

Review

Administering amphotericin B—a practical approach

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Despite the introduction in recent years of novel antifungal agents, the potency and broad spectrum of activity of amphotericin B have ensured that it remains the treatment of choice for most deep-seated mycoses. However, this agent is not without significant toxicity, particularly in patients who are already seriously ill and/or who are receiving other potentially nephrotoxic drugs. We review the various routes by which amphotericin B can be administered, focusing mainly on the intravenous route. The use of more rapid infusion rates, lipid-complexed preparations, sodium supplementation in salt-depleted patients and strategies to reduce the incidence of infusion-related reactions and nephrotoxicity are also considered. Finally, detailed recommendations for the administration of amphotericin B are provided.

Introduction

Amphotericin A and B are polyene compounds which were originally isolated from the soil actinomycete, *Streptomyces nodosus*. Amphotericin B is either fungistatic or fungicidal, depending on the concentration of the drug achieved in the serum or tissues and the susceptibility of the pathogen; its activity is maximal over the pH range 6.0–7.5. It has good in-vitro and in-vivo (clinical) activities against *Candida* spp., including *Candida (Torulopsis) glabrata* (but not the majority of *Candida lusitanae* isolates), most *Aspergillus* spp., *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, *Blastomyces dermatitidis*, *Sporothrix schenckii* and *Rhodotorula rubra*. Its activity is limited against *Trichosporin beigellei*, *Fusarium* spp. and the aetiological agents of mucormycosis, and absent against *Pseudallescheria boydii*. Amphotericin B has also been used as treatment for visceral and mucocutaneous leishmaniasis and amoebic meningitis, but it possesses no antibacterial activity. More recently, derivatives of amphotericin B have been found to have some in-vitro activity against the human immunodeficiency virus (Hansen *et al.*, 1990), although the clinical significance of this observation is uncertain. Despite its potential toxicity and the introduction of many novel antifungals in recent years, the potency and broad spectrum of activity of amphotericin B have ensured that it remains the treatment of

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choice for most deep-seated mycoses. This review focuses on the various routes of administering amphotericin B and strategies for limiting its toxicity whilst, at the same time, preserving its efficacy. The clinical indications for the use of this agent and appropriate dosages are outside our remit and have been well-reviewed elsewhere (Meyer, 1992).

Mechanism of action

Amphotericin B acts by binding to sterols in the fungal cell wall and altering membrane permeability, thereby allowing the leakage of cytoplasmic components which eventually leads to cell death. Despite a greater affinity for fungal sterols, it is likely that some of the toxic effects of the drug (e.g. nephrotoxicity) result from damage to the host cell membrane.

Acquired resistance to amphotericin is rare (Warnock, 1991) and routine susceptibility testing is considered unnecessary when treating most infections caused by *Candida* spp., *Aspergillus* spp., *C. neoformans* and the agents of mucormycosis (British Society for Antimicrobial Chemotherapy Working Party, 1991), unless there is failure of treatment or relapse, with re-isolation of the causative organism. On the other hand, resistance may develop during therapy for infections caused by *C. lusitaniae* (Blinkhorn, Adelstein & Spagnuolo, 1989) or when prolonged courses of the drug have been administered (e.g. for fungal endocarditis), under which circumstances susceptibility testing may be advantageous.

Formulations

Because it is relatively unstable, amphotericin B is commercially available as a complex with sodium desoxycholate (Fungizone, Bristol-Meyers Squibb). After reconstitution with distilled water, the mixture is diluted in 5% dextrose to give an infusion solution with a final concentration of up to 0.25 g/L (Ellis *et al.*, 1992). At concentrations of up to 1.4 g/L, the preparation is stable for at least 36 h (Kintzel & Kennedy, 1991). The addition of sodium heparin or hydrocortisone to the infusion does not affect its stability (Trissel, 1992), but electrolyte-containing solutions will cause the amphotericin to precipitate and diluents other than those recommended should therefore be avoided. The commonly-held belief that diluted solutions must be protected from light and used within 6 h does not apply to amphotericin B which is stable for at least 24 h when exposed to light at room temperature (Trissel, 1992).

The efficacy of amphotericin B, notwithstanding the side-effects associated with its administration, has led to the development of several different formulations of the drug. An attempt in the late 1970s to produce salts of the methyl ester resulted in a preparation which caused central nervous system toxicity (Ellis, Sobel & Neilsen, 1982). More recently, amphotericin B has been combined with a number of lipid compounds (Bennett, 1992) which are listed in the table. These lipid-associated preparations have been shown to have a reduced potential for causing toxicity in animal models, and probably in humans as well. The methods of preparation, storage and administration and the tissue distribution of each formulation differ from those of conventional amphotericin B and vary from product to product. Although most preparations have reduced efficacies when compared with amphotericin B-desoxycholate on a dosage-for-dosage basis (three- to four-fold higher dosages being required to produce equivalent

Table. Intravenous formulations of amphotericin B

Formulation	Manufacturer	Carrier	Colloidal type	Current status	Cost (£) per 50 mg	Target dosage (mg/kg/day)
Fungizone	Bristol-Myers Squibb	Sodium desoxycholate	micelle lipid emulsion	licensed	3.70	0.5-1.5
Fungizone in 100 mL of 20% Intralipid	Kabi Pharmacia			undergoing clinical studies	10.25	?1-5
AmBisome	Vestar Inc.	DSPG ^a	unilamellar liposome	licensed in Europe (not USA)	119	1-4
Amphocil (ABCD) ^b	Liposome Technology Inc.	cholesteryl sulphate	lipid discs	Phase III clinical studies in UK and USA, licensed in some European countries	N/A	1-4
Amphotericin B Lipid Complex (ABL) ^c	The Liposome Co.	DMPC ^d DMPG ^e	ribbons	Phase II clinical studies in UK	N/A ^f	?1-5

^aDistearoylphosphatidyl glycerol.

^bAmphotericin B colloidal dispersion.

^cNot commercially available in UK.

^dDimyristoylphosphatidyl choline.

^eDimyristoylphosphatidyl glycerol.

activity), their therapeutic indices, where they have been determined, are improved. Consequently, these novel formulations may facilitate the administration of larger dosages of amphotericin B where therapy with full parenteral dosages of the standard preparation has failed. Lipid-associated formulations may have a particular role in reducing the nephrotoxicity experienced by patients who are also receiving cyclosporin. Comparative studies of the efficacies of each new preparation are awaited with interest, but until the results are available, the use of lipid-associated (including liposomal) amphotericin B should be restricted to patients for whom there are few therapeutic alternatives, who are intolerant of or who fail to respond to conventional preparations, or who are participating in clinical trials in which these agents are being evaluated.

Much interest has recently been generated as the result of combining amphotericin B (Fungizone) with a lipid emulsion (Intralipid, Kabi Pharmacia) (Caillot *et al.*, 1992; Chavanet *et al.*, 1992) in an attempt to reduce the toxicity of the former. Data relating to the stability of such formulations are conflicting (Kirsch *et al.*, 1988; Washington, Lance & Davis, 1993), although they appear to retain their antifungal activities. While optimal dosing regimens have not yet been defined, in common with the lipid-associated preparations described above, it may be both possible and, indeed, necessary to administer larger dosages of amphotericin B than are required when this drug is given alone. There may also be problems associated with ensuring sterility. None the less, limited experience to date suggests that this strategy is associated with reduced toxicity. Further evaluation in prospective, comparative clinical trials is clearly indicated.

Pharmacokinetics

Although highly protein-bound, free amphotericin B rapidly leaves the blood compartment. Serum concentrations immediately following an infusion do not normally exceed 2 mg/L, even with dosages of ≥ 50 mg. As a result, only a small proportion of the biological activity of the drug is retained in the plasma (Bindschadler & Bennett, 1969). After leaving the circulation, it slowly accumulates within some tissue compartments (e.g. bone), giving rise to a prolonged half-life of about 15 days (Daneshmend & Warnock, 1983). Excretion is principally by the kidneys and amphotericin B can be detected in urine for up to 7 weeks after discontinuing therapy. As a consequence of its complex pharmacokinetics (an initial short plasma half-life followed by a slow elimination phase), the concentrations of amphotericin B in the blood do not accurately reflect the concentrations in the tissues, and measuring them is, therefore, of little value. Because of its high protein binding, amphotericin B is not significantly cleared by dialysis.

Despite crossing the placenta (McCoy, Ellenberg & Killam, 1980), amphotericin B has been administered during all stages of pregnancy without adverse effects to the fetus (Briggs, Freeman & Yaffe, 1990). There is a paucity of data concerning secretion into breast milk.

Dosage and administration

Amphotericin B is usually administered by slow iv infusion over a period of approximately 4 h. The targeted daily dosage varies from 0.5–1.5 mg/kg, depending on the severity of the infection, the nature of the pathogen, renal function and drug tolerance.

Higher dosages are necessary for infections caused by filamentous fungi, particularly those causing zygomycosis and invasive aspergillosis, and in the treatment of neutropenic patients. In patients with life-threatening infections, dosages of between 0.5 and 1.0 mg/kg should be given as the first dose, with the target dosage (defined for each patient) reached over the next 24 h. In less severely-ill patients, the targeted dosage can be achieved in 3–4 days. If therapy is resumed after an interruption of more than 1 week, a lower starting dosage should again be administered, the dosage being gradually increased thereafter. A test dose which is advisable when commencing all new courses of treatment should immediately precede the first dose; a small amount of drug (e.g. 20 mL of a solution containing 0.1 g/L) should be infused over 10 min and the patient carefully observed for the next 30 min.

Some reports suggest that rapid infusion rates (45–60 min) are well-tolerated (Fitzsimmons *et al.*, 1989; Oldfield *et al.*, 1989). However, a small, prospective, controlled study revealed that the incidence of side-effects and adverse reactions was higher with rapid infusions (Ellis *et al.*, 1992); even then, tolerance may develop in some patients. If infusions of shorter duration are required, we suggest administering the amphotericin B over 1.5–2 h, increasing to 4 h should adverse reactions become apparent. Rarely do infusions need to be administered over periods of more than 4 h.

For some infections, such as chronic disseminated histoplasmosis, it is believed that the total dosage of amphotericin B that a patient receives, irrespective of the duration over which it is administered, is more important than the amount of drug given on a daily basis. However, in rapidly-progressive fungal infections, the rate of administration (daily dosage) is probably more significant. Owing to the long half-life of the drug, infusions of twice the daily dosage can be administered on alternate days after the first week or two of therapy. This may reduce the incidence of infusion-related toxicity and phlebitis. Dosing on alternate days is inappropriate for patients with life-threatening infections who require high dosages (e.g. 1 mg/kg/day) unless there has already been some response to therapy.

Other routes of administration

Amphotericin B is too irritant and is absorbed too poorly to allow it to be given by the intramuscular route. Since systemic absorption is minimal, oral administration is suitable only for the prevention of fungal colonization of the gastrointestinal tract. Oropharyngeal candidosis responds to both amphotericin B lozenges and mouthwashes if they are used frequently.

Following iv administration, only 2–4% of the simultaneous serum concentration reaches the CSF (Daneshmend & Warnock, 1983). Therefore, instillation directly into the CSF by the intralumbar, intracisternal or intraventricular routes has been used, in addition to iv therapy, in patients with cryptococcal or coccidioidal meningitis. However, this form of delivery may cause neurological deficits and should be used with great caution. The dosage range is 0.05–0.5 mg/day in 5 mL of 10% glucose to which is added 5–25 mg of hydrocortisone to reduce the incidence of headache, fever and nausea. The drug should be given no more than once daily by these routes and the dosage should be increased gradually to the maximum which is tolerated. Once the infection is under control, the frequency of administration can be reduced. Intraarticular injections (5–15 mg) have been administered for joint infections caused by *C. immitis* or *S. schenckii* but are rarely necessary now that oral azole therapy is

available. Bladder instillation of an aqueous solution containing 50 mg/L (Wise *et al.*, 1973) has been used for persistent candiduria; treatment can be either by continuous irrigation or intermittent instillation (three or four times daily) with a dwell time of at least 2 h.

Intraocular instillation has been recommended for the treatment of patients with fungal endophthalmitis (Denning & Stevens, 1990) and intravitreal administration may be a useful adjunct to vitrectomy; subconjunctival instillation is probably of little value.

Nebulized amphotericin B (8–40 mg in sterile water or 5% glucose in daily divided doses) has been used in an attempt to eradicate fungal colonization of the respiratory tract, but with little success. More recently, interest has been focused on the prevention of pulmonary aspergillus infection in neutropenic patients, with the amphotericin B being either nebulized or administered via a nasal spray; however, the results of these strategies have been variable (Meunier-Carpentier *et al.*, 1984; Jorgensen *et al.*, 1989; Jeffery *et al.*, 1991).

Administration of amphotericin B by the intraperitoneal route has been used to treat fungal peritonitis in patients receiving dialysis (Bayer *et al.*, 1976). However, these patients usually develop adhesions which impede the free flow of the antifungal and removal of the catheter is an essential component of their management. Intravenous therapy is also appropriate in this setting.

Contraindications

The only absolute contraindication to prescribing amphotericin B is anaphylaxis which is fortunately uncommon, occurring in approximately 1% of treatment courses (Gross, Pickard & Perfect, 1987). Relative contraindications include significant renal impairment, the concurrent administration of cyclosporin and other potentially nephrotoxic drugs and lack of iv access. Lipid-associated preparations may be of benefit where significant renal toxicity exists or is likely to develop.

Adverse effects

Patients who require treatment with amphotericin B tend to be already seriously ill from their underlying diseases and may have organ dysfunction. For this reason, and because amphotericin B is usually administered for prolonged periods, they are particularly susceptible to drug toxicity.

Infusion-related side-effects

While earlier formulations of amphotericin B were contaminated with small amounts of endotoxin which resulted in a high incidence of adverse reactions (Pai *et al.*, 1989), improvements in the manufacturing process have significantly reduced the frequency of these complications. However, side-effects associated with iv administration are still relatively common and include fever, rigors and nausea. Their frequency can be reduced further by the prophylactic administration of chlorpheniramine, aspirin (or other non-steroidal anti-inflammatory agents) or either pethidine or meperidine (25–50 mg) and by slowing the rate of infusion. Intravenous hydrocortisone should not be given routinely, although it may be necessary for patients who experience severe reactions; dosages of between 25 and 50 mg are usually adequate for this purpose. It is worth bearing in mind that patients often develop tolerance to these side-effects.

Administration by the iv route may also cause peripheral venous thrombosis or thrombophlebitis. Infusion concentrations of more than 0.1 g/L in particular are associated with increased risks of thrombophlebitis if amphotericin B is given via a peripheral line (Ellis *et al.*, 1992). The frequency of this complication can be minimized by infusing the antifungal through a central line. Filtering the amphotericin B solution has not been shown to affect the incidence of phlebitis or other adverse reactions (Gotz, Rand & Kramer, 1985) and in-line filters with pore sizes of less than 0.45 μm may actually remove some of the drug. The addition of small amounts of heparin (500–2000 units) to the infusion may reduce the likelihood of thrombophlebitis developing (Sarosi, 1990).

Prolonged treatment with amphotericin B may produce a normochromic, normocytic anaemia which is due to either direct marrow toxicity or a reduction in the patient's ability to respond to erythropoietin (Lin *et al.*, 1990); this effect is reversible following discontinuation of the drug. Cardiac toxicity, manifested primarily as arrhythmias, is uncommon and is usually related to very rapid infusion rates. There have been a few reports of fatal pulmonary reactions when leucocyte transfusions have been administered concomitantly (Wright *et al.*, 1981) and, very rarely, amphotericin B may affect platelet function (with or without thrombocytopenia) which reverses itself when treatment is terminated.

Nephrotoxicity and electrolyte abnormalities

Renal toxicity, reported in up to 80% of patients, has been the major factor which has discouraged the use of amphotericin B in clinical practice and limited its dosage on many of the occasions when it has been prescribed. The precise mechanism by which the kidneys are affected is uncertain but possibilities include direct tubular damage and/or a reduction in the glomerular filtration rate secondary to a decrease in renal blood flow (Branch, 1988). These abnormalities can in turn lead to raised serum creatinine and urea concentrations, a decreased ability to concentrate urine, hypokalaemia or renal tubular acidosis. Excessive loss of magnesium via the kidneys may also be detected, in which case the hypokalaemia can be corrected only after the magnesium has been replaced. Hyperkalaemia, due to the intracellular release of potassium, has been reported rarely. Renal impairment following a cumulative amphotericin B dosage of less than 4 g is almost always reversible.

Reducing nephrotoxicity

The serum electrolyte concentrations, additional biochemical parameters of renal function and fluid balance must be monitored frequently in patients with renal impairment. The concomitant administration of other potentially nephrotoxic drugs, such as loop diuretics and aminoglycosides (Stein *et al.*, 1988), should be avoided wherever possible.

There is evidence from both animal (Gerkens & Branch, 1980) and human (Heidemann *et al.*, 1983) studies suggesting that sodium supplementation may prevent or reduce the likelihood of nephrotoxicity in the salt-depleted state. Patients receiving ticarcillin (with an obligatory salt load of at least 90 mEq/day) are also less likely to develop amphotericin B-related nephrotoxicity (Stein *et al.*, 1988). Because sodium restriction is associated with an increased risk of nephrotoxicity (Butler *et al.*, 1964), it has been recommended that 500 mL of 0.9% saline should be infused before and/or after the administration of iv amphotericin B (Branch, 1988).

The co-administration of amiloride (10 mg daily) has been shown to reduce potassium loss via the kidneys and hypokalaemia (Cruz *et al.*, 1991) and is beneficial to patients who are able to tolerate oral medication. Neither mannitol (Bullock *et al.*, 1976) nor sodium bicarbonate (Heidemann *et al.*, 1983) have been demonstrated convincingly to protect against nephrotoxicity. The efficacies of experimental methods, including the use of either dopamine combined with saralasin, an angiotensin II antagonist (Reiner & Thompson, 1979), or aminophylline (Gerken *et al.*, 1983), in reducing the incidence of amphotericin B-induced renal vasoconstriction have yet to be confirmed in the clinical setting. Oral pentoxifylline may reverse renal impairment due to the combined effects of amphotericin B and cyclosporin in bone marrow transplant patients (Bianco *et al.*, 1991).

In transplant patients, attempts should be made, wherever possible, to reduce the dosage of cyclosporin; the sodium status of these patients should also be monitored closely. In patients with severe, pre-existing renal impairment, dosage modifications should not be made initially. However, when there is evidence of a clinical response, less frequent administration (e.g. at 36 h intervals) of the same dosage may be appropriate. For those patients who develop renal impairment during courses of therapy for severe or life-threatening fungal diseases, the dosage should not be modified until the serum creatinine concentration is three times the upper limit of normal (or, in children, three times the pre-treatment value). If and when this threshold is exceeded, treatment with amphotericin B should be discontinued for 1 day, and then resumed at one-half the previous dosage, followed by a gradual escalation, renal function permitting, over 2–3 days until the target dosage is reached.

Drug interactions

The potassium-depleting effect of amphotericin B may potentiate the actions of neuromuscular-blocking agents and increase the toxicity of cardiac glycosides. The concurrent administration of corticosteroids may enhance potassium loss due to amphotericin B. In-vitro studies suggest that the tetracyclines and rifampicin, neither of which are active alone against fungi, are capable of potentiating the antifungal activity of amphotericin B, possibly by increasing its penetration into the fungal cells (Edwards *et al.*, 1980; Hughes *et al.*, 1984); at present, however, there is little in-vivo data to support the use of these agents in the treatment of systemic mycoses. The combination of amphotericin B and flucytosine is considered to be synergic against *C. neoformans* and *Candida* spp. (Medoff, Comfort & Kobayashi, 1971), although this effect has not yet been demonstrated with the liposomal formulation of amphotericin B. There have been conflicting reports of both synergy and antagonism between amphotericin B and the azoles, ketoconazole and miconazole, depending on the fungus and the method of susceptibility testing (Warnock, 1991). The mechanisms of action of the azoles and amphotericin B suggest that antagonism is likely and that their use together should be avoided. Finally, because of the nephrotoxic potential of amphotericin B, it should not, ideally, be administered with anti-neoplastic agents or other drugs which might also cause renal toxicity.

Summary of recommendations

In patients who have experienced adverse reactions, the administration of iv hydrocortisone (25–50 mg) and/or chlorpheniramine (10 mg) 30 min before infusing the amphotericin B may reduce the incidence of fever, rigors and nausea, thereby improving

tolerance. A test dose is advisable at the start of all new courses of treatment. The infusion time should not normally exceed 4 h and can be as short as 2 h, although some patients may not tolerate such rapid infusions. Fluid balance and renal and haematological functions should be monitored closely in all patients. The regular assessment of sodium balance is essential to minimize the risk of renal impairment and, wherever possible, salt restriction and drugs which potentiate sodium loss (e.g. diuretics) and nephrotoxicity should be avoided. Sodium replacement, usually 150 mEq, in addition to the normal daily dietary intake of 150–200 mEq, should be implemented in patients who are salt-depleted. In some patients, however, salt loading exacerbates cardiac failure, peripheral oedema and ascites and the benefits of this strategy must be weighed against the risks. Amiloride may prevent hypokalaemia in patients who are able to take oral medication. The current lack of data relating to efficacy, as well as the high costs, preclude the routine administration of novel lipid-complexed or liposomal preparations of amphotericin B, unless these agents are being evaluated in clinical trials or have been prescribed because of previous toxicity or therapeutic failure with conventional formulations.

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