive fungal infections; Antifungal therapy; Nephrotoxicity; Amphotericin B; Amphotericin B lipid complex; Liposomal amphotericin B

1. The clinical importance of renal failure

Renal failure is a significant concern to physicians who are responsible for the medium- and long-term health of the patient (e.g. the nephrologist, transplant physician). Fig. 1 shows the relatively high incidence of chronic renal failure following organ transplantation [1].

Renal failure can be assessed by measuring the percentage change in serum creatinine levels from baseline. An increase or decrease of 20–30% is considered normal, but an increase of 100% or more is indicative of renal failure. However, if possible, renal function should be calculated using glomerular filtration rate (GFR), because this value provides the most accurate assessment.

At present, most clinical studies of nephrotoxicity use measures of serum creatinine to determine renal function. However, absolute serum creatinine values do not take into account certain patient-specific variables (e.g. weight). Consequently, analyses of existing literature reveal that renal failure is variously defined as serum creatinine >2 mg/dL, >2.5 mg/dL, or >3 mg/dL. High serum creatinine values can have an adverse effect on long-term clinical outcome. In a study designed to determine the factors that predict the development of end-stage renal disease (median follow-up, 5.8 years), it was found that, compared to patients with serum creatinine values ≤1.7 mg/dL, patients with high serum creatinine values (>1.7 mg/dL) were significantly more likely to develop the disease (38% versus 11%, $P < 0.001$) [2].

Acute renal failure has also been found to affect patient survival. A study of 707 patients who received amphotericin B deoxycholate (AmBd) evaluated the survival of patients who developed acute renal failure ($N = 212$) compared with those whose renal function remained normal ($N = 495$). The researchers found that the presence of acute renal failure significantly increased the mortality rate from 16.0% (in patients with no renal failure) to 54.2% ($P = 0.001$) [3].

To enable clinicians to make a balanced judgement between efficacy, renal safety and potential clinical outcome, the remainder of this article describes nephrotoxicity data associated with common antifungal therapies.

2. Nephrotoxicity of conventional amphotericin B

Amphotericin B-induced nephrotoxicity has been investigated in several clinical trials. For example, the renal effects of AmBd were studied in 239 immunosuppressed patients with suspected or proven aspergillosis. The mean and median durations of treatment were 20.4 and 15.0 days, respectively. The creatinine level doubled in 53% of patients and exceeded 2.5 mg/dL in 29%. The overall mortality rate was 60%, although this rate was significantly lower in patients on dialysis ($P = 0.03$) [4].

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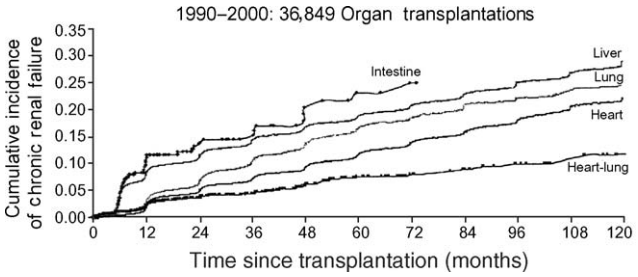

Fig. 1. Incidence of chronic renal failure following organ transplantation. Reprinted with permission [1]. © 2003 Massachusetts Medical Society. All rights reserved.

Several dose-dependent physiological mechanisms have been proposed for AmBd-induced renal failure. Firstly, a change in the membrane permeability of the renal tubular cells results in hypokalaemia, hypomagnesaemia and distal tubular acidosis. This is accompanied by changes in vascular smooth muscle function that lead to constriction of the afferent glomerular arterioles and reduced GFR [5,6]. Dose-dependent tubular dysfunction normally manifests 7–14 days after treatment, prior to the onset of renal insufficiency. Glomerular dysfunction (i.e. 25% rise in serum creatinine or decrease in GFR to <60 mL/min) usually occurs at a later date [7].

Not all patients receiving AmBd experience an equal nephrotoxic risk. Several risk factors have been identified, including: abnormal renal function at baseline; dehydration; use of diuretics; sepsis; increased patient age; pre-existing atherosclerosis, diabetes or heart failure and cumulative AmBd dosage.

The use of certain concomitant medications can also exacerbate renal risk. Agents to avoid include: non-steroidal anti-inflammatory drugs, iodine, aminoglycosides, vancomycin, β-lactams, acyclovir, trimethoprim–sulfamethoxazole, chemotherapy, and immunosuppressants such as cyclosporine or tacrolimus [8].

3. Renal benefits of lipid-based amphotericin B

Studies show that tissue concentrations of liposomal amphotericin B (L-AmB) and amphotericin B lipid complex (ABLC) are significantly different to AmBd in both animals and humans [9–11]. Importantly, although ABLC reaches the lung, liver, and spleen in high concentrations, compared with both AmBd and L-AmB, renal concentrations of ABLC are much lower (Table 1) [9–11].

Table 1
Amphotericin B concentrations in human tissues

Formulation	Tissue concentration (μg/g)					
	Brain	Heart	Lung	Liver	Spleen	Kidney
AmBd	N.S.	4	13	93	59	19
ABLC	2	5	222	196	290	7
L-AmB	1	4	17	176	202	23

ABLC, amphotericin B lipid complex; AmBd, amphotericin B deoxycholate; L-AmB, liposomal amphotericin B; N.S., not significant. Reprinted with permission [10]. © 1998 The University of Chicago Press.

Table 2
List of studies comparing AmBd with lipid-based formulations (ABLC and L-AmB) [12]

Meta-analysis (eight publications)			
Author	Year	*N*	Type of study
Walsh et al.	1999	702	Multicentre, double-blind
White et al.	1998	213	Multicentre, double-blind
Leenders et al.	1998	106	Multicentre, double-blind
Luke et al.	1998	258	Multicentre, non-blind
Prentice et al.	1997	338	Multicentre, non-blind
Leenders et al.	1997	30	Multicentre, non-blind
Sharkey et al.	1996	55	Multicentre, non-blind
Anaissie et al.	1995	231	Multicentre, non-blind

ABLC, amphotericin B lipid complex; AmBd, amphotericin B deoxycholate; L-AmB, liposomal amphotericin B.

ABLC and L-AmB have been directly compared with AmBd in several clinical trials. These are summarized in Table 2 [12]. Lipid-based products significantly reduced the risk of all-cause mortality by an estimated 28% compared with conventional AmBd. A meta-analysis of these studies found that lipid-based formulations had distinct advantages over conventional AmBd in terms of reduced risk of mortality and renal toxicity, as shown in Fig. 2 [12].

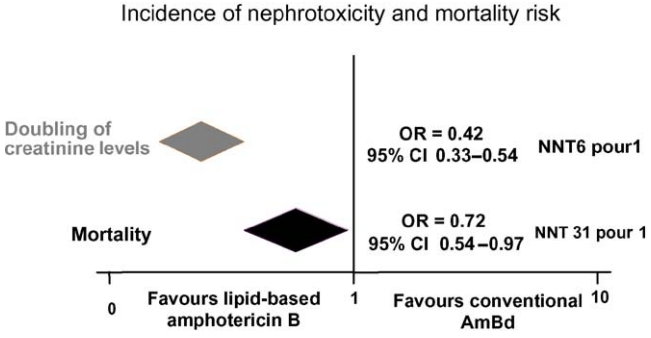

Fig. 2. Comparison of nephrotoxicity and mortality between AmBd and lipid-based amphotericin B [12]. AmBd, amphotericin B deoxycholate; CI, confidence interval; OR, odds ratio.

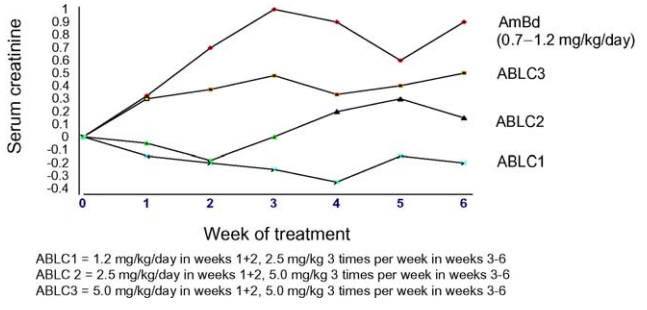

Fig. 3. Direct nephrotoxicity comparison of ABLC and AmBd. Fifty-five patients with AIDS-associated cryptococcal meningitis randomly assigned to 6 weeks of therapy. ABLC, amphotericin B lipid complex; AmBd, amphotericin B deoxycholate. Reprinted with permission [13]. © 1996 The University of Chicago Press.