

Retrospective Analysis of the Use of Lipid-Based Formulations of Amphotericin B in a Pediatric Hospital

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ABSTRACT

Background: The use of antifungal agents has been increasing in the growing population of immunocompromised patients. To address the problem of renal and infusion-related toxic effects of conventional amphotericin B, several lipid-based formulations of this drug have been developed. At the authors' pediatric institution, recommendations for the use of these products were established in 2001.

Objective: To evaluate the use of lipid-based formulations of amphotericin B and to make any necessary changes to the current recommendations.

Methods: The charts of patients who received amphotericin B lipid complex or liposomal amphotericin B between April 2003 and July 2004 were reviewed. Practices in the use of lipid-based formulations of amphotericin B were compared with the recommendations.

Results: Eighteen patients were identified for the chart review. The major reasons for prescribing lipid-based formulations of amphotericin B were current documented renal dysfunction or history of such dysfunction with conventional amphotericin B (9 patients) and serious infusion reactions (3 patients) with conventional amphotericin B. Liposomal amphotericin B was the most commonly prescribed initial therapy (13 patients), and all but one of the patients were eventually switched to this form of therapy. For 7 patients (39%), the reason for using either liposomal amphotericin B or amphotericin B lipid complex was consistent with the recommendations. In 8 cases (44%), amphotericin B lipid complex should have been used first, and in 3 cases there was no apparent reason for giving a lipid-based formulation of amphotericin B.

Conclusions: Institutional recommendations for the use of lipid-based formulations of amphotericin B should be clearer and better enforced. They should specify that if amphotericin B is selected to treat a documented or suspected fungal infection, conventional amphotericin B should be given; that in patients with pre-existing impairment of renal function, a history of serious infusion reactions or renal impairment with conventional amphotericin B, and for those receiving concomitant nephrotoxic drugs or undergoing bone marrow transplantation,

RÉSUMÉ

Historique : On a de plus en plus recours aux antifongiques dans la population grandissante de patients immunodéprimés. Pour résoudre le problème de toxicité rénale et de toxicité associée à la perfusion avec l'amphotéricine B classique, plusieurs préparations lipidiques de cet antifongique ont été mises au point. L'établissement auquel est rattaché l'auteur de cet article a établi en 2001 des recommandations concernant l'emploi de tels produits.

Objectif : Évaluer l'emploi des préparations lipidiques d'amphotéricine B et apporter les changements nécessaires aux recommandations courantes.

Méthodes : Les dossiers médicaux de patients qui ont reçu une préparation d'amphotéricine B en complexe lipidique ou d'amphotéricine B liposomique entre avril 2003 et juillet 2004 ont été examinés. Les habitudes de prescription des préparations lipidiques d'amphotéricine B ont été comparées aux recommandations.

Résultats : On a passé en revue 18 dossiers-patients. Ils révèlent que les préparations lipidiques d'amphotéricine B ont été prescrites principalement à cause d'un dysfonctionnement rénal actuel documenté ou d'antécédents d'un tel dysfonctionnement dû à l'amphotéricine B classique (9 patients sur 18) et de réactions graves liées à la perfusion d'amphotéricine B classique (3 patients sur 18). L'amphotéricine B liposomique était la préparation la plus prescrite comme traitement initial (13 patients), et tous les patients, sauf un, sont passés à un moment ou à un autre à ce type de préparation. Chez 7 patients (39 %), la raison expliquant le recours à l'amphotéricine B liposomique ou à l'amphotéricine B en complexe lipidique était conforme aux recommandations. Chez 8 patients (44 %), on aurait dû employer d'abord l'amphotéricine B en complexe lipidique, et chez 3 patients on n'a observé aucune raison apparente justifiant l'emploi d'une préparation lipidique d'amphotéricine B.

Conclusions : Les recommandations de l'établissement sur l'emploi des préparations lipidiques d'amphotéricine B doivent être plus claires et mieux appliquées. Elles devraient notamment préciser que si l'on a recours à l'amphotéricine B pour traiter une infection fongique confirmée ou soupçonnée, on devrait d'abord utiliser l'amphotéricine B classique; que chez les

amphotericin B lipid complex should be the formulation of choice; and that liposomal amphotericin B should be restricted to patients whose clinical condition has deteriorated while receiving amphotericin B lipid complex and those in whom previous therapy with amphotericin B lipid complex has failed.

Key words: amphotericin B, liposomal amphotericin B, AmBisome, amphotericin B lipid complex, Abelcet, pediatrics, guidelines, drug-use evaluation

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patients ayant une insuffisance rénale préexistante, des antécédents de réactions graves liées à la perfusion ou d'insuffisance rénale secondaires à l'amphotéricine B classique, ainsi que chez ceux qui reçoivent simultanément des médicaments néphrotoxiques ou qui subissent un greffe de moelle osseuse, l'amphotéricine B en complexe lipidique devrait être la préparation de choix; et que l'amphotéricine B liposomique devrait être réservée aux patients dont l'état clinique s'est détérioré avec l'administration de préparations d'amphotéricine B en complexe lipidique et aux patients dont un traitement antérieur par une préparation d'amphotéricine B en complexe lipidique a échoué.

Mots clés : amphotéricine B, amphotéricine liposomique, AmBisome, amphotéricine en complexe lipidique, Abelcet, pédiatrie, lignes directrices, évaluation de l'utilisation des médicaments

INTRODUCTION

The rising number of children receiving chemotherapy or undergoing transplantation at the Children's & Women's Health Centre of British Columbia (C&W) has resulted in a growing population of immunocompromised patients at risk of fungal infections. The use of anti-fungal agents to prevent and treat these infections has also been increasing. Amphotericin B desoxycholate, or conventional amphotericin B, is considered the treatment of choice for suspected or proven fungal infections.^{1,2} Limitations to the use of this agent include serious toxic effects, such as nephrotoxicity, hepatotoxicity, hypokalemia, and infusion-related reactions.³ In adults, the incidence of acute renal failure secondary to the use of conventional amphotericin B is reportedly between 49% and 65%.^{4,5} Prentice and others⁶ reported that among children the incidence of nephrotoxicity (an increase of 100% or more in baseline serum creatinine) was 21%.

To reduce the potential for toxic effects with conventional amphotericin B, lipid-based formulations of the drug have been developed. Two such formulations are currently approved for use in Canada: amphotericin B lipid complex and liposomal amphotericin B.

Several reviews comparing the various formulations have suggested that the lipid-based formulations are as effective as the conventional formulation and that they are associated with fewer adverse reactions and are better tolerated.^{7,9} In a meta-analysis comparing the incidence of adverse effects of antifungal therapies, Girois and others³ reported that a lower percentage of patients experienced nephrotoxicity (defined as a doubling in baseline serum creatinine) with the lipid-based formulations (14.6% with the liposomal formulation, 16.5% with the lipid complex, and 33.2% with conventional amphotericin B). However, these studies included a wide variety of dosing regimens and patient populations, and

the definitions of nephrotoxicity and other adverse events were variable.

Because evidence suggesting superior efficacy or a better toxicity profile of one lipid-based formulation over the other is lacking for the pediatric population, the Pharmacy, Therapeutics and Nutrition Committee at C&W decided in 2001 to include both of the lipid-based products in the drug formulary. Since then, in-hospital recommendations have restricted the use of these products to the treatment of presumed or documented fungal infections in patients with failure to respond to or lack of tolerance to the conventional formulation. After 4 years of use and prompted by the high cost of the lipid-based formulations, the Pharmacy, Therapeutics and Nutrition Committee revisited the need to have both formulations on the formulary and requested a review of the current literature as background to reconsidering current recommendations for use.

The purpose of this study was to evaluate the use of liposomal amphotericin B and amphotericin B lipid complex at C&W and to propose changes to the current recommendations on the basis of these findings and the most recent literature.

METHODS

Setting and Study Design

This descriptive drug utilization review was performed at British Columbia's Children's Hospital (BCCH), a 240-bed acute care (tertiary and quaternary care) university-affiliated pediatric hospital. Ethics approval was obtained from the Behavioural Research Ethics Board of the University of British Columbia and from the Children's and Women's Research Review Committee.



Data Collection

Patients who received one or more courses of either of the lipid-based formulations between April 1, 2003, and July 15, 2004, were identified through the pharmacy computer system. The following data were collected retrospectively from the patients' charts: age, sex, weight, and hospital ward, primary underlying condition(s), indication for initial antifungal therapy (treatment of a documented or presumed fungal infection, associated or not with febrile neutropenia), rationale for the use of a lipid-based formulation, and mention of consultation with an infectious diseases specialist. The following pharmacy-related information was also collected: antifungal drug used, dose and duration of treatment, switch from one formulation to another, concurrent treatment with other nephrotoxic drugs or drugs that potentiate nephrotoxicity (e.g., aminoglycosides, cyclosporine, tacrolimus, vancomycin, furosemide, acyclovir, and some antineoplastic agents), and use of premedication or supplementation drugs (e.g., acetaminophen, diphenhydramine, meperidine, sodium chloride infusion). During the same study period, the number of patients treated exclusively with conventional amphotericin B was also determined.

The following laboratory test results were collected: culture results, site of infection, serum creatinine value, glomerular filtration rate before the start of antifungal therapy, and serum potassium levels.

Consistency with Recommendations

As of March 2001, both liposomal amphotericin B and amphotericin B lipid complex were approved for the management of fungal infections in patients who were admitted to the institution and who were unable to receive the conventional formulation because of toxic effects or treatment failure (see Appendix 1). The proportion of courses of lipid-based amphotericin B that were consistent with institutional guidelines was determined.

The rationale for giving a lipid-based formulation was considered consistent with the recommendations if it met one of the following criteria:

- renal dysfunction before start of therapy or deterioration of renal function with conventional amphotericin B, based on available laboratory results (i.e., a 2-fold decrease in the glomerular filtration rate and/or a serum creatinine level greater than 2 times the baseline value)
- history of renal dysfunction due to administration of conventional amphotericin B
- hypokalemia (serum potassium concentration below 3 mmol/L) due to conventional amphotericin B, despite optimal potassium supplementation

- serious, intolerable infusion-related reactions (e.g., chills, rigours, decrease in blood pressure) despite optimal management (e.g., premedication with acetaminophen, diphenhydramine, and meperidine; increased infusion time)
- clearly stated clinical judgement, based on the specific site and/or type of fungal infection, as well as the underlying condition

In addition, the rationale for giving liposomal amphotericin B rather than amphotericin B lipid complex was considered consistent with the recommendations only if there was a documented intolerance to or treatment failure with the latter.

RESULTS

Twenty-one patients received a lipid-based formulation of amphotericin B during the 15.5-month study period. No patient received more than one course of the same lipid-based formulation. One chart was missing and data were incomplete for 2 patients; therefore only 18 patients were included in the analysis. Patient characteristics are presented in Table 1. During the study period, 34 patients were treated exclusively with conventional amphotericin B.

The rationale for prescribing a lipid-based formulation and consistency with current in-hospital recommendations are presented in Table 2. The most common rationale for using a lipid-based formulation was currently documented or history of renal dysfunction (50%). Use of a lipid-based formulation was consistent with the recommendations in 7 cases (39%). In the other 11 cases (61%), the choice of therapy was considered inconsistent with the recommendations, either because there was no apparent reason for giving a lipid-based product (3 cases) or because the patients should have received the lipid complex instead of the liposomal formulation (8 cases).

Liposomal amphotericin B at doses ranging from 2.4 to 5 mg kg⁻¹ day⁻¹ was most frequently chosen as the first-line lipid-based formulation (for 13 patients, 72%); amphotericin B lipid complex at 5 mg kg⁻¹ day⁻¹ was prescribed initially for the other 5 patients. All patients were eventually switched to the liposomal formulation, except for one patient who was switched from the liposomal formulation to the lipid complex (because of back pain, thought to be associated only with the latter).

DISCUSSION

The 21 patients who received a lipid-based formulation of amphotericin B represented 38% of the 55 patients treated with amphotericin B during the study period. In addition, half of the patients who received a lipid-based formulation had first received conventional amphotericin



Table 1. Characteristics of 18 Patients Receiving Lipid-Based Formulation of Amphotericin B

Characteristic	No. (%) of Patients
Sex: no. (%) male	6 (33)
Mean age (range)	8.9 yr (2 wk to 17 yr)
Underlying condition	
Bone marrow transplantation	7 (39)
Malignancy	7 (39)
Other*	4 (22)
Indication for initiating antifungal therapy	
Presumed infection associated with febrile neutropenia	10 (55)
Presumed infection not associated with febrile neutropenia	1 (6)
Documented fungal infection	7 (39)
Receiving CAMB before lipid-based product	9 (50)
Receiving concomitant nephrotoxic drug(s)	15 (83)

CAMB = conventional amphotericin B.

*Congenital heart disease, cystic fibrosis, or DiGeorge syndrome.

B. Thus, the conventional formulation remained the most frequently used formulation for treatment of presumed and documented fungal infections at this institution. Most (78%) of the patients for whom a lipid-based formulation was prescribed had malignancy as the underlying condition, which suggests a lower threshold for initiating lipid-based therapy in an immunocompromised population.

In this review of patterns of use, liposomal amphotericin B was the preferred lipid-based formulation: 13 patients received this formulation as first choice, and all but one of the patients were eventually switched to this formulation because of adverse effects (infusion reactions or worsening of renal function). The main reason for using a lipid-based formulation was current documented renal dysfunction or a history of such dysfunction.

In 39% of the cases (7/18), use of a lipid-based formulation was considered consistent with the current recommendations. In 8 of the 11 cases where use of a lipid-based formulation was considered inconsistent with the recommendations, the patients should have been treated with the lipid complex first (being switched to the liposomal form only if the adverse reactions persisted). This high rate of inconsistency suggests that the in-hospital recommendations are not clear enough to ensure adherence or are not strictly enforced. Although there is evidence that lipid-based formulations are less toxic than conventional amphotericin B, there have been only a small number of head-to-head comparisons between the 2 lipid forms: only 4 published trials were identified comparing the safety and efficacy of amphotericin B lipid complex and liposomal amphotericin B.¹⁰⁻¹³ These studies

Table 2. Rationale for Prescribing Lipid-Based Formulations of Amphotericin B and Consistency with Current Institutional Recommendations

Rationale and Consistency	No. (%) of Patients
Rationale for lipid-based product	
Current documented renal dysfunction	7 (39)
History of renal dysfunction with CAMB	2 (11)
Electrolyte abnormalities	1 (6)
Serious infusion reactions	3 (17)
Other*	2 (11)
No apparent reason	3 (17)
Consistency with recommendations	
Consistent	7 (39)
Inconsistent: no rationale for lipid product	3 (17)
Inconsistent: ABLC should have been given first	8 (44)

CAMB = conventional amphotericin B, ABLC = amphotericin B lipid complex.

*In one patient, the choice was based on the particular pathogen and site of infection; in the other patient, the choice was caused by a transient shortage of CAMB.

showed similar efficacy and adverse events in selected populations. In their case-control study, Clark and others¹⁰ showed that the liposomal formulation administered to adults at mean doses of 1.9 mg kg⁻¹ day⁻¹ was as effective as the lipid complex at mean doses of 4.8 mg kg⁻¹ day⁻¹ with a significantly lower incidence of rigours. In a double-blind comparative trial involving 244 neutropenic patients 2 to 84 years of age, the liposomal formulation was associated with a significantly lower rate of infusion reactions on the first day of infusion (premedication not allowed) than was the case for the lipid complex.¹¹ Nephrotoxicity (doubling of the baseline serum creatinine value) was observed more often with the lipid complex at 5 mg kg⁻¹ day⁻¹ (42% of patients) than with the liposomal formulation at either 3 mg kg⁻¹ day⁻¹ (14%) or 5 mg kg⁻¹ day⁻¹ (15%) ($p < 0.01$). The incidence of nephrotoxicity did not differ between the two doses of the liposomal formulation (3 or 5 mg kg⁻¹ day⁻¹). The authors concluded that the safety profile of the liposomal formulation was superior.¹¹ An unblinded prospective randomized controlled trial in adults¹² concluded that the 2 lipid-based formulations are equally effective for the treatment of suspected and documented fungal infections in patients with leukemia. The incidence of mild to moderate infusion-related reactions and increased serum creatinine level were higher with the lipid complex, whereas liver toxicity (elevation in liver function tests) was associated with use of the liposomal formulation. In an observational study of 67 patients 4 to 79 years of age, Cannon and others¹³ did not observe any significant differences in clinical response or nephrotoxicity.



Among children, there is evidence that lipid-based formulations are effective and do not increase the risk of nephrotoxicity: in a prospective trial, Walsh and others¹⁴ reported that 70.4% of pediatric patients treated with amphotericin B lipid complex at 5 mg kg⁻¹ day⁻¹ had a complete or partial response and no significant changes in serum creatinine levels from baseline to the end of therapy. Herbrecht and others¹⁵ conducted a retrospective analysis of use of amphotericin B lipid complex (5 mg kg⁻¹ day⁻¹) in 46 immunocompromised children with documented invasive fungal infections. Overall, 83% responded to the therapy, and no significant changes in serum creatinine were observed. In the pediatric subgroup of the randomized prospective trial conducted by Prentice and others,⁶ there was no significant difference in the incidence of nephrotoxicity between groups treated with conventional amphotericin B (1 mg/kg) or 2 different doses of liposomal amphotericin B (1 mg/kg or 3 mg/kg). In a recent review of the efficacy and safety of amphotericin B lipid complex, 548 children and adolescents with invasive fungal infections were treated with a median dose of 4.92 mg kg⁻¹ day⁻¹ at the start of therapy.¹⁶ Serum creatinine was elevated to greater than 1.5 times baseline in 24.8% of the patients and to greater than 2.5 times baseline in 8.8% of the patients.¹⁶

The efficacy and safety differences between amphotericin B lipid complex and liposomal amphotericin B are not clear-cut, especially among children. There is a role for lipid-based formulations of amphotericin B in the population that is at high risk of renal dysfunction, such as patients undergoing bone marrow transplantation or receiving several other nephrotoxic drugs.^{5,15,17} In addition, one randomized controlled trial showed an advantage of the liposomal formulation over the lipid complex in neutropenic patients.¹¹

On the basis of the evidence in these publications,^{3-5,11,15,17} the following high-risk patients should receive a lipid-based formulation as first-line therapy:

- patients with compromised renal function, defined as glomerular filtration rate less than 25 mL min⁻¹ 1.73 m⁻² (body surface area) or serum creatinine concentration greater than 1.5 times the upper limit for their age or serum creatinine concentration greater than 2 times their baseline value
- patients with documented deterioration of renal function with previous treatment with conventional amphotericin B
- patients with serum potassium levels below 3 mmol/L despite maximal potassium supplementation
- patients with documented, severe infusion-related adverse reactions (chills, rigours, fever) unresponsive

to acetaminophen, diphenhydramine, and meperidine treatment

- patients taking one or more drugs known to be associated with a significant frequency of nephrotoxicity or known to potentiate the nephrotoxicity of other drugs in children (e.g., aminoglycosides, cyclosporine, tacrolimus, vancomycin, furosemide, acyclovir, and some antineoplastic agents)
- patients undergoing bone marrow transplantation

Given that the current acquisition cost of amphotericin B lipid complex is less than that of the liposomal formulation, given that the lipid complex has been proven safe and effective in both adults and children,^{15,17,18} and given that no studies have shown lower efficacy for conventional amphotericin B relative to lipid-based formulations among children, the following recommendations for rational use of lipid-based formulations of amphotericin B at the authors' institution were formulated. If amphotericin B is chosen to treat a documented or suspected fungal infection, the formulation of choice should remain conventional amphotericin B 1 to 1.5 mg kg⁻¹ day⁻¹. For patients with impaired renal function who have previously experienced serious infusion reactions despite appropriate therapy and for those with a history of renal impairment attributable to conventional amphotericin B, as well as for patients receiving concomitant nephrotoxic drugs or undergoing bone marrow transplantation, amphotericin B lipid complex should be used as first-line therapy. Liposomal amphotericin B should become a restricted drug, used only for patients whose condition deteriorates with the lipid complex or with history of treatment failure with the lipid complex.

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Appendix 1. Recommendations for Use of Lipid-Based Formulations of Amphotericin B at British Columbia Children's and Women's Hospitals (March 2001)

Both LAMB and ABLC are approved for the management of fungal infections in patients who are unable to receive CAMB because of toxicity or treatment failure. ABLC may be considered for use in cases of impaired renal function. As per recommendations, impaired renal function is defined as pre-existing renal impairment or deteriorating renal function where alternate day dosing of CAMB and/or sodium load* is inappropriate or has failed, also considering whether adjustment of concomitant nephrotoxic agents is appropriate. Similarly, ABLC may also be considered in patients unable to maintain adequate serum potassium concentrations despite optimal supplementation, and in patients experiencing intolerable infusion related reactions despite optimal management. LAMB may be considered when use of ABLC is considered to be inadequate to avoid or ameliorate toxicity. Clinical judgement in product selection may also depend on the specific site/type of fungal infection, and/or underlying disease state

LAMB = liposomal amphotericin, ABLC = amphotericin B lipid complex, CAMB = conventional amphotericin B.

*Sodium load = infusion of sodium chloride 0.9% prior to CAMB infusion.

