CME CREDIT

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Lipid formulations of amphotericin B

ABSTRACT

Amphotericin B has long been the mainstay in the treatment of systemic fungal infections, but its nephrotoxicity limits the dosage that can be used. New lipid-based forms may allow higher dosing with less nephrotoxicity. Unfortunately, these new forms are substantially more expensive, and data from randomized clinical trials of their relative efficacy are as yet limited.

KEY POINTS

Renal function usually improves over time after amphotericin B is discontinued, but some renal impairment may be permanent.

The role of lipid-based forms of amphotericin B in the treatment of severe systemic fungal infections is not yet clear.

PLACING EXISTING DRUGS into lipid-based complexes may theoretically provide drugs that are safer, easier to use, and capable of delivering higher doses of drug to the target site. Drugs that are relatively toxic, such as amphotericin B, are good candidates for some type of lipid formulation (see "Formulations of amphotericin B").

Amphotericin B deoxycholate has been the mainstay of antifungal therapy for the treatment of systemic fungal infections for four decades, yet its use is hampered by infusion-related adverse drug reactions, electrolyte disturbances, and nephrotoxicity. New lipid-based products appear to be less nephrotoxic while allowing the administration of higher doses. This article reviews these controversial agents in terms of pharmacokinetics, efficacy, toxicity, and cost compared with standard amphotericin B.

STANDARD AMPHOTERICIN B

Introduced into clinical use in 1955,[1] amphotericin B deoxycholate is usually reserved for progressive and potentially fatal systemic fungal infections.[2] Amphotericin B works by binding to ergosterol in the fungal cell membrane and allowing leakage of intracellular constituents, leading to subsequent cell death. This mechanism of action is the same for all amphotericin B products.

Adverse reactions related to amphotericin B may be infusion-related or occur later in therapy. Typical adverse reactions related to intravenous infusions of amphotericin B include headaches, fever, hypotension, and chills or rigors. Other infusion-related adverse effects include malaise, muscle and joint pain, and gastrointestinal symptoms. The most difficult to manage of all of the infusion-related reactions are the fever and chills.

TABLE 1

Comparison of amphotericin B formulations: dosages and approved indications for intravenous infusion

FORMULATION	BRAND NAME	RECOMMENDED DOSE	APPROVED INDICATIONS	COMMENTS
Amphotericin B deoxycholate	Fungizone	0.25 to 1.0 mg/kg/day	Potentially fatal fungal infections	No filters may be used in preparation or administration
Amphotericin B cholesteryl sulfate complex (ABCD)	Amphotec	3 to 4 mg/kg/day to start; increase up to 6 mg/kg/day if needed	Invasive aspergillosis, if renal impairment or toxicity precludes use of conventional amphotericin B	No filters may be used in preparation or administration
Amphotericin B lipid complex (ABLC)	Abelcet	5 mg/kg/day	Aspergillosis in patients with refractory infection or intolerance to standard amphotericin B	Coarse (5-μm) filtration for preparation; infusion containers must be shaken every 2 hours
Liposomal amphotericin B	Ambisome	3 to 5 mg/kg/day	If renal impairment or toxicity precludes use of conventional amphotericin B; leishmaniasis; empirical treatment of fungal infections in febrile, neutropenic patients	In-line membrane filter with a 1-μm mean pore diameter may be used

Each form of amphotericin B has slightly different pharmacokinetic behavior

Amphotericin B toxicities not related specifically to infusion include anemia, electrolyte disturbances, and nephrotoxicity. Nephrotoxicity is characterized by azotemia and by a decrease in glomerular filtration rate, creatinine clearance, and renal plasma flow. There is subsequent loss of potassium, magnesium, uric acid, and protein. Renal function usually improves over time after the drug is discontinued, but some renal impairment may be permanent.

PHARMACOKINETICS OF LIPID FORMULATIONS

Each amphotericin B product exhibits slightly different pharmacokinetic behavior. Unfortunately, it is unclear at this time whether the physical and chemical differences among the products are of clinical significance. The lipid-based amphotericin products, Amphotec and Abelcet, appear to be taken up by the reticuloendothelial system (FIGURE 1). The lipid complexes accumulate in the liver, spleen, and lungs. The drug is then slowly released from the complexes, providing a sustained, slow release of free amphotericin B. The reduced amount of free amphotericin B available at any given time in the blood stream may account for the reduced nephrotoxicity of the lipid-based preparations compared to the standard formulation.[3] Even when substantially larger doses of lipid-complexed amphotericin B are given, the peak amphotericin blood levels do not rise proportionately. It is assumed that tissue uptake is responsible for this phenomenon.[3]

Liposomal amphotericin B (Ambisome) is also taken up by the reticuloendothelial system; however, it can exert its activity even while the amphotericin B is within the liposome. Renal accumulation also seems to be reduced with this liposomal product.

The lipid-based forms, therefore, make larger doses of amphotericin B possible to administer without an increase in nephrotoxicity. It is unknown, however, whether more amphotericin B is actually available at the site of infection or at the organism level, even though more drug is administered. TABLE 1 com-

Distribution of lipid-based amphotericin B

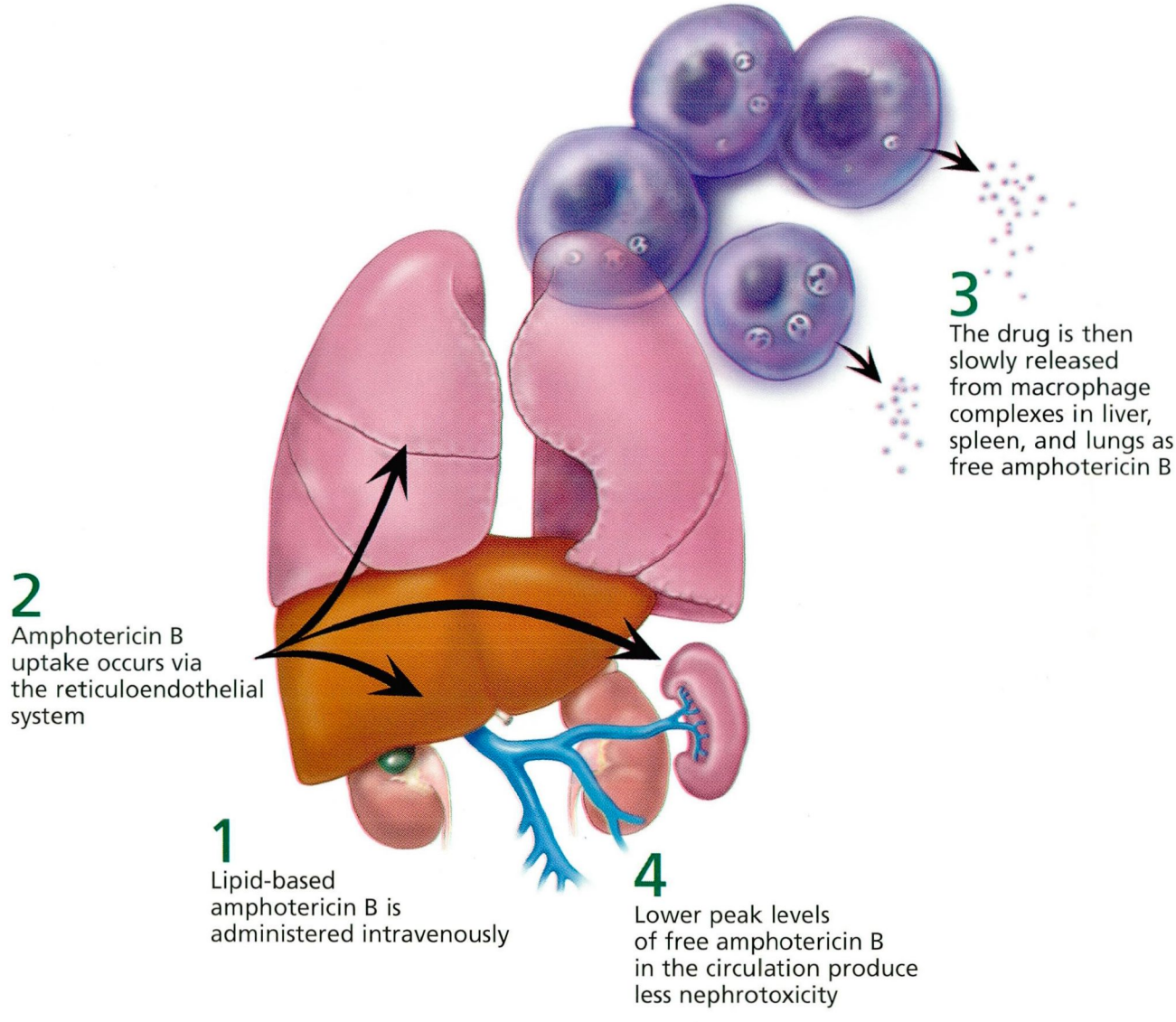

FIGURE 1

pares the dosage of the standard amphotericin B deoxycholate formulation with those of the lipid-based forms.

CLINICAL TRIALS

The majority of pivotal trials of lipid-based amphotericin B for US Food and Drug Administration approval were not the usual randomized, double-blind controlled trials that have come to be the standard for most other drugs.[4,5] Since amphotericin B is used to treat fungal infections on a presumptive basis, and since correct diagnosis can take several days, it is difficult to conduct a rigorous randomized trial. Patients were entered into some of these studies to receive lipid-based amphotericin B treatment if, in the judgement of their physicians, conventional amphotericin B therapy had failed, or if

Formulations of amphotericin B

RESEARCHERS SOUGHT LONG for a form of amphotericin B that causes fewer and less serious adverse effects and that can deliver higher doses of drug more safely. Research into improved forms of amphotericin B focused on combining it with lipid carriers such as cholesteryl sulfate, phosphatidyl choline, or phosphatidyl glycerol. It culminated in the development of three lipid-based forms: amphotericin B cholesteryl sulfate complex (ABCD, Amphotec); amphotericin B lipid complex (ABLC, Abelcet); and liposomal amphotericin B (Ambisome).

STANDARD AMPHOTERICIN B

Because amphotericin B is insoluble in water, standard parenteral amphotericin products use deoxycholic acid to create a stable colloidal dispersion.

AMPHOTERICIN B LIPID COMPLEX

Amphotericin B lipid complex (Abelcet) is a complex of amphotericin B with phosphatidyl choline and phosphatidyl glycerol. The product consists of particles ranging in size from 1,600 nm to 11,000 nm. The particles are described as "ribbon-like" in shape.

AMPHOTERICIN B CHOLESTERYL SULFATE COMPLEX

Amphotericin B cholesteryl sulfate complex (Amphotec) is a complex of amphotericin B with cholesteryl sulfate. The particles of this complex range in size from 120 nm to 140 nm. They are described as "disk-shaped."

LIPOSOMAL AMPHOTERICIN B

Liposomal amphotericin B (Ambisome) contains small single-layer vesicular particles of 60 nm to 70 nm composed of hydrogenated soy phosphatidyl choline and distearoylphosphatidyl glycerol stabilized by cholesterol and amphotericin B.

Better trials are needed to delineate the role of lipid-based amphotericin B

patients had significant renal insufficiency, either preexisting or secondary to standard amphotericin B use.[4–7]

The results of these types of trials have indicated that lipid-based forms of amphotericin B are as effective as conventional amphotericin B, but less toxic. Doses of the lipid-based products in these trials exceeded the conventional amphotericin B doses by threefold to fivefold. Because of their design, these types of trials are very difficult to interpret in terms of real comparisons of efficacy and toxicity. Because the majority of patients are placed into these studies after a significant trial of amphotericin B, outcomes of patients initially placed on the lipid-based products is unknown.

An example of a randomized, controlled clinical trial was performed with liposomal amphotericin B.[8] Standard amphotericin B was compared with liposomal amphotericin B in patients with neutropenic fever. There were no differences between the groups in primary outcome parameters. There was a significant difference in the nephrotoxicity between the groups, but the clinical significance of this is unknown (see below).

More well-controlled comparative trials are necessary to better delineate the role of these lipid-based products. Trials comparing one lipid product to another are also necessary to determine differences among the products.

MANAGING ADVERSE EFFECTS

Available lipid-based amphotericin B products appear to produce acute infusion-related reactions including fever, chills, hypotension, nausea, or dyspnea, with approximately the same or less frequency and intensity compared with conventional amphotericin B products. As with conventional amphotericin B, these effects are usually more severe with the initial doses and tend to diminish as subsequent doses are given. These can be managed by pretreatment with acetaminophen, nonsteroidal anti-inflammatory agents with or without antihistamines, and, if necessary, corticosteroids.

Nephrotoxicity has been shown to be lower with lipid-based products as compared with conventional agents in almost all trials. These data are difficult to interpret because of study design problems. In one double-blind, controlled trial, there was a significant difference in nephrotoxicity between liposomal amphotericin B (Ambisome) and conventional amphotericin B.[8] The differences in both the mean peak serum creatinine level and the mean change from baseline of the serum creatinine level were very small, although statistically significant. The clinical significance of these differences is yet to be determined.

COST CONSIDERATIONS

Costs of the amphotericin B products are shown in TABLE 2. They are listed as equivalent daily doses to the best of our ability. Average wholesale prices are given. These may not reflect prices given under purchasing group contracts.

TABLE 2

Cost comparison of amphotericin B formulations

NAME	COST PER 50 MG*	COST PER DAY PER 70 KG*
Amphotericin B deoxycholate (standard formulation)	$5.06	$1.77 to $7.08†
Amphotericin B cholesteryl sulfate complex	$93.33	$391.99 to $522.65‡
Amphotericin B lipid complex	$86.67§	$606.69‖
Liposomal amphotericin B	$196.25	$824.25 to $1,373.75¶

*All prices are average wholesale price
†Based on 0.25 to 1 mg/kg/day recommended dose
‡Based on 3–4 mg/kg/day recommended dose
§No 50-mg vial available; price reflects one half of 100-mg vial
‖Based on 5 mg/kg/day recommended dose
¶Based on 3 to 5 mg/kg/day recommended dose

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SUMMARY

The new lipid-based amphotericin products have limited application at this time. They are less nephrotoxic than standard amphotericin B, but the clinical significance of this is unknown. There are also variable differences in infusion-related adverse events, with no comparative data among the various lipid-based products in regard to the differences in toxicity.

Compelling data that demonstrate meaningful differences in efficacy are not yet available. These agents have been shown to be effective in patients who did not tolerate standard amphotericin B, and in some patients whose infections progressed despite therapy with standard amphotericin B.

The lipid-based amphotericin B products are substantially more expensive than standard amphotericin B. In addition, the lipid products are not interchangeable due to differences in administration technique, recommended doses, and preparation procedures. The role of lipid-based forms of amphotericin B in the treatment of severe systemic fungal infections is not yet clear.

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