In search of the amazing technicolour dream coat for amphotericin B

Major strides in organ transplantation, cancer chemotherapy, use of medical devices, and the increasingly successful treatment of patients with AIDS have led to increased incidence of invasive fungal infection over the past two decades. Despite advances in the area of antifungal chemotherapy with the introduction of the azoles during the past 10 years, amphotericin B remains the drug of choice for most serious systemic fungal infections including mucormycosis, aspergillosis, and cryptococcal meningitis in non-AIDS patients (1). Amphotericin B was first isolated in 1956 from the soil actinomycete, *Streptococcus nodosus*, and may be either fungistatic or fungicidal depending on the concentration of the drug achieved at the site of infection and the intrinsic susceptibility of the pathogen (1). It has both in vitro and in vivo activity against most *Candida* species (with the exception of *Candida lusitaniae*), most aspergillus species, *Candida neoformans, Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Sporothrix schenckii*, certain *Mucorales* species and the agents responsible for visceral and mucocutaneous leishmaniasis and amoebic meningoencephalitis (2).

Amphotericin B is a highly lipophilic rod-like molecule that acts by binding to sterols in the fungal cell wall and altering permeability, thereby leading to loss of intracellular potassium and other intracytoplasmic molecules and cell death. The drug also binds to sterols in the mammalian cell membrane but with a much lower affinity for these sterols. Nonetheless, it is assumed that some of the toxic effects of amphotericin B result from altered permeability in selected host cell membranes.

The major disadvantage of amphotericin B has been a relatively high incidence of adverse effects including fever, intense malaise, rigors, nausea, vomiting, hypotension, nephrotoxicity, hypokalemia, hypomagnesemia, anemia, thrombocytopenia and occasionally elevated serum aminotransferases (1,3).

With toxicity limiting the use of higher doses of amphotericin B, high failure rates for the treatment of invasive fungal infections in severely compromised hosts (4,5), and increasing concerns about the development of amphotericin B-resistant fungal strains (6), considerable efforts have been made over the past few years to develop new formulations of the compound and to identify new methods for delivery (7-9).

Several preparations of amphotericin B are available or are under evaluation in clinical settings, including amphotericin B desoxycholate (conventional amphotericin B), a lipid emulsion of amphotericin B desoxycholate, one liposomal preparation and two lipid-associated liposome-like preparations. Since amphotericin B is intrinsically unstable it was complexed with sodium desoxycholate, and this preparation (Fungizone, Squibb) after reconstitution, is usually diluted in dextrose solutions and given as an intravenous infusion. The preparation remains stable for 36 h (10). Although it is often stated that the solution should be protected from light and administered within a few hours of its preparation, recent evidence suggests that this is not necessary and that there is no degradation on exposure to light (11,12).

An amphotericin B lipid emulsion has been used in recent years in an attempt to reduce the toxicity and adverse effects of conventional amphotericin B (13-15). Amphotericin B sodium desoxycholate prepared in a parenteral lipid emulsion (Intralipid 20%, Pharmacia Inc) and administered as an intravenous infusion has demonstrated a reduction in toxicity in two small case series (13). Clinical efficacy appears to be retained and, although optimal dosing regimens are not known, higher dosages of between 1 and 1.5 mg/kg/day have been successfully administered. Recent observations, however, have suggested that amphotericin B may not emulsify in the 20% Intralipid as readily as first thought (16, 17). Further prospective randomized comparative trials will be required to evaluate this preparation fully.

Another method of reducing toxicity to amphotericin B is to entrap it in liposomes. Liposomal preparations of amphotericin B have not only been associated with reduced toxicity but their preserved antifungal activity and increased dosing may result in an improved therapeutic index. Although the methods of preparation, storage and administration differ for each of the liposomal or liposome-like formulations, all of the preparations require three- or fourfold higher doses than conventional amphotericin B.
Liposomes are microscopic lipid vesicles consisting of one or more concentric phospholipid bilayers enclosing discrete hydrophobic cores. Based on liposome morphology, liposomes can be grouped into three main categories: large multilayered liposomes of variable size termed multilamellar vesicles; large single-layered liposomes with a more homogeneous particle size (less than 0.1 μm in diameter) termed large unilamellar vesicles and small single-layered liposomes (with a particle size of less than 0.15 μm) termed small unilamellar vesicles (SUV) (18). The chemical composition, size and number of layers determine the pharmacological and biological properties of the liposomes. The intravenous formulations of amphotericin B complexed with liposomes or liposome-like particles, which are available in Canada only for emergency or compassionate use, include liposomal amphotericin B (Ambisome, Vestar Ltd, Cambridge, England), amphotericin B colloidal dispersion (ABCD) (Amphocil, Sequeus Pharmaceuticals, California) and amphotericin B lipid complex (ABLC) (Abelcet, The Liposome Company Inc, New Jersey).

Liposomal amphotericin B consists of SUVs of about 80 nm each containing 10 mol% amphotericin B. Due to its small diameter this liposome is cleared less rapidly than others, resulting in relatively high serum levels compared with equivalent doses of conventional amphotericin B (19). This agent is registered for use in several European countries and is used at doses of 3 to 5 mg/kg. The published trials (19-24) on the use of this formulation have concerned compassionate use or noncomparative case series, and though the drug was well tolerated, the efficacy data are difficult to interpret in the absence of a concomitant control group. However, in comparison with historical controls liposomal amphotericin B appears to be as effective as conventional amphotericin B.

ABCD is not a true liposomal formulation but a complex of amphotericin B and cholesteryl sulphate in a 1:1 ratio arranged in small lipid discs. Similar to other lipid formulations of amphotericin B, reduced toxicities have been demonstrated for doses of 1 to 5 mg/kg. Following infusion, ABCD is rapidly taken up by the reticuloendothelial system and peak plasma concentrations are about one-half those for corresponding doses of conventional amphotericin B (25,26). Initial results from dose escalating studies and case series suggest that response rates are comparable to historical controls (27-30). A double-blind, randomized comparative study of ABCD versus conventional amphotericin B for the treatment of invasive aspergillosis is underway in North America and should provide solid efficacy data on this formulation in this setting.

ABLC consists of amphotericin B in a 35 mol% concentration complexed to sheets of two phospholipid carriers (dimyrstoylphosphatidyl choline and dimyristoylphosphatidyl glycerol) in a 7:3 ratio and thus is not a true liposomal formulation. The large size of the sheets results in significant trapping in the reticuloendothelial system, and peak concentrations are lower than with corresponding doses of conventional amphotericin B. Initial case series studies indicated tolerance of doses over 1 mg/kg (31,32), and a recent prospective randomized multicentre trial of ABLC versus conventional amphotericin B in the treatment of invasive candidiasis using a dose of 5 mg/kg of ABLC found equal efficacy but significantly less nephrotoxicity (33).

The available literature on the use of new formulations of amphotericin B does suggest that they are associated with less toxicity. The reasons for the observed reductions in toxicity are not fully understood, though it is thought that the use of liposomes or lipid carriers may result in enhanced selective delivery of amphotericin B to fungal cells rather than mammalian cells (34). The results of prospective randomized comparative trials currently underway will allow a more appropriate assessment of the contribution of these new formulations of amphotericin B with regard to their efficacy and their overall contribution to antifungal chemotherapy. One cannot discuss these new formulations without addressing costs. The cost of amphotericin B in 20% Intralipid and liposomal amphotericin B are three to 30 times, respectively, the cost of conventional amphotericin B and any use in the clinical setting would require a careful assessment of the risk-benefit ratio for a given patient. If they are found to be at least equally efficacious, then these varied lipid formulations may truly represent the technicolour dreamcoat for amphotericin B with respect to lessened toxicities.

REFERENCES


