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AMPHOTERICIN B. New Formulations

A Position Statement of the NSW Therapeutic Assessment Group Inc.

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EXECUTIVE SUMMARY

Amphotericin B is a polyene macrolide antifungal which in spite of toxicity and formulation problems remains the agent of choice for progressive and potentially fatal fungal infections.

New formulations of amphotericin have been developed in an attempt to reduce the complications associated with therapy, including renal toxicity and infusion-related adverse effects. To this end amphotericin deoxycholate has been used as an admixture to lipid emulsion and several liposomal preparations have been formulated. Liposomal formulations are expensive alternatives to amphotericin deoxycholate, therefore requiring an assessment of clinical benefits relative to increased cost.

The three liposomal preparations which have been trialed are Ambisome (Nexstar), Abelcet (Liposome Company Inc) and Amphocil (Zeneca). Of these only Ambisome is licensed for use in Australia although Abelcet is used by some hospitals (on Special Access Scheme) because of its lower cost. The TGA approved indication for Ambisome is prophylaxis in liver transplant patients at risk of systemic candida and aspergillus and cryptococcus infection and treatment of systemic candida, aspergillus or cryptococcus infections and treatment of visceral leishmaniasis. The respective liposomal preparations differ in size, structure, pharmacokinetics, antifungal activity and possibly clinical efficacy. Comparative clinical data between the relevant preparation or against amphotericin deoxycholate is generally lacking.

The NSW Therapeutic Assessment Group believe that evidence to date supports the following:

- Use of Ambisome for treatment of susceptible systemic fungal infections in patients at risk of nephrotoxicity and for prophylaxis of fungal infection in immunocompromised patients who are considered to be at risk of or who present with pre-existing renal impairment.
- Use of Amphocil and Abelcet within controlled clinical trials only.

Furthermore, current evidence does not support the use of amphotericin deoxycholate as an admixture to lipid emulsion for use in any patient group.

Economic evaluations of liposomal amphotericin are limited. Moreover, prior to economic comparisons, comparisons of efficacy and safety between liposomal and conventional amphotericin therapy are required to determine the relative benefits of this therapy.

1 INTRODUCTION

Amphotericin B is a polyene macrolide antifungal. It is insoluble in water at neutral pH and is formulated as a colloidal dispersion in deoxycholate. Absorption from the gastrointestinal tract is negligible, necessitating administration by intravenous infusion. The drug is highly bound to proteins in plasma and to tissues, giving a terminal half-life of around 15 days. It penetrates the cerebrospinal fluid poorly.

Clinical activity of amphotericin B has been shown against *Candida* species, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Torulopsis glabrata*, *Coccidioides immitis*, *Paracoccidioides braziliensis*, *Aspergillus* species, and species causing mucormycosis. The newer triazole antifungal drugs, including fluconazole and itraconazole, have activity against many of these organisms. Although triazole antifungals have good oral bioavailability and are well tolerated, amphotericin B remains the antifungal of choice for progressive and potentially fatal infections with susceptible organisms.

Infusion related adverse effects are common with amphotericin B. These include fever and chills, which begin 1-2 hours after commencement of infusion and may last 2-4 hours. Dyspnoea and tachycardia may precede the fever. Other reported reactions include headache, anorexia, nausea and vomiting, malaise, dyspepsia, diarrhoea, generalised pain, cramping epigastric pain and local venous pain with phlebitis and thrombophlebitis. Premedications, such as antihistamines, aspirin and antiemetics, are often used to reduce the severity of these reactions. Normo- or hypochromic, normocytic anaemia is usual but reverses after treatment. Less immediate adverse effects are also common, with by far the most severe and frequent being the development of renal dysfunction. This is manifest as hypokalaemia, renal tubular acidosis, azotemia, nephrocalcinosis and hyposthenuria. Renal toxicity is dose dependent and usually improves on cessation of therapy, but permanent impairment may occur at doses >3-4g for an adult.

Whilst the use of amphotericin B as first-line treatment for many conditions is well supported, the effectiveness of attempts to decrease the incidence and severity of adverse effects is less clear. The latter include measures such as potassium supplementation, loading with sodium chloride by infusion and changing the amphotericin B formulation. New formulations use technologies for incorporation into liposomes, formulation with lipid emulsions and complexation with cholesterol.

Liposomal formulations are expensive alternatives to the amphotericin deoxycholate product, and as such require assessment of cost impact with proven clinical benefits. The pharmacokinetic properties of different liposomal delivery formulations are reported to be very different. Ambisome (Nexstar) is licensed for use in Australia for prophylaxis in liver transplant patients at risk of systemic candida and aspergillus and cryptococcus infection and treatment of systemic candida, aspergillus or cryptococcus infections and treatment of visceral leishmaniasis. Other formulations, including Abelcet (Liposome Company Inc) and Amphocil (Zeneca) are not marketed in Australia, although the former preparation is used by some hospitals (on Special Access Scheme) because of its lower cost. The respective liposomal preparations differ in size, structure, pharmacokinetics, antifungal activity and possibly clinical efficacy.

2 CLINICAL TRIALS OF LIPOSOMAL OR LIPID FORMULATIONS

Simple measures have been fairly ineffective in reducing adverse reactions to amphotericin. The incidence of infusion-related adverse effects and the efficacy of pre-treatment regimens in preventing them, was studied in 397 inpatients¹. The common pretreatment regimens were not significantly better at preventing infusion related adverse effects nor was use of a test dose of amphotericin B able to consistently predict major allergic reactions. Administration of heparin appeared to have no effect on the development of thrombophlebitis. However, the prime motivation for development of new formulations of amphotericin has centred on reducing nephrotoxicity, the adverse effect which most commonly limits the usefulness of therapy.

There is a paucity of clinical trials, particularly randomised, controlled studies, directly comparing liposomal and/or lipid emulsion formulations with conventional amphotericin deoxycholate in dextrose infusion.

2.1 Amphotericin deoxycholate admixed in lipid emulsion

The use of amphotericin admixtures in lipid 20% emulsion by many French centres has supplied evidence that this formulation is better tolerated than the conventional dextrose preparation. Questions remain however concerning the comparative efficacy and the physical compatibility of the lipid and drug.

In 1994 Caillot et al published a controlled trial of amphotericin B infused in dextrose or in Intralipid fat emulsion². Forty two patients with haematological malignancies were randomised to either formulation and assessed for infusion related clinical tolerance, such as nephrotoxicity and electrolyte disturbances, and biological tolerance. Serum amphotericin B concentrations were also measured by high performance liquid chromatography in 254 samples from 30 patients. They reported an increase in clinical tolerance and particularly a decreased incidence of chills, in the lipid group (43% vs 3.7% $p=0.0001$). Renal toxicity, as measured by serum creatinine increase ($p=0.0001$), and decreased creatinine clearance ($p=0.025$), was also significantly lower. There was no significant difference in the requirement of electrolyte supplementation, including potassium, magnesium and sodium, to maintain normal serum ranges. Serum amphotericin B trough levels were significantly reduced in patients receiving lipid although peak levels were not significantly different.

Earlier studies also suggesting this increased tolerability have been published. In 1992 Chavanet et al presented data collected in a randomised controlled trial from 22 HIV positive patients with oral candidiasis who were treated with amphotericin 1mg/kg/day given in either dextrose 5% or fat emulsion³. In addition to clinical and biological tolerance and disease outcome, serum drug concentrations were also measured. The lipid formulation was better tolerated, both in infusion-related (94.7% vs 22.7% $p=.0001$) and renal toxicity ($p=0.01$). The reduction in clinical score of oral candidiasis was similar in both groups with all patients improving. Amphotericin serum concentrations showed a modification of pharmacokinetics when the drug was infused in dextrose. The initial volume of distribution for the lipid formulation was significantly higher, although at

steady state this difference was only slight. In addition the plasma concentrations of amphotericin given in lipid at trough, peak and 12 hours post infusion were significantly lower.

Results from a randomised prospective study by Moreau et al were published in the same year, looking at 32 patients with haematological malignancies treated with either amphotericin B in 5% dextrose or Intralipid and assessing renal toxicity and clinical tolerance⁴. The results showed that there was a significant decrease in incidence of both infusion-related fever & rigors ($p < 0.05$) and renal toxicity ($p < 0.05$).

A more recent study assessing the in vitro renal toxicity and in vivo therapeutic efficacy of amphotericin B associated with Intralipid against murine cryptococcosis concluded that the amphotericin B in lipid is as efficient as in glucose, as measured by mice survival and reduced colony forming (CFU) unit counts of *Cryptococcus neoformans* in infected tissue, and is better tolerated, as measured in vitro by damage to renal tubular cells in primary culture, and in vivo by maximum tolerated dose⁵.

A research report recently presented a prospective, randomised study conducted in twenty patients with neutropenia and assessing clinical and biological tolerance⁶. Both formulations of the amphotericin B were infused over one hour and there was no statistical significant difference in the incidence of clinical (infusion related) adverse effects. Renal toxicity, as measured by serum creatinine and urea, was significantly lower in the lipid emulsion group, but comparative efficacy was not assessed.

The conviction of French centres that this formulation is a preferable alternative to that recommended by the manufacturer is reflected in recent correspondence replying to doubts published by Swenson et al that there was no significant change in the biophysical characteristics, as analysed by circular dichroism spectroscopy, of amphotericin B formulated in lipid emulsion when compared to dextrose, or no attenuation of 50% lethal dose or maximum tolerated dose in mice⁷.

Also in a letter⁸, Trissel expressed concerns about the use of amphotericin B mixed with lipid emulsion because of the lack of data published about the compatibility or stability. After tests involving both centrifuging of the two formulations and counting of particles using a light-obscuration particle size-counter it was concluded that the amphotericin B does not merge with the lipid phase of the fat emulsion but remains as a solid precipitate which would be filtered out if an in-line filter was used. Moreover in 20% lipid emulsion, 43% of the amphotericin is contained in particles $> 10\mu\text{m}$. He postulates that reports of reduced toxicity may be a result of the reduced amount of drug reaching the patient although reduced efficacy would also be expected. Cleary⁹ found that admixtures of amphotericin in lipid emulsion were unstable with creaming over the infusion period resulting in changes to the amphotericin concentration.

2.2 Liposomal formulations of amphotericin

2.2.1 Ambisome®

Ambisome is a spherical small, unilamellar liposome with antifungal activity similar to amphotericin B. Ambisome is slowly cleared from the circulation by the reticuloendothelial system.

Tollemar et al ¹⁰ conducted a randomised, placebo-controlled study looking at the efficacy of liposomal amphotericin (Ambisome) 1mg/kg/day, given as prophylaxis for five days from liver transplantation, compared to placebo. The overall incidence of invasive fungal infections was 0/40 (0%) in the Ambisome group versus 6/37 (16%) in the placebo group ($p < 0.01$). Patient survival at 30 days was similar (92% vs 94%) and no comparison was made with amphotericin B deoxycholate.

In an earlier study, Tollemar ¹¹ compared the efficacy and safety of liposomal amphotericin (Ambisome) for prophylaxis of invasive fungal infections in bone marrow transplant recipients with placebo. Thirty six patients received Ambisome 1mg/kg/day whilst neutophils were below $0.5 \times 10^9/L$, versus 40 patients receiving placebo. The clinical course did not differ between the two groups. Patient survival at one year was 62 vs 73% for treated vs placebo groups. The Ambisome treated group had significant increases between pre and post-treatment blood urea nitrogen ($p < 0.01$) and creatinine ($p < 0.001$) levels but creatinine remained within normal range. Colonisation with *Candida* species was higher in the Ambisome treated group prior to treatment (55 vs 41%) but was significantly reduced post treatment (33 vs 62%; $p = 0.05$). There was no significant difference in the incidence of suspected or proven fungal infections occurring between the two treatment groups. Proven fungal infection occurred in 1/36 receiving Ambisome and 3/40 with placebo. Suspected fungal infections occurred in 5/36 vs 7/40 patients.

A broader look at the efficacy of amphotericin B encapsulated in liposomes (Ambisome) in the treatment of invasive fungal infections in immunocompromised patients was undertaken by Ringden et al (1991) ¹². One hundred and twenty six patients were treated for 137 episodes of fungal infections. In a concurrent study Meunier et al ¹³ looked at safety in 133 of these episodes. The study involved treatment of a variety of different disease states, fungal pathogens, treatment regimens and disease severity. Forty nine of 137 patients were treated with Ambisome after toxicity from previous amphotericin B and 41 of 137 after failure of previous antifungal treatment. The results were classified as response rates for various pathogens (including complete response or improvement): 61% for proven invasive aspergillosis; 84% for proven invasive candidiasis. The cure rate in patients with proven *Candida* infection was 76% and in proven aspergillus infection 32%. The safety data collected showed Ambisome to be generally well tolerated despite the relatively rapid infusion over 30-60 minutes. Infusion-related adverse effects included nausea and vomiting (3/133) and fever/chills (2/133). Hypokalaemia was observed in 18%. A rise in serum creatinine was found in 9% but in 17/50 patients initially elevated creatinine levels returned to normal range during treatment. Increased liver enzyme levels were observed in 22 of 60 patients with initial normal levels, but in 42 patients with initially elevated alkaline phosphatase 11 recovered during therapy.

Two recent presentations at the 2nd International Symposium on Febrile Neutropenia held in Brussels in December 1995 have shown much awaited data which directly compares liposomal amphotericin

(Ambisome) to conventional amphotericin B both for efficacy and safety. In the first study, 193 patients with fever unresponsive to antibiotic therapy for 96 hours or confirmed mycosis were randomised to receive amphotericin B 1mg/kg/day or Ambisome 1mg/kg/day or Ambisome 3mg/kg/day¹⁴. The results showed the two Ambisome arms were at least equi-effective in reducing fever in patients with pyrexia of unknown origin and in achievement of clinical cure and mycological eradication in the patients with confirmed mycosis. The overall prevalence of adverse effects was found to be higher in the amphotericin B treated group (p=0.001) who also had more nephrotoxicity (p=0.001) and infusion related chills (p=0.05).

The second study¹⁵ presented data on 203 neutropenic paediatric patients with fever of unknown origin not responsive to 96 hours antibiotic therapy, from a randomised, comparative trial. Patients were given either amphotericin B 1mg/kg/day or Ambisome 1mg/kg/day or Ambisome 3mg/kg/day. The results showed an overall reduction in clinical adverse effects in the groups randomised to Ambisome (p=0.02), but no significant difference in the prevalence of rash or chills. Nephrotoxicity, as defined by a 100% increase in serum creatinine compared to baseline, was reduced but not significantly in the Ambisome groups (p=0.34). Efficacy, both complete resolution and resolution of fever over three consecutive days, was superior in the Ambisome groups (p=0.02 in both).

If the published results of these trials confirm the early findings, they will provide valuable support for the argument that Ambisome has equal or increased efficacy to conventional amphotericin B and better biological tolerance. There is also evidence for improved clinical tolerance. Other issues such as the possibility of treating with escalated doses and using faster infusion rates with the improved tolerance are yet to be investigated.

2.2.2 Abelcet®

Abelcet forms a ribbon-like structure of relatively large size, containing 35% amphotericin B. It is rapidly cleared from the circulation by the reticuloendothelial system. Abelcet has been reported to have two to four times less antifungal activity than amphotericin B¹⁶.

Abelcet 5mg/kg/day has been used in a small number of trials which are unpublished or available only as abstracts. A review of this data¹⁷ reported good mycological response for open label use in candidiasis (70%) and aspergillosis (47%) in adults and children. Abelcet is frequently associated with fever and chills after administration but appears to have fewer effects on renal function than conventional therapy¹⁷. Randomised controlled or comparative efficacy data are lacking at present.

2.2.3 Amphocil®

Amphocil is formed from equimolar amounts of amphotericin B and cholesterol sulphate. It has a disc-like form and undergoes rapid uptake by the liver. Amphocil has slightly higher minimal fungicidal concentrations than amphotericin B¹⁸.

In an open label trial, 168 patients received up to 6mg/kg/day of Amphocil for documented or presumed systemic mycoses¹⁹. Complete clinical response or improvement was reported in 48 of 97 evaluable patients. Hypokalaemia developed in eight patients but little change was observed to

baseline serum creatinine. A review ¹⁷ of safety and efficacy data, including unpublished data, found that administration adverse events were common, occurring in more than 50% of patients. Nephrotoxicity appeared to be reduced compared with amphotericin B but randomised comparative data are lacking for both efficacy and safety.

3 RECOMMENDATIONS

The current clinical evidence supports the use of Ambisome for:

- Treatment of susceptible systemic fungal infections in patients at risk of nephrotoxicity.
- Prophylaxis of fungal infection in immunocompromised patients at risk of or with pre-existing renal impairment.

Economic arguments for selection of amphotericin B or Ambisome are summarised in the following section.

There is insufficient published data to support use of Amphocil and Abelcet outside controlled clinical trial settings.

The evidence does not support the use of amphotericin in lipid emulsion for use in any patient groups until more is understood about the stability of this formulation.

4 ECONOMIC CONSIDERATIONS

A cost-effectiveness analysis was reported ²⁰, based on retrospective review of 58 patient records from transplantation patients treated with amphotericin B or liposomal amphotericin (Ambisome) from 1981 to 1991. This review found that treatment time was similar in the two patient groups, more adverse effects were documented for amphotericin B (2 patients requiring dialysis) and there were more deaths in the conventionally treated group. The average cost per life year gained with liposomal amphotericin compared to conventional therapy was approximately \$40,000 for liver transplants and \$30,000 for kidney and bone marrow transplants (converted to \$AUS from Swedish Krona). The usefulness of this data is difficult to assess, however, as it will be confounded by other variables that influenced cost, transplant survival and overall survival over the review period.

In a prospective study of fungal prophylaxis in liver transplant patients, Ambisome prophylaxis was less expensive than treatment of proven fungal infection following placebo prophylaxis. The overall incidence of invasive fungal infection was 0% with Ambisome prophylaxis and 16% with placebo.

The comparative drugs cost for an amphotericin treatment course at recommended doses is as follows:

Ambisome (3mg/kg/day for 4 weeks) - \$42,000

Abelcet (5mg/kg/day for 4 weeks) - \$22,500 to \$30,000

Amphocil - not currently in use in Australia

Amphotericin B deoxycholate (0.5-1.0mg/kg/day for 4 weeks) - \$500 to \$1,000

Good quality economic evaluations are needed to better ascertain the advantages of using liposomal amphotericin preparations. This will require good data on comparative efficacy data, however, in the first instance followed by economic comparisons.

NOT CURRENT

REFERENCES

1. Goodwin S, Cleary J, Walawander C, Taylor J, Grasela, T. Pretreatment regimens for adverse events related to infusion of amphotericin B. *Clin Infect Dis* 1995; 20: 755-61.
2. Caillot D, Reny G, Solary E, Cassasnovas O, Chavanet P, Bonnotte B, Perello L, Dumas M, Entezam F, Guy H. A controlled trial of the tolerance of amphotericin B infused in dextrose or in Intralipid in patients with haematological malignancies. *J Antimicrob Chemother* 1994; 33: 603-13.
3. Chavanet P, Garry I, Charlier N, Caillot D, Kisterman J, D'Athis M, Portier H. Trial of glucose versus fat emulsion in preparation of amphotericin for use in HIV infected patients with candidiasis. *Br J Med* 1992; 305: 921-5.
4. Moreau P, Milpied N, Fayette N, Ramee J, Harousseau J. Reduced renal toxicity and improved clinical tolerance of amphotericin B mixed with Intralipid compared with conventional amphotericin B in neutropenic patients. *J Antimicrob Chemother* 1992; 30: 535-41.
5. Joly V, Farinotti R, Saint-Julien L, Cheron M, Carbon C, Yeni P. *Antimicrob Agents & Chemother.* 1994; 38: 177-83.
6. Pascual B, Ayestaran A, Montoro, J, Oliveras J, Estibalez A, Julia A, Lopez A. Administration of lipid-emulsion versus conventional amphotericin B in patients with neutropenia. *Ann Pharmacother* 1995; 29: 1197-201.
7. Swenson CE, Bolcsak LE, Perkins WR, Janoff AS. Lipid-based formulations of amphotericin B. *J Antimicrob Chemother* 1995; 35: 709-11.
8. Trissel LA. Amphotericin B does not mix with fat emulsion. *Am J Health-Syst Pharm.* 1995; 52: 1463-4.
9. Cleary JD. Amphotericin B Formulated in a lipid emulsion. *Ann Pharmacother* 1996; 30: 409-12
10. Tollemar J, Hockerstedt K, Ericzon BG, Jalanko H, Ringden O. Liposomal amphotericin B prevents invasive fungal infections in liver transplant recipients. A randomised, placebo-controlled study. *Transplantation* 1995 Jan 15; 59(1): 45-50.
11. Tollemar J, Ringden O, Andersson S, Sundberg B, Ljungman P, Tyden G. Randomised double-blind study of liposomal amphotericin B (Ambisome) prophylaxis of invasive fungal infections in bone marrow transplant recipients. *Bone Marrow Transplant* 1993; 12: 577-82.
12. Ringden O, Meunier F, Tollemar J, Ricci P, Tura S, Kuse E, Viviani MA, Gorin NC, Klastersky J, Fenaux P, Prentice HG, Ksionski G. Efficacy of amphotericin B encapsulated in liposomes (Ambisome) in the treatment of invasive fungal infections in immunocompromised patients. *J Antimicrob Chemother* 1991; 28,Suppl B: 73-82.

13. Meunier F, Prentice HG, Ringden O. Liposomal amphotericin B (Ambisome): safety data from a phase II/III clinical trial. *J Antimicrob Chemother* 1991; 28,Suppl B: 83-91.
14. Prentice HG, Catovsky D, Aoun M, Kvaloy S, Jacobs S, Herbrecht R, Schey SA, Bell AJ, Ellegaard J, Fiedler E, Fauser AA. Ambisome versus amphotericin B in patients with fever unresponsive to antibiotic therapy for 96 hours, or with confirmed fungal infection. 2nd International Symposium on Febrile Neutropenia 1995 Abstract.
15. Hann IM, Stevens RF, Pinkerton CR, Darbyshire PJ, Gibson BES, Oakhill A, Eestermans GH. Safety and efficacy of two dose regimens of Ambisome versus amphotericin B as empirical antifungal treatment in neutropenic paediatric patients. 2nd International Symposium on Febrile Neutropenia 1995 Abstract.
16. Clark J, Whitney RR, Olsen SJ, et al. Amphotericin B Lipid Complex therapy of experimental fungal infections in mice. *Antimicrob Agents Chemother* 1991; 35: 615-21.
17. Tollemar J, Ringden O. Lipid formulations of amphotericin B. Less toxicity but at what economic cost? *Drug Safety* 1995; 13: 207-18.
18. Harrison LH, Stevens DA. Comparison of antifungal activity of amphotericin B deoxycholate suspension with that of amphotericin B sulphate colloidal dispersion. *Antimicrob Agents Chemother* 1992; 36: 486-8
19. Oppenheim BA, Herbrecht R, Kusne S. The safety and efficacy of amphotericin B colloidal dispersion in the treatment of invasive mycoses. *Clin Infect Dis* 1995; 21: 1145-53
20. Persson U, Tennvall RG, Andersson S, Tyden G, Wettermark B. Cost-effectiveness analysis of treatment with liposomal amphotericin B versus conventional amphotericin B in organ or bone marrow transplant recipients with systemic mycoses. *Pharmacoeconomics* 1992; 2: 500-8.