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LIPOSOMAL AMPHOTERICIN B-REVIEW OF CLINICAL EXPERIENCE AND FUTURE DIRECTIONS

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ABSTRACT

Over the past two years, there has been a dramatic rise in the prescription of lipid formulations of amphotericin B at the hospitals. These compounds now account for a significant proportion of all expenditure on antimicrobial agents. Only one randomized controlled trial has assessed the efficacy of lipid formulations in treating proven fungal infections. Most of the available evidence on the use of lipid formulations is in the form of case series. There are therefore limited data to justify the widespread use of these compounds, and there are few circumstances when their administration is warranted. Therefore, local policies should be drawn up for the prescription of lipid formulations of amphotericin B**,** and, until more compelling data are available, that these drugs only be administered after discussion with microbiologists or infectious diseases physicians. Liposomal amphotericin B (LAmB) is a unique lipid formulation of amphotericin B. LAmB is a standard of care for a wide range of medically important opportunistic fungal pathogens. LAmB has a significantly improved toxicity profile compared with conventional amphotericin B deoxycholate (DAmB). Its long terminal half-life and retention in tissues suggest that single or intermittent dosing regimens are feasible, and these should be actively investigated in both preclinical models and in clinical trials. Significant gaps remain in knowledge of pharmacokinetics and pharmacodynamics in special populations such as neonates and children, pregnant women and obese patients.

KEYWORDS: Liposomal amphotericin B, Amphotericin B deoxycholate, Lipid formulations of amphotericin B.

1. INTRODUCTION

Amphotericin B is a polyene antifungal agent with a broad range of activity against yeasts and molds, as well as the protozoan parasite Leishmania spp. Liposomal amphotericin B binds to ergosterol in the fungal cell membrane leading to ion leakage and cell death. The initial formulation was amphotericin B deoxycholate (DAmB), which was developed in the 1950s. For many decades DAmB was the only antifungal agent available for the treatment of invasive fungal diseases. However, the significant dose-limiting toxicity of DAmB (most notably nephrotoxicity and infusion- related reactions) provided the impetus to develop new less toxic formulations. Liposomal amphotericin B (LAmB) is a unique lipid formulation of amphotericin B that has been used for nearly 20 years to treat a broad range of fungal infections. While the antifungal activity of amphotericin B is retained following its incorporation into a liposome bilayer, its toxicity is significantly reduced.[1]

1.1 MOLECULAR PHARMACOLOGY OF LIPOSOMAL AMPHOTERICIN B

Since their first description in 1965, liposomes have been extensively investigated for use in drug delivery. They are spherical vesicles characterized by an aqueous core surrounded by a lipid bilayer. The composition of the liposome has a significant impact on the resultant pharmacokinetic properties. Liposomes can be engineered to maximize antifungal activity and minimize drug-related toxicity. The liposome specifically used in LAmB was designed to enable parenteral administration, facilitate the stability of amphotericin B within the liposome, yet enable the active compound to engage with the fungus when encountered within various tissue sites.[2]

The unilamellar lipid structure of LAmB has three major components. The first is hydrogenated soy phosphatidylcholine, which comprises the majority of the lipid bilayer. It has the advantage of a gel to liquid-crystal phase transition point of [37 degree celsius] meaning it is not readily hydrolyzed at body temperature. Second, distearoyl phosphatidylglycerol was selected as its fatty acid chain is similar in length to that of the hydrophobic region of amphotericin B and has a net negative charge. Under the slightly acidic conditions used to prepare liposomes, the amino group of amphotericin B, with its net positive charge, forms an ionic complex with the distearoyl phosphatidylglycerol thus promoting the retention of amphotericin B within the liposomal bilayer.[3] The third component, cholesterol, was added as it binds amphotericin B and further facilitates the retention of amphotericin B within the liposome bilayer. Currently available lipid

formulations of amphotericin B are not orally bioavailable, although early efforts to develop a lipid formulation suitable for oral administration are promising.[4]

1.2 Mechanism of Action

Amphotericin B binds to ergosterol in the fungal cell membrane, which leads to the formation of pores, ion leakage and ultimately fungal cell death. The binding of the liposome (both 'loaded' with amphotericin B and empty liposomes) to the cell wall of pathogenic yeasts and molds has been demonstrated in vitro and in vivo using fluorescently labeled liposomes and gold-labeled liposomes. Liposomes without LAmB bind to the fungal cell wall, but both the 'empty' liposomes and the fungal cell remain intact. In contrast, binding of amphotericin B-containing liposomes results in fungal cell death suggesting that binding results in liposomal disruption and release of amphotericin B, which is then free to exert its fungicidal activity by binding to ergosterol in the fungal cell membrane.[5]

The precise mechanism by which amphotericin B is transferred from the liposome through the fungal cell wall to the fungal membrane is not known. It is likely that the process is facilitated by the higher binding affinity of amphotericin B for ergosterol (the sterol present in fungal cell membranes) compared with cholesterol, which is the principal lipid component of the liposome. Temperature also appears to be important in the transfer of amphotericin B between the liposome and the fungus and occurs most efficiently at body temperature.[6]

2. MICROBIOLOGY

2.1 Activity In Vitro and In Vivo

Liposomal amphotericin B has shown *in vitro* activity comparable to amphotericin B against the following organisms: *Aspergillus fumigatus, Aspergillus flavus, Candida albicans, Candida krusei, Candida lusitaniae, Candida parapsilosis, Candida tropicalis, Cryptococcus neoformans,* and *Blastomyces dermatitidis.*[7]

2.2 Drug Resistance

Mutants with decreased susceptibility to amphotericin B have been isolated from several fungal species after serial passage in culture media containing the drug, and from some patients receiving prolonged therapy. Drug combination studies *in vitro* and *in vivo* suggest that imidazoles may induce resistance to amphotericin B. However, the clinical relevance of drug resistance has not been established.[7]

3. PHARMACOKINETICS

3.1 Bioanalytical Issues

Concentrations of liposomal amphotericin B can be measured using high performance liquid chromatography (HPLC), liquid chromatography–mass spectrometry (LC–MS/MS), or bioassay. The assay has a significant impact on what exactly is being measured (i.e. total amphotericin B, protein-bound drug, liposome-associated drug and freely circulating drug). Caution, therefore, is required with the interpretation of drug concentrations. Extraction of amphotericin B from the liposome is a critical step in the bioanalysis of liposomal amphotericin B. Destruction of the liposome with release of active drug can be achieved with organic solvents such as methanol or dimethyl sulfoxide (DMSO). Assays have been developed to measure both free and liposome-bound amphotericin B. Failure to completely disrupt the liposome results in an underestimation of the total concentration of amphotericin B within the matrix.

The current understanding of the pharmacokinetic and pharmacodynamic properties of liposomal amphotericin B is largely based on measurement of total concentrations of amphotericin B in both plasma and tissues. However, only a fraction of total amphotericin B concentrations in any matrix is biologically active: some is liposome-associated, and fractions that are not liposome-associated may be bound (to plasma proteins or tissues) or exist as free drug. Moreover, measuring concentrations from tissue homogenates has the inherent limitation of being unable to distinguish which specific sub-compartment the drug is residing in, and therefore how much biologically active drug is available at the site of infection.[8]

3.2 PHARMACOKINETICS IN HUMANS

As in laboratory animals, circulating liposomal amphotericin B probably largely consists of intact liposomes. There are also likely to be pools of relatively low concentrations of non-liposomal- associated drug that is bound to human serum albumin (HSA) and alpha 1-acid glycoprotein (AAG) as well as a smaller pool of free drug.[9]

The key findings from human pharmacokinetic studies are as follows

- Clearance is approximately 1–2 L/h and the volume of the central compartment is approximately 20 L, which is significantly less than estimates for members of the triazole class of antifungal.[10]

- Liposomal amphotericin B has a long terminal half-life in plasma (approx. 152 h in one study).[9]
- Total plasma concentrations of amphotericin B are higher than observed with DAmB, even following correction for the higher weight-based dosages that are used for LAmB. The majority of circulating drug is likely to be biologically inactive. The liposome acts as a ‘‘pool’’ or ‘‘sump’’ of drug. Biologically active drug is not released until there is direct contact with the fungus.[9]
- Urinary clearance of LAmB is 4.5 % of the dose after the end of the first week, which is significantly lower than for DAmB. Similarly, fecal clearance is significantly lower than observed with DAmB. Both these observations suggest that the amphotericin B in the liposome is not ‘‘seen’’ or ‘‘available’’ to these clearance mechanisms.[9]
- As in experimental models, the distribution of LAmB, rather than its metabolism, is the primary determinant of the shape of the concentration-time profile—studies in patients have consistently failed to detect any amphotericin B metabolites.[9]
- The uptake of drug by the RES may be non-linear, with dosages C7.5 mg/kg resulting in lower drug exposures than predicted on the basis of the pharmacokinetics from studying lower dosages. In this case, tissue uptake is not saturated. Rather, dosage escalation results in activation or induction of an additional pathway that leads to accelerated clearance and lower-than-expected drug exposure.[11]
- Urinary excretion of free drug occurs rather than secretion, reabsorption or metabolism. Active excretion of non-liposomal amphotericin B into bile does occur, but to a lesser extent than DAmB. Amphotericin B undergoes moderate hepatic extraction and is unlikely to be affected by changes in hepatic blood flow. Excretion of intact liposomes into the bile does not occur.[9]

4. TOXICITY

4.1 Nephrotoxicity

Liposomal amphotericin B is consistently the least nephrotoxic of all commercially available lipid formulations of amphotericin B. At regimens as high as 10–15 mg/kg/day, liposomal amphotericin B is associated with significantly less renal toxicity in infected animals compared with amphotericin B deoxycholate. These preclinical findings have been confirmed in numerous clinical studies, where liposomal amphotericin B is consistently less nephrotoxic than DAmB. This may result from fewer high-density lipoprotein receptors in the kidney, which are preferential receptors for the binding of liposomal amphotericin B. The preferential

distribution of liposomal amphotericin B to the liver and spleen as compared to the renal tract may also lead to relatively lower concentrations in the kidneys and therefore less renal toxicity. Renal toxicity is likely to result from free or readily diffusible amphotericin B interacting with the renal distal tubules. The active drug in liposomal amphotericin B is locked into the liposome and not free to engage with various sub-compartments within the kidney. There is no glomerulofiltration due to the size of the liposomes, which may explain the lower renal toxicity of liposomal amphotericin B.[12]

4.2 Infusion Reactions

Infusion-related toxicity is a recognized side effect of DAmB, causing acute fevers and chills, possibly due to a proinflammatory cytokine response mediated by toll-like receptor 2 (TLR2) and cluster of differentiation 14 (CD14) cells. The infusion of liposomal amphotericin B may result in an idiosyncratic reaction that manifests as a classic triad of chest pain/discomfort, flank/abdominal pain, and dyspnea in the first few minutes of infusion. These symptoms resolve with cessation of the infusion and administration of an anti-histamine agent. The reaction is not a dosedependent phenomenon. As the clinical syndrome of infusion reaction is more similar to other liposome-associated drugs (such as liposomal doxorubicin) than to DAmB, the reaction may be to the liposome rather than the active drug. The mechanism remains unclear but is postulated to be complement-mediated. The infusion-related toxicity of liposomal amphotericin B is consistently lower than other polyene formulations such as DAmB and amphotericin B lipid complex (ABLC).[13]

4.3 Hepatotoxicity

LAmB may result in deranged liver function tests. There is no evidence that this phenomenon is dose-dependent. A retrospective case-controlled study of 587 bone-marrow transplant patients found that one-third of patients receiving liposomal amphotericin B had an increase in serum bilirubin, and that liposomal amphotericin B therapy was independently associated with a rise in transaminases; whereas, treatment with DAmB was not. However, this has to be interpreted with caution due to confounding factors such as the co-administration of other hepatotoxic agents and the retrospective study design. A study of tolerability of 141 treatment courses of liposomal amphotericin B in pediatric patients (median dose 2.8 mg/kg, median duration 13 days) observed mild to moderate increases in hepatic transaminases in 59 % of cases, but this only resulted in cessation of the treatment course in a single patient. The mechanism of hepatotoxicity with liposomal amphotericin B remains unknown.[14]

5. NEW STRATEGIES FOR LIPOSOMAL AMPHOTERICIN B

The lack of new antifungal agents on the market necessitates optimizing the use of currently available drugs. Until recently, liposomal amphotericin B essentially was used as a straight substitute for DAmB while retaining the same intravenous dosing schedules. However, greater recognition of its pharmacokinetics/pharmacodynamics has led to efforts to investigate shortened or intermittent dosing schedules and investigate novel routes of administration.

5.1 Alternative Routes of Administration: Aerosolized Therapy

Given the lung is the primary site of infection for many invasive fungal diseases, aerosolized LAmB has been investigated for its potential to deliver amphotericin B directly to the site of infection. DAmB can be nebulized, but is associated with a higher incidence of bronchospasm compared with LAmB. LAmB can also be nebulized without disrupting liposomes. One experimental model reported that lung tissue of mice exposed to aerosolized LAmB for 3 x 20-min periods accumulated a maximum concentration of 43 lg/g at 1 h after the third exposure. Even after 336 h, the lung concentration of amphotericin B remained high enough (24 lg/g lung tissue) to prevent subsequent pulmonary infection with Cryptococcus neoformans. Similarly, mice treated with aerosolized LAmB for three 1-h intervals and had [200 lg/g in the lungs 24 h after the last dose. A small amount of amphotericin B is deposited in the upper airway, but there was no systemic drug exposure. These intrapulmonary concentrations prevented the establishment of invasive infection following intranasal challenge with Aspergillus. fumigatus.[15]

5.2 Catheter Lock Therapy

Fungal biofilms in catheters complicate the treatment of fungal infection. The biofilm shields fungal cells from otherwise effective concentrations of drug and limits immunological responses. Although conventional DAmB appears to be inhibited by Candida biofilms, LAmB appears to retain activity in this setting. An indwelling catheter model in rabbits suggests that 3-day old C. albicans biofilms can be effectively treated with LAmB as a lock therapy. The drug lock was administered at 10 mg/Ml for 8 h each day. After 7 days of AmBisome lock therapy, scanning EMs showed that AmBisome-treated catheters were free of biofilm and all catheter cultures were negative. While echinocandins are currently favored for catheter lock therapy in patients, individual case reports have reported successful catheter salvage. LAmB may be a useful agent in this setting; however, at present this remains strictly

an investigational approach and requires significant further clinical study before it is likely to be adopted in routine clinical practice.[16]

6. THE CHALLENGE OF CLINICAL TRIALS FOR DRUG REGISTERATION

As a related but distinct issue, the question of adoption of LAmB as a standard approach has a special implication in the context of clinical trials and drug registration. Although clinical trials can take many forms, a state-of-the-art therapeutic clinical trial for a new anti-infective agent generally requires that the new drug or intervention in question be compared in a randomized and blinded fashion with an agent that is already licensed for treatment of the infection under study. Ideally, this will clearly assess whether the new intervention offers either efficacy or safety advantages over the comparator. Placebo-controlled trials are generally not suitable in this area. In addition, it is often thought desirable to have results available from ⩾2 independently conducted studies.[17]

Meeting these challenges with antifungal agents is difficult both because of the limited number of patients with mycoses that can be readily studied and because of the paucity of suitable comparative agents. Even though mycoses are clearly a major and growing cause of morbidity and mortality, the lack of adequate diagnostic tools makes timely diagnosis difficult. Further compounding this difficulty is the fact that DAmB is the only agent licensed as initial therapy for many mycoses. At the time of its licensure in 1959, DAmB's open-label activity against a variety of mycoses was sufficiently striking that its acceptance was prompt and durable. To date, DAmB remains the agent with the broadest spectrum of action and the least potential for resistance of any known antifungal agent. Despite its formidable toxicity, both clinical investigators and regulatory agencies have thus long thought that DAmB was the most suitable comparator for many trials of antifungal agents. However, DAmB's toxicity also limits its acceptance by the patient and clinicians, and the increasing availability of alternative antifungal agents makes patient enrollment onto and retention in clinical trials very difficult.[18]

The availability of less toxic LAmB has begun to change this equation. Because these agents were not licensed on the basis of head-to-head comparisons with DAmB, there was initially some reluctance to use them as substitutes for DAmB in clinical trials. Concerns over differences in pharmacokinetics and tissue delivery have been mentioned as reasons to continue to rely upon the classical DAmB formulation. However, data on the safety and efficacy of LAmB have accumulated steadily, and we now think that LAmB have clearly

been demonstrated to be at least as efficacious as—and much safer than—DAmB. Indeed, we believe that only cost issues now prevent LAmB from becoming the standard of care. Clinicians and researchers should consider that these cost issues are clearly offset when considering the cost of renal failure, monitoring, and other complications, as well as the "enrollment cost" that has been associated with the use of DAmB. The many toxicities of DAmB might be tolerable in an otherwise healthy patient with a limited invasive mycosis, but the induction of even small amounts of nephrotoxicity in critically ill adults can be devastating. For example, a recent study examined outcomes of patients treated with DAmB and found that onset of acute renal failure during DAmB therapy increased the likelihood of death 6.6-fold. Stated differently, an increase in the creatinine level from 1 to 3 mg/dL during treatment of cryptococcal meningitis in an otherwise healthy young adult is quite well tolerated, but a similar increase during therapy for invasive aspergillosis in patient with a hematological malignancy is associated with increased mortality. The use of LAmB as comparators during testing of new antifungal agents as initial therapy for invasive mycoses is the next logical step.[19,20]

7. SITUATIONS WHERE CONVENTIONAL AMPHOTERICIN B IS STILL EFFECTIVE

Despite the many advantages of LAmB, DAmB does retain some uses. First, it remains a standard option for intrathecal therapy of meningitis due to *Coccidioides immitis*. Second, the lower AmB tissue levels produced in the kidney by LAmB lead to a theoretical possibility of reduced efficacy at that site that should be kept in mind. Third, DAmB produces little nephrotoxicity in neonates, and its continued use for these patients seems appropriate. Fourth, brief low-dose courses of DAmB may be well tolerated by selected adults. For example, a recent analysis found a 28% rate of acute renal failure associated with DAmB therapy if the patient was either receiving cyclosporine, in an intensive care unit, or in an intermediate care unit at the time of initiation of therapy. On the other hand, patients who lacked all of these risk factors had only an expected 4% rate of acute renal failure. Daily dose was also relevant, and patients with any of those risk factors who also received ⩾30 mg of DAmB per day had a 33% rate of acute renal failure. Finally, rare individuals may actually tolerate DAmB better than LAmB.[21]

8. CLINICAL EXPERIENCE WITH LIPOSOMAL AMPHOTERICIN B

Liposomal Amphotericin B is used in wide variety of clinical scenarios. At the time of writing, Federal Drug Administration (FDA) approval for specific indications with recommended dosing includes empiric therapy in febrile neutropenia (3 mg/kg/day), systemic aspergillosis, candidiasis, (both 3–5 mg/kg/day), visceral leishmaniasis (3 mg/kg/day first 5 days then on days 14 and 21) and more recently cryptococcal meningitis (6 mg/kg/day), as well as for patients for whom DAmB is not appropriate due to the risk of renal toxicity. In Europe, approval is granted by individual countries rather than the European Medicines Agency (EMA). For example, in the UK approved indications by the Medicines and Healthcare Products Regulatory Agency (MHRA) include visceral leishmaniasis, empiric therapy in febrile neutropenia, and the broad indication of severe systemic and/or deep mycoses, with no specific dosing guidelines.[22]

8.1 Prophylaxis for Invasive Fungal Infections

Invasive fungal infection (IFI), most commonly caused by Aspergillus spp., is a devastating and often fatal complication in patients receiving immunosuppressive therapy. Therefore, prevention is a key clinical priority. Several studies using laboratory animal models of infection have demonstrated the ability of LAmB to prevent or minimize invasive fungal infection caused by Candida albicans. Similar studies have been performed for molds such as Aspergillus spp., as well as the dimorphic fungus Histoplasma capsulatum. Collectively, these data demonstrate the potential efficacy of LAmB for preventing invasive infections caused by yeasts and molds; however, the minimum effective concentration required for effective prophylaxis is not known.[23]

8.2 Empiric Therapy in Prolonged Febrile Neutropenia

Persistent fever in neutropenic patients that is refractory to antibacterial agents is often treated with antifungal agents because of concerns of underlying undiagnosed invasive fungal infection. An early randomized trial compared DAmB (1 mg/kg/day) with LAmB at doses of 1 mg or 3 mg/kg/day for patients with febrile neutropenia unresponsive to antibacterials.[24] Treatment success in each group was 49, 58, 64 %, respectively, although a Kaplan-Meier analysis of time to defervescence did not reach statistical significance. Significantly fewer severe toxicityrelated events were observed in LAmB-treated patients (1 %) compared with 12 % in the DAmB group (p\0.01). Another randomized trial compared DAmB (0.6 mg/kg) with LAmB (3 mg/kg). Survival was similar in both groups (93 vs 90 %) but there were

fewer confirmed cases of breakthrough invasive fungal disease in the LamB group (3.2 vs 7.8 %, p = 0.009).[25]

8.3 Cryptococcal Meningitis

Cryptococcal meningitis is a neglected infection that is a leading cause of global infectious morbidity and mortality. The majority of cases occur in resource poor settings and in patients with HIV/AIDS. In high resource settings, cryptococcal meningitis is also seen in the context of solid organ transplantation. There are limited pre-clinical data for LAmB that specifically relate to cryptococcal meningitis. LAmB was comparable in efficacy to DAmB in an early murine study of systemic cryptococcosis. More recently, a murine model of cryptococcal meningitis was used to investigate the pharmacodynamics of LAmB and flucytosine (5FC). Mice were treated with 3, 10 and 20 mg/kg of LAmB. A dose-dependent reduction in organism burden in the brain was observed. A regimen of 3 mg/kg/day was submaximal, while the highest dose (20 mg/kg/day) resulted in a decline in fungal cerebral burden without achieving sterilization.[26]

8.4 Leishmaniasis

Leishmaniasis is caused by the protozoan parasite Leishmania spp., and is transmitted by the sand fly. Its most severe form, visceral leishmaniasis (VL), can be fatal and is most common in resource-limited settings such as India and East Africa. A study using a murine model of VL studied exposure-response relationships of LAmB.[27] A dose of 0.8 mg/kg reduced the parasite load by log10 4–6 parasites/g tissue in the liver and spleen compared with controls. Dosages of LAmB 5 mg/kg and 50 mg/kg, given on alternate days for six doses, resulted in complete sterilization of the liver, spleen and lungs. Several clinical studies have demonstrated excellent outcomes with the use of LAmB in VL, with the WHO recommending a cumulative dose of 20 mg/kg.[28] However, the minimum effective dose remains unknown. This is especially important because most cases occur in resource-limited settings, where the cost of LAmB is prohibitive.

8.5 Invasive Candidiasis

Invasive candidiasis is a growing clinical problem due to increasing use of indwelling medical devices and ever increasing use of immunosuppressive therapies, broadspectrum antibacterial agents and total parenteral nutrition (TPN), all of which are major risk factors for the development of invasive candidiasis. Several laboratory animal studies have demonstrated the efficacy of LAmB treatment for invasive infections caused by Candida

species. Dosages of 2.5–10 mg/kg are comparable to the efficacy of DAmB (0.75 mg/kg/day) for disseminated Candida albicans infection.[29] In a study of mice infected with Candida glabrata, a dose-dependent reduction of kidney fungal burden was observed for dosages up to 20 mg/kg/day; however, complete clearance was only achieved in combination with caspofungin or micafungin.[30] The majority of early clinical studies for invasive candidiasis and candidemia were performed using DAmB as the ‘‘gold standard’’. A clinically effective dosage of LAmB was not demonstrated until relatively recently. Two clinical trials performed in adults and in children compared the response to LAmB 3 mg/kg with micafungin, an echinocandin. Both studies demonstrated comparable clinical outcomes for both study arms. LAmB was associated with more infusion reactions and nephrotoxicity compared with micafungin.[31]

9. Other Lipid Formulations of Amphotericin B

9.1 Amphotericin B Lipid Complex(ABLC)

Infusion of ABLC into mice leads to higher levels of amphotericin B in the liver and spleen than when animals are given equal doses of DAmB; as in all other studies on the pharmacokinetics of amphotericin B, total amphotericin B was measured with no estimate of free or bound drug. Experiments in mice with disseminated fungal infections (e.g. candidosis, aspergillosis, cryptococcosis and histoplasmosis) suggested that DAmB is two to four times more effective than ABLC in a dose-for-dose comparison. However, as the LD50 of ABLC in mice was more than an order of magnitude higher than that of the parent compound, ABLC has a higher therapeutic index than DAmB. ABLC was infused in doses of up to 0.5 mg/kg into eight healthy volunteers, and plasma levels of amphotericin B were lower than in a group given the same dose of the parent compound. Infusion-related side effects were lower in the ABLC group, although transient elevations in serum transaminases were detected. It has been suggested that the large particle size of ABLC (1.6-11 pm) leads to its rapid clearance by reticuloendothelial cells, resulting in lower plasma levels.[32]

9.2 Amphotericin B in lipid emulsion (AmB-IL)

Little is known about the effect of mixing fat emulsions with amphotericin B. A recent report indicates that a significant proportion of amphotericin B precipitates in 20% Intralipid; approximately 74000 particles/mL were found in a mixture of Intralipid and DAmB. The only published animal model examining the efficacy of this compound is in systemic candidosis of non-neutropenic mice. The effect of treatment was assessed using a single bolus

of drug given 48 h after intravenous challenge with *Candida albicans*. In this model, AmB-IL was equipotent with DAmB and had a maximum tolerated dose 10-fold higher than that of the parent compound.[33]

9.3 Amphotericin B colloid dispersion (ABCD)

In experimental models, ABCD appears to be equally or slightly more efficacious than DAmB; the models included candidosis, aspergillosis and cryptococcosis. Doses of up to 1.5 mg/kg have been given to healthy volunteers; there were mild side effects and no hepatic or renal impairment, and a preliminary report suggested that doses of up to 7 mg/kg were well tolerated in patients with fungal infection.[34]

10. DISCUSSION

Extensive preclinical studies have provided a reasonable understanding of drug distribution, elimination and antifungal effect. There is expanding knowledge related to the pharmacodynamics of LAmB for invasive candidiasis, invasive aspergillosis and cryptococcal meningitis. There are, however, many remaining questions that are related to the pharmacology and optimal clinical use of LAmB. Perhaps one of the most interesting and underexploited properties of LAmB is its prolonged mean residence time in tissues. This property suggests that for some indications, LAmB could be given intermittently, as a short course or even as a single dose without compromising efficacy. This has the potential to significantly reduce both the cost and possible adverse events, and extend the use of LAmB to ambulatory settings. Moreover, these shortened regimens could have a major impact particularly in infections such as cryptococcosis and leishmaniasis, which overwhelmingly are seen in parts of the world where the cost of LAmB is otherwise prohibitive. There is a striking paucity of clinical data in special populations such as neonates, young children, pregnant women and morbidly obese patients. This needs to be urgently addressed. AmBisome is now in its second decade of clinical use. There are still opportunities to better utilize this agent for the treatment of life-threatening invasive fungal diseases. This is especially important given the rising threat of antifungal drug resistance and the relative paucity of new antifungal agents.

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