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Amphotericin-B Colloidal Dispersion

A Review of its Use Against Systemic Fungal Infections and Visceral Leishmaniasis

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Data Selection

Sources: Medical literature published in any language since 1966, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'amphotericin-B', 'ambisome', 'amphocil', 'amphotec', 'abcelet' and 'ablc'. Medline and EMBASE search terms were 'amphotericin-B', 'abisome', 'amphocil' and 'ablc'. Searches were last updated 30 June 1998.

Selection: Studies in patients with fungal or leishmanial infections who received colloidal amphotericin B. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: amphotericin B, colloidal dispersion, lipid, antifungal, fungal infection, visceral leishmaniasis, pharmacokinetics, pharmacodynamics, therapeutic use.

Contents

Summary

Abstract

Formulation of amphotericin B with sodium cholesteryl sulphate alters the pharmacokinetic properties of the drug, particularly reducing its distribution to the kidneys. The antifungal activity *in vitro* of amphotericin B colloidal dispersion (ABCD) is similar to that of conventional amphotericin B (C-AmB) against true pathogenic organisms including *Blastomyces, Coccidioides, Histoplasma* and *Paracoccidioides* species and the opportunistic organisms such as *Candida* and *Cryptococcus* species. In animal models, ABCD was generally less effective than an identical dose of C-AmB, but overall was more effective because of its improved therapeutic index.

Although ABCD appeared to be more effective than C-AmB in resolving infection and improving survival in patients with proven or probable invasive aspergillosis, the retrospective design of the study and the greater prevalence of neutropenia in patients treated with the conventional formulation necessitate cautious interpretation of the results. ABCD has been effective and seldom caused nephrotoxicity in patients with fungal infection who had previously failed to adequately respond or had developed renal toxicity with C-AmB. Similarly, ABCD was effective in patients with proven or suspected fungal infection after bone marrow transplantation. Preliminary results from a pilot study comparing ABCD and C-AmB in patients with neutropenia and persistent fever reported similar response rates with both formulations.

ABCD is an effective treatment for visceral leishmaniasis in immunocompetent patients.

In 1 study, about 12% of ABCD recipients discontinued the drug because of adverse events; infusion-related events were the most common cause of discontinuation. The renal tolerability of ABCD is better than that of C-AmB.

ABCD appears to be an effective alternative to conventional amphotericin B in patients with invasive aspergillosis or visceral leishmaniasis and in those with proven or suspected systemic fungal infection who are intolerant of the conventional formulation or have pre-existing renal impairment. Preliminary data also suggest that ABCD is an alternative to C-AmB when used empirically in patients with neutropenia and fever. Nevertheless, the efficacy of ABCD compared with that of the conventional formulation has yet to be adequately demonstrated and the role of ABCD relative to that of liposomal and other lipid-based formulations has not been determined.

Conclusions: ABCD, like other lipid-based and liposomal formulations of amphotericin B, has been designed to deliver the active drug to the target site, while reducing renal toxicity. The aim of increasing the therapeutic index compared with C-AmB has been achieved.

Antifungal Activity

Limited comparative data indicate that the activity of amphotericin B colloidal dispersion (ABCD) and conventional amphotericin B (C-AmB) *in vitro* is similar against true pathogenic organisms such as *Blastomyces dermatitidis, Coccidioides immitis* and *Paracoccidioides brasiliensis* as well as *Candida albicans, C. tropicalis* and *Cryptococcus neoformans*. However, ABCD tended to be less active than C-AmB against *Aspergillus fumigatus, Aspergillus flavus* and *Candida glabrata*. There are no clear breakpoints for susceptibility or diminished susceptibility of fungi to amphotericin B and reported minimum inhibitory concentrations need to be correlated with *in vivo* response to antifungal therapy in animal models of

systemic infection or clinical outcome. Such studies have been conducted with C-AmB, but not with ABCD.

ABCD has been generally less effective than an identical dose of C-AmB in animal models of coccidioidomycosis and pulmonary aspergillosis but the lipid-based formulation was more effective overall because animals tolerated up to 10-fold higher doses of the new formulation. In contrast, ABCD was more effective than an identical dose of C-AmB in eliminating hepatic parasites in hamsters infected with *Leishmania donovani*, and equally effective against cryptococcosis.

Pharmacokinetic Properties

Formulation of amphotericin B with sodium cholesteryl sulphate in a ratio of 1:1 alters the pharmacokinetic properties relative to the conventional formulation, resulting in lower maximum plasma amphotericin B concentrations, an increased volume of distribution and a longer elimination half-life. The volume of distribution of the central compartment and total body clearance increase with ABCD dosage.

There have been no direct comparisons of the pharmacokinetic properties of ABCD and C-AmB in humans, but such studies in rats highlight the differences in distribution pattern of the 2 formulations. Amphotericin B concentrations in rat liver were higher and those in spleen and kidney lower with ABCD than C-AmB. Increases in kidney amphotericin B concentrations were less than proportional when the dose of ABCD was increased from 1 to 5 mg/kg.

Plasma elimination half-life values for ABCD and C-AmB in healthy volunteers have varied markedly between studies and differences may have in part resulted from methodological variations. Mean half-life values were 86 and 50 hours after 0.25 mg/kg doses of ABCD and C-AmB, respectively, but that of ABCD increased to 244 hours when the dose was increased to 1 mg/kg.

Therapeutic Potential

In patients with proven or suspected invasive aspergillosis, treatment results obtained in noncomparative clinical trials of intravenous ABCD 0.5 to 8 mg/kg/day (median 23.5 days) were compared retrospectively with those achieved with C-AmB 0.1 to 1.4 mg/kg/day (median 22 days). Complete resolution of all radiological and clinical evidence and partial clearance of infection was achieved in 48.8% of patients treated with ABCD compared with 23.4% of C-AmB recipients. Overall, mortality was significantly higher with the conventional formulation than with ABCD. Nevertheless, results should be interpreted cautiously, given the study design and that a significantly greater proportion of patients treated with C-AmB were neutropenic at baseline.

Many patients treated with ABCD in noncomparative studies had responded incompletely to C-AmB, had developed renal toxicity to this formulation or had pre-existing renal impairment. In such patients, clinical response (complete plus improvement) rates were 57.6 to 77.8% in patients with candidal infection (excluding disseminated infections), 45.5 to 75% in patients with cryptococcal infection and 34.4% in patients with aspergillosis. Response also varied according to the site of infection.

A successful therapeutic outcome was reported in 59% of patients with documented infection caused by *Candida* or *Aspergillus* species following bone marrow transplantation. In a dose-escalation study, complete response rates, which were not related to dosage, were 41 to 47% with ABCD 0.5 to 6 mg/kg/day and 54% at the maximum tolerated dosage of 7.5 mg/kg/day in patients with proven or suspected fungal infection after bone marrow transplantation.

In a small number of patients with zygomycosis, 67% responded completely or partially to treatment with ABCD 4.3 mg/kg/day (mean).

Preliminary results from a pilot study comparing empirical treatment with ABCD 4 mg/kg/day or C-AmB 0.8 mg/kg/day in patients with neutropenia and persistent fever indicated similar success rates based on post-treatment survival, absence of evidence of infection and absence of toxicity necessitating treatment withdrawal.

Symptomatic visceral leishmaniasis was eradicated in all but 1 of 30 Brazilian patients treated with ABCD 2 mg/kg/day for 10, 7 or 5 days. Clinical manifestations of the disease were absent 12 months after treatment and there was no evidence of *Leishmania* amastigotes in bone marrow aspirates 2 weeks after treatment.

Tolerability

Alteration of the pharmacokinetic profile of amphotericin B by formulation with sodium cholesteryl sulphate results in a smaller proportion of a dose being distributed to the kidney. This probably contributes to the reduced propensity for renal toxicity of ABCD.

Adverse events reported in ≥5% of 572 patients with systemic fungal infections treated with ABCD 3 to 6 mg/kg/day (mean 25 days) which were considered probably or possibly associated with the drug included chills (50%), fever (33%), increased creatinine level (12%), tachycardia (10%), hypotension (10%), nausea (8%), thrombocytopenia (6%), vomiting (6%), dyspnoea (5%), hypoxia (5%) and headache (5%). There was a tendency for adverse events to be more frequent with daily dosages of >4 mg/kg than with ≤4 mg/kg.

Treatment with ABCD did not alter mean serum creatinine levels in 474 patients for whom baseline and post-treatment data were available. In a randomised study, recipients of ABCD 4 mg/kg/day were significantly less likely than recipients of C-AmB 0.8 mg/kg/day to experience renal toxicity. Limited changes in biochemical values reflecting liver function occurred during treatment with ABCD.

Dosage and Administration

ABCD is administered intravenously. The recommended initial dosage in adults and children is 3 to 4 mg/kg/day. The rate of infusion should be 1 mg/kg/hour. The optimum duration of therapy varies according to the type of infection and patient characteristics. After reconstitution with water for injection, the resultant solution should be further diluted with 5% dextrose to about 0.6 mg/ml.

The potential for renal toxicity with ABCD may be enhanced by concomitant administration of antineoplastic agents, cyclosporin, tacrolimus and other nephrotoxic drugs such as aminoglycosides and pentamidine.

1. Rationale for Liposome and Lipid-Based Formulations

The conventional formulation of amphotericin B (C-AmB), which contains sodium desoxycholate as a solubilising agent, has for many years played a major role in the management of most systemic fungal infections.[1-3] However, its clinical usefulness is limited by its acute toxicity (e.g. fever, chills and anaphylaxis) and chronic toxicity (e.g. nephrotoxicity) associated with intravenous administration. Renal damage may occur at dosages <0.5 mg/kg/day when coadministered with other nephrotoxic drugs.

Amphotericin B is a highly lipophilic drug that can effectively be encapsulated into liposomes or bound to lipid carriers.[4,5] During the 1980s, formulations of amphotericin B in lipid vehicles were

developed by hospitals and more recently, commercially, in an attempt to reduce the toxicity of the drug. Available liposome and lipid-based formulations include liposomal amphotericin B (AmBisome®, AmBi), amphotericin B lipid complex (Abelcet®, ABLC) and amphotericin B colloidal dispersion (Amphotec®, Amphocil®, ABCD). This last formulation, in which amphotericin B is intercalated in a 1:1 ratio with cholesteryl sulphate, is the subject of this review.

The above formulations have been designed to deliver amphotericin B to the target sites without harming the kidney.[6] When incorporated into liposomes or complexed with lipids, amphotericin B may be transferred in a selective manner to the ergosterol-containing fungal cell membrane without interfering with the cholesterol-containing human cell membrane.[7] The exact mechanism leading to the reduced toxicity of amphotericin B when associated with lipids is not known, but the selective transfer of the drug to fungal cells and reduced uptake into certain human cells is believed to be an important factor in reducing toxicity.[8] Pharmacokinetic differences between the 2 formulations are likely also important (section 3).

All of the described lipid-associated formulations have shown an increased therapeutic index compared with C-AmB,[2] enabling intravenous administration of substantially higher dosages and use in patients who developed renal toxicity with C-AmB.

2. Pharmacodynamic Properties

2.1 Antifungal Susceptibility Testing

Historically, antifungal susceptibility testing has been much less developed than antibacterial susceptibility testing. Without standardisation, the various methods of testing have produced widely discrepant results between laboratories because minimum inhibitory concentration (MIC) data may be influenced by inoculum size, medium composition, liquid versus solid media, pH, and incubation time and temperature.[9] However, standardised methods for antifungal susceptibility testing are now available.

The National Committee for Clinical Laboratory Standards (NCCLS) has recently developed a standard method for *in vitro* antifungal susceptibility of yeast isolates (M27-A)[10] which defines inoculum size (0.5×10^3 to 2.5×10^3 colony forming units/ml), standardised medium (RPMI 1640, buffered to pH 7 with morpholinepropane sulphonic acid), incubation temperature (35°C) and incubation time (48 hours for *Candida* spp. and 72 hours for *Cryptococcus neoformans*).

Interpretive breakpoint data have been published for fluconazole, itraconazole and flucytosine, although not for amphotericin B.[11-13] Although the method is not well suited to detect resistance to amphotericin B,[9,14] suitable adaptations do exist,[11-13] and a recent study[15] suggests that *in vitro* methods may predict clinical outcome to some degree.

As use of the NCCLS method appears to enable reliable interlaboratory antifungal susceptibility testing for yeast isolates,[16,17] susceptibility data from studies that strongly based their methods on those proposed by the NCCLS are given prominence in this review.

2.1.1 *Activity* In Vitro

C-AmB at a concentration of 0.5 or 1.0 mg/L is active *in vitro* against *Candida* species and *Cryptococcus neoformans* which are increasingly becoming important fungal pathogens in immunocompromised patients.[21] The activity of C-AmB compared with that of the azole derivatives fluconazole, itraconazole and flucytosine is shown in table I, and appears generally similar.

There are relatively few data comparing the activity of ABCD and C-AmB, although the activity of the two drugs appears generally similar against true pathogenic organisms such as *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis* (table II). The drugs were also of similar activity against opportunistic organisms such as *Candida albicans*, *C. tropicalis* and *Cryptococcus neoformans*, but ABCD tended to be less active than

Table I. Representative studies of the antifungal activity of amphotericin B compared with that of azole derivatives and flucytosine against yeast clinical isolates. All studies used methodology recommended by the National Committee for Clinical Laboratory Standards or a microdilution modification of that methodology

Organism	No. of isolates	MIC_{50} (mg/L)				MIC_{90} (mg/L)				Reference
		C-AmB	FLUC	ITRA	FLCY	C-AmB	FLUC	ITRA	FLCY	
Candida albicans	166	0.5	0.25	0.03	0.25	1	2	0.25	4.0	18
	119	0.5	0.5	0.12	≤0.25	1	128	>8	4.0	19
Candida glabrata	60	1	8	0.5	0.06	1	128	2	0.12	18
	18	1	4	0.25	≤0.25	1	8	0.5	0.5	19
Candida parapsilosis	24	1	0.5	0.12	0.12	1	1	0.12	0.25	18
	81	0.5	0.5	0.12	≤0.25	1	1	0.25	≤0.25	19
Candida tropicalis	57	1	0.5	0.06	0.25	1	1	0.12	1	18
	37	0.5	0.25	0.06	≤0.25	1	1	0.5	≤0.25	19
Candida krusei	36	1	32	0.5	16	1	64	0.5	16	18
	11	1	32	0.5	16	1	64	0.5	16	19
Cryptococcus neoformans	53	0.5	4	0.12	2	1	8	0.25	8	20

C-AmB = amphotericin B; **FLCY** = flucytosine; **FLUC** = fluconazole; **ITRA** = itraconazole; **MIC_{50}** = minimum inhibitory concentration for 50% of isolates; **MIC_{90}** = minimum inhibitory concentration for 90% of isolates.

conventional amphotericin B against *Candida glabrata*, *Aspergillus fumigatus* and *Aspergillus flavus*[22](table II). However, activity *in vitro* may not be predictive of efficacy against infection. Ideally, the relationship between MIC and the likelihood of a successful clinical outcome should be determined, but to date only a limited number of studies have related *in vitro* test results to clinical antifungal efficacy in humans.[23] Animal models of infection can be used to provide an indication of such a relationship (section 2.1.2).

2.1.2 Activity In Vivo

The correlation between antifungal susceptibility and *in vivo* response to antifungal therapy in animal models of systemic fungal infection has been studied with C-AmB,[24] but not with ABCD.

The activity of ABCD *in vivo* has been studied in models of cryptococcosis and coccidiomycosis in mice, aspergillosis in rabbits and visceral leishmaniasis in hamsters (table III). In a murine model of systemic cryptococcosis ABCD and AmBi were of similar efficacy to C-AmB on a mg per kg basis.

Table II. Comparison of the *in vitro* antifungal activity of amphotericin B colloidal dispersion (ABCD) and conventional amphotericin B (C-AmB). Activity against true pathogenic fungi and opportunistic organisms.[22] Inoculum size was 10^3 cells/ml

Organism	No. of isolates	Minimum inhibitory concentration range (mg/L)[a]	
		ABCD	C-AmB
Blastomyces dermatitidis	3	≤0.125-0.5	0.5
Coccidioides immitis	4	0.125-0.25	0.5-1.0
Histoplasma capsulatum	2	≤0.125	0.25
Paracoccidioides brasiliensis	2	0.5-1.0	1.0-2.0
Candida albicans	6	1.0-2.0	0.5-2.0
C. tropicalis	2	1.0	1.0-2.0
C. parapsilosis	2	1.0	0.5-2.0
C. glabrata	2	4.0-8.0	1.0-2.0
Cryptococcus neoformans	5	0.5-1.0	0.5-1.0
Aspergillus fumigatus	5	4.0-8.0	2.0
A. flavus	3	4.0->16	4.0

a Defined as the lowest concentration resulting in no evident growth.

Table III. Efficacy of amphotericin B colloidal dispersion (ABCD) *in vivo* compared with that of other amphotericin B lipid formulations and conventional amphotericin B (C-AmB) against experimental fungal or parasitic infections in animals

Animal model	Drug and dosage (mg/kg × no. of doses administered)	Clearance of fungi or parasites		Effect on survival	Reference
		brain	other organs		
Murine cryptcoccosis	ABCD 1 × 6[a] IV			50[b]	25
	ABCD 5 × 6 IV	>C-AmB, ABCD 1, AmBi 1, ABLC 1&5		100*[b]	
	ABCD 10 × 6 IV	>C-AmB, ABCD 1&5, AmBi 1&5, ABLC 1,5&10		100*[b]	
	AmBi 1 × 6 IV			30[b]	
	AmBi 5 × 6 IV	>C-AmB, AmBi 1, ABLC 1&5		100*[b]	
	AmBi 10 × 6 IV	>C-AmB, ABCD 1&5, AmBi 1&5, ABLC 1,5&10		100*[b]	
	ABLC 1 × 6 IV			20[b]	
	ABLC 5 × 6 IV			50[b]	
	ABLC 10 × 6 IV	>C-AmB, ABLC 1		90*[b]	
	C-AmB 1 × 6 IV			10[b]	
	ABCD 0.8, 3.2, 6.4, 12.8, 19.2 × 6 IV	ABCD ≡ C-AmB	ABCD ≡ C-AmB	ABCD > controls C-AmB > controls ABCD ≥ C-AmB	26
	C-AmB 0.2, 0.8, 3.2 × 6 IV				
Murine[c] coccidioidomycosis	ABCD 0.66, 1.3, 2.5, 5.0, 7.5 × 6 IV		> controls[d] ABCD 5 ≡ C-AmB 1.3	> controls[d]	27
	C-AmB 0.22, 0.66, 1.3 × 6 IV		> controls[d]	controls[d]	
Pulmonary aspergillosis in granulocytopenic rabbits	ABCD 1, 5, 10 × 10 IV		ABCD 5&10 > controls	ABCD 1&5 > controls ABCD 5 > C-AmB 1	28
	C-AmB 1 × 10 IV		> controls C-AmB 1 > ABCD 1	> controls	
Visceral leishmaniasis in hamsters	ABCD 0.1, 0.4 ,1.5 × 1 IC[e] C-AmB 0.1, 0.4, 1.5 × 1 IC[e]		ABCD 0.4 ≡ C-AmB 1.5		29

a Treatment began 4 days after challenge.

b Percentage of mice alive at 49 days.

c Mice were infected with 200 arthroconidia of *Coccidioides immitis*.

d Control mice received diluent.

e Drugs were administered 10 days after intracardiac challenge with about 10^7 *Leishmania donovani* amastigotes.

ABLC = amphotericin B complexed with dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol; **AmBi** = amphotericin B encapsulated in liposomes containing phosphatidylcholine, cholesterol and distearoylphosphatidylglycerol; **IC** = intracardiac injection; **IV** = intravenous administration; > indicates significantly better efficacy; ≡ indicates similar efficacy; ≥ indicates a trend towards greater efficacy; * p = 0.0001 *vs* C-AmB.

Intravenous challenge with *Cryptococcus neoformans* resulted in lethal infection in 90% of untreated mice 15 to 34 days after challenge.[26,30] Five and 10 mg/kg of ABCD or AmBi and 10 mg/kg of ABLC were more effective than 1 mg/kg of C-AmB (all given as 3 doses per week for 2 weeks) in improving survival and reducing the fungal burden in brain.[30] ABCD and AmBi were similarly effective, and both drugs were more effective than ABLC in reducing the infectious burden in brain, kidney and lungs. ABCD exhibited the greatest activity in the spleen and AmBi was the most effective drug in the liver.[30] In a similarly conducted study, ABCD 0.8 to 12.8 mg/kg and C-AmB 0.8 mg/kg similarly improved survival and reduced fungal burdens in the brain, kidney and lungs of mice with disseminated cryptococcosis. C-AmB 3.2 mg/kg was acutely lethal in all animals and ABCD 12.8 and 19.2 mg/kg caused early death in 10 and 20% of mice, respectively. Neither drug cured animals of brain infection.[26]

The therapeutic index of ABCD was also greater than that of C-AmB in a murine model of coccidioidomycosis. Mice were infected with 180 or 200 arthroconidia of *Coccidioides immitis* and all of the untreated mice challenged with the higher inoculum died 14 to 23 days after challenge.[27] *C. immitis* was cleared from the spleen, livers and lungs of all mice treated with ABCD 5 mg/kg or C-AmB 1.3 mg/kg. The conventional formulation was more effective than an identical dose of the colloidal dispersion in reducing the residual burden of *C. immitis* from organs of infected mice, but the conventional formulation was also >5 to ≥8-fold more toxic (as indicated by tissue damage detected on necropsy).[27]

ABCD has also been shown to be effective against experimental invasive pulmonary aspergillosis in persistently granulocytopenic rabbits.[28] ABCD 5 and 10 mg/kg/day for 10 consecutive days significantly reduced the lung burden of *Aspergillus fumigatus* (measured by colony forming units/g of tissue and percentage of culture-positive lobes) but the residual burden in animals treated with 1mg/kg/day did not differ from that in untreated control animals. ABCD and C-AmB 1mg/kg/day similarly improved survival, although at this dosage C-AmB effected greater microbiological clearance than ABCD.

Although ABCD was less effective than an identical dosage of C-AmB in animal models of coccidioidomycosis and pulmonary aspergillosis, on a mg per kg basis the colloidal dispersion formulation was more active than conventional amphotericin B in treating *Leishmania donovani*-infected hamsters[29] and in treating murine cryptococcosis.[25] Suppression of 99% of hepatic parasites compared with untreated controls 3 days after challenge was achieved with ABCD 0.4 mg/kg of bodyweight, C-AmB 6 mg/kg and pentavalent antimony (meglumine antimonate) 416 mg/kg (data not tabulated). When the drugs were administered 10 days after challenge, ABCD 0.4 mg/kg was about as active as C-AmB 1.5 mg/kg in suppressing proliferation of *L. donovani* (table III).[29]

3. Pharmacokinetic Properties

The pharmacokinetic properties of amphotericin B after intravenous infusion of ABCD have been studied in healthy volunteers and patients with systemic fungal infections after bone marrow transplantation. Formulation of amphotericin B with sodium cholesteryl sulphate in a ratio of 1:1 (ABCD) results in lower maximum plasma amphotericin B concentrations (C_{max}), an increased volume of distribution and a longer elimination half-life than are observed after the same dose of the conventional formulation. The area under the plasma concentration-time curve (AUC) was similar following equal doses of either formulation in different studies (table IV). Increases in AUC values were approximately linear when single doses of ABCD were increased from 0.25 to 1.5 mg/kg in healthy volunteers.

A population pharmacokinetics study in 51 patients with systemic fungal infection after bone marrow transplantation who received ABCD 0.5 to 8 mg/kg/day indicated that volume of distribution of the central compartment and total body clearance increased with dosage.[33]

The pharmacokinetic parameters of amphotericin B after intravenous infusion of C-AmB and ABCD have not been directly compared in humans, although direct comparisons in rats[34] and dogs[35] confirmed the lower C_{max} values, similar AUC values and greater volume of distribution at steady state (V_{ss}) with ABCD than with C-AmB observed in separate studies in volunteers. Distribution studies in animals indicated that 24 or 48 hours after intravenous infusion of the 2 formulations, amphotericin B concentrations are highest in the reticuloendothelial system.[34-36] Amphotericin B concentrations in the rat liver were higher and concentrations in spleen were lower with ABCD than C-AmB 24 hours after the last of 14 consecutive doses of 1 mg/kg daily.[36] In this study, amphotericin B concentrations in kidney after ABCD were 3.4-fold lower than after the same dose of C-AmB and concentrations in lung 2.8-fold lower. A 5-fold increase in ABCD dose, from 1 to 5 mg/kg, resulted in an 11.5-fold increase in spleen

amphotericin B concentration, but an increase of only 2.9-fold in kidney concentration of the drug in rats.[34]

Elimination half-life values for amphotericin B after intravenous infusion of ABCD and C-AmB have varied markedly, possibly because of methodological differences between studies. When plasma samples were obtained for up to 48 hours after a single dose of ABCD, elimination half-life increased from 86 to 244 hours when dosage was increased from 0.25 to 1 mg/kg.[31] The mean elimination half-life value for amphotericin B was 50 hours after 0.25 mg/kg of the conventional formulation, although few plasma samples were obtained more than 24 hours after administration.[32]

4. Therapeutic Potential

The efficacy of ABCD in the treatment of documented or suspected systemic mycoses has mostly been studied in patients who had failed to adequately respond to treatment with C-AmB, developed amphotericin B-induced nephrotoxicity or had pre-existing renal impairment. A small number of studies have also assessed the efficacy of ABCD in the treatment of patients who developed proven or suspected invasive fungal infection after bone marrow transplantation or with visceral leishmaniasis (kala azar). Preliminary results are available from a prospective comparison of ABCD and C-AmB used empirically in patients with neutropenia and fever. The efficacy of ABCD in the treatment of patients with documented invasive mycoses has been compared with that of C-AmB only retrospectively. Of note, partial or complete overlap occurs in the patients included in several publications reported in this section.[37-41]

4.1 Invasive Mycoses

4.1.1 Retrospective Comparison with Conventional Amphotericin B

Invasive aspergillosis is an opportunistic infection which is life-threatening if untreated and has become increasingly common in neutropenic patients[42,43]

Results of treatment of proven or probable invasive aspergillosis with ABCD 0.5 to 8 mg/kg/day in 82 patients studied in noncomparative clinical trials were compared retrospectively with those in 261 patients who had received treatment with C-AmB 0.1 to 1.4 mg/kg/day at 6 cancer treatment or transplant centres (median 23.5 and 22 days' treatment, respectively).[44] Treatment groups were similar with respect to underlying diseases, sex distribution and use of systemic corticosteroids, but C-AmB-treated patients were more likely to be neutropenic ($\leq 0.5 \times 10^9$ neutrophils/L) at baseline (42.5 *vs* 15.9%) and less likely to have renal dysfunction (serum creatinine ≥176.8 μmol/L; 8.7 *vs* 40.7%) than those treated with ABCD.

Complete resolution of all radiographic evidence of infection and disappearance of all clinical signs of aspergillosis (complete response) and clinical improvement with partial clearance of in-

Table IV. Pharmacokinetic parameters of amphotericin B after intravenous infusion of the deoxycholate suspension (C-AmB) or colloidal dispersion formulation (ABCD) in healthy volunteers

Formulation (n)	Dose (mg/kg)	C_{max} (mg/L)	AUC (mg/L • h)	V_{ss} (L/kg)	CL (L/h/kg)	$t_{½}$ (h)	Reference
ABCD (23)	0.25	0.80[a]	9.4	3.4	0.03	86[b]	31
	0.5	0.84[a]	21.0	5.7	0.026	157[b]	
	1.0	2.20[a]	46.3	7.2	0.022	244[b]	
	1.5	2.50[a]	57.3	7.9	0.028	235[b]	
C-AmB (8)	0.1	0.54	3.9	0.5	0.01	30.8[c]	32
	0.25	0.99	8.6	0.74	0.01	50.0[c]	

a Values at the end of infusion.

b Calculated from samples taken for 28 days after administration.

c Few samples taken longer than 24 hours after infusion.

AUC = area under the plasma concentration-time curve; **CL** = total body clearance; $\mathbf{C_{max}}$ = mean maximum plasma concentration; **n** = number of volunteers studied; $\mathbf{t_{½}}$ = elimination half-life; $\mathbf{V_{ss}}$ = volume of distribution at steady state.

fection or stabilisation of radiographic evidence (partial response) were achieved in significantly more patients treated with ABCD (48.8%) than with C-AmB (23.4%; $p < 0.001$). Overall, mortality was significantly higher in patients treated with C-AmB than in those given ABCD (table V). Patients who had pulmonary aspergillosis or haematological abnormality, had undergone bone marrow transplantation or were never neutropenic during treatment responded significantly more often to ABCD than to C-AmB (table VI). Despite the higher response and survival rates in patients treated with ABCD, results must be interpreted with caution given that the study was retrospective and that a significantly greater proportion of patients treated with C-AmB were neutropenic at baseline.

4.1.2 Patients Unresponsive to or Intolerant of Conventional Amphotericin B

Prospective[37] and retrospective[45] studies have assessed patients with systemic mycoses who had responded incompletely to at least 7 days' treatment with C-AmB, had experienced nephrotoxicity or other treatment-limiting toxicity with C-AmB or had pre-existing renal impairment and were treated with ABCD 0.5 to 4 mg/kg/day (or occasionally up to 6 mg/kg/day). The results of these studies are summarised in table VII. Rates of complete clinical response plus improvement (complete: absence of pretreatment signs and symptoms of systemic mycosis; improvement: decrease in severity or number of pretreatment signs and symptoms) were 57.6 to 77.8% in patients with *Candida* infection (including candidaemia), 34.4% in those with aspergillosis and 45.5 to 75% in patients with cryptococcal infection. A lower response rate (15%) was achieved in patients with disseminated candidal disease.[45]

4.1.3 Infection after Bone Marrow Transplantation

After bone marrow transplantation, invasive candidal infection occurs in about 11% of patients and aspergillosis in 5 to 12% of patients.[38] The efficacy of ABCD in the treatment of proven or suspected fungal infection after bone marrow transplantation has been studied in a phase I dose-escalation study involving 61 evaluable patients[38] and in a multicentre trial in 177 patients, 73 of whom had documented fungal infection[48] (table VIII). In the latter study, available only as an abstract, a 'successful therapeutic response' was achieved with ABCD (median dose 4 mg/kg/day) in 59% of the 73 patients (69% candidal, 30% aspergillosis, 50% other or multiple infections). The total response rates (complete plus partial) were 68% in patients who had received an autologous transplant and in 56% of allogeneic transplant recipients. Survival rates were 28 and 58%, respectively, in allogeneic and autologous transplant recipients.[48] In the dose-escalation study, the most common infections were fungaemia (41% of patients), pneumonia (36%) and visceral infection (11%) and were most often caused, respectively, by *Candida* species, *Aspergillus* species and *Candida* species. Response to ABCD was not dose related. The complete response rate to ABCD 0.5 to 6 mg/kg/day was 41 to 47% compared with 54% at the maximum tolerated dose of 7.5 mg/kg/day.[38] The overall response rates (complete plus partial) were similar in patients with fungaemia, pneumonia or

Table V. Retrospective comparison of the therapeutic efficacy of amphotericin B colloidal dispersion (ABCD) and conventional amphotericin B (C-AmB). ABCD receipients had proven or probable invasive aspergillosis and most had failed to respond adequately to or were intolerant of C-AmB[44]

No. of patients	Drug and dosage (mg/kg/day)	Response (%)				Survival (%)
		complete[a]	partial[b]	failed	undetermined	
82	ABCD 0.5 - 8	12.2	36.6	42.7	8.5	50*
261	C-AmB 0.1 - 1.4	8.8	14.6	70.5	6.1	28.4

a Complete response: complete resolution of all radiographic evidence of infection and disappearance of all clinical signs of aspergillosis.

b Partial response: clinical improvement with partial clearing of infection or stabilisation of radiographic evidence.

* $p < 0.001$ *vs* C-AmB.

Table VI. Response to treatment with either amphotericin B colloidal dispersion (ABCD) or conventional amphotericin B (C-AmB) according to diagnosis or underlying condition in patients with invasive aspergillosis[44]

Diagnosis or underlying condition	No. of responding pts[a]	
	ABCD	C-AmB
Pulmonary aspergillosis	32/66** (48.5%)	48/198 (24.2%)
Sinus infection	4/8 (50%)	3/16 (18.8%)
Bone marrow transplantation (all patients)	14/39* (35.9%)	22/113 (19.5%)
allogeneic	12/32 (37.5%)	18/86 (20.9%)
autologous	2/7 (28.6%)	4/27 (14.8%)
Haematological malignancy	18/24** (75%)	16/86 (18.6%)
Transient neutropenia[b]	5/7 (71.4%)	12/38 (31.6%)
Persistent neutropenia[c]	0/3 (0%)	2/43 (4.7%)
Never neutropenic	23/44* (52.3%)	30/102 (29.4%)

a Patients achieving a complete or partial response. See text for definitions.

b Absolute neutrophil count ≤500/mm^3 at baseline with subsequent improvement.

c Absolute neutrophil count ≤500/mm^3 throughout treatment.

* $p < 0.05$ *vs* C-AmB; ** $p < 0.001$ *vs* C-AmB.

visceral infection, although complete response was achieved more often in patients with fungaemia than in those with pneumonia or visceral infection (fig. 1).

4.1.4 Zygomycosis

Zygomycosis is an uncommon but frequently fatal group of infections caused by members of the class Zygomycetes.

The efficacy of ABCD (mean dosage 4.3 mg/kg/day; mean duration 61 days) was studied retrospectively in 22 patients with zygomycosis.[39] Infection was caused by *Rhizopus* species in 7 of the 9 patients in whom the pathogen was identified. Overall, 12 patients (67%) responded (8 completely, 4 partially) to ABCD treatment (response not defined). Response was complete in 7 (53.8%) of the

Table VII. Summary of results of studies of amphotericin B colloidal dispersion A (ABCD) in patients with suspected or proven invasive mycoses who failed to respond to conventional amphotericin B (C-AmB), had experienced renal toxicity with this formulation or had pre-existing renal impairment

Pathogen	No. evaluable patients	Dosage (mg/kg/day) [duration in days]	Response (%)			Reference
			complete[a]	partial[a]	failure[a]	
Candida species	33	0.5 - 6 [11.5-41]	48.5	9.1	42.4	37
Aspergillus species	32		15.6	18.8	65.6	
Cryptococcus species	11		0	45.5	54.5	
Other fungi[b]	21		42.9	19.0	38.1	
Candida species (candidaemia)	67	3.8 (mean) [15, mean]	58	7	34	45[c]
Candida species (disseminated)	21		10	5	86	
Candida species	9	0.8 - 4 [4-41][d]		77.8[e]	22.2	46
Cryptococcus species	4	4 - 6 [not stated][d]		75[f]	25	47

a Where defined, complete clinical response was the absence of pretreatment signs and symptoms of systemic mycosis, partial response (improvement) was a decrease in the severity or number of pretreatment signs and symptoms and failure as lack of change or worsening of pretreatment signs and symptoms.

b Other fungi included *Mucor* (4), *Fusaria*(4), *Alternaria* (1), *Histoplasma* (1), *Blastoschizomyces* (1), and multiple organisms which involved *Aspergillus* species in combination with *Candida* species (2), *Cryptococcus neoformans* (1), *Geotrichum capitata* (1), *Alternaria* species (1), or *Mucor* species (1).

c Retrospective study.

d All patients received ABCD after developing nephrotoxicity during C-AmB 0.3 to 1.0 mg/kg/day therapy.

e Total response rate.

f Response defined as negative fungal cultures.

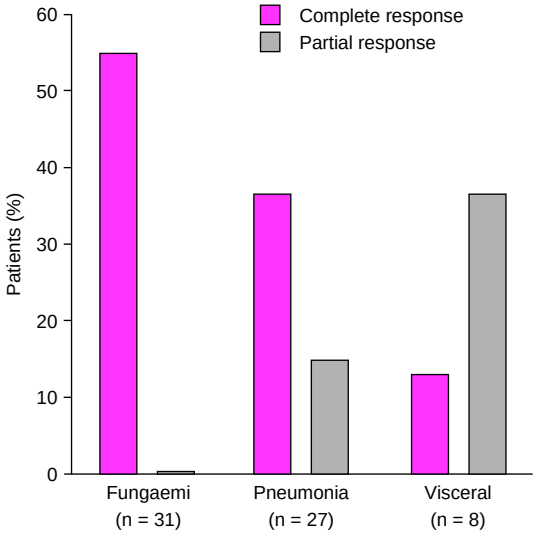

Fig. 1. Clinical response to amphotericin B colloidal dispersion (ABCD). Response to treatment with ABCD 0.5 to 8 mg/kg/day according to site of infection in 66 patients who developed invasive fungal infections following bone marrow transplantation.[38] For definitions of clinical response see table VIII.

13 who also underwent surgical debridement compared with 1 of 5 who received only medical treatment.

An additional report[49] of ABCD use in patients with diabetes mellitus and life-threatening rhinocerebral zygomycosis indicated that 3 of 3 patients had good responses to the combination of surgical debridement and ABCD (4 to 6 mg/kg/day for 4 to 8 weeks, as a continuation of, or precursor to, C-AmB therapy). Two patients experienced complete cures; the third was symptom free for 1 year before he died of an illness which predated the development of zygomycosis. In all of these patients, ABCD therapy was initiated following an decline in renal function observed during C-AmB therapy.

4.1.5 Coccidiomycosis

ABCD has shown some promise against chronic coccidiomycosis, an uncommon but potentially serious infection caused by *Coccidioides immitis*. 24 patients with active chronic (>3 months) pulmonary, musculoskeletal and skin or soft tissue coccidiomycosis received ABCD 0.5 to 2 mg/kg/day for 12 weeks.[50] Overall at final follow-up, 38% of patients had achieved minor responses, 9% major responses and 54% had relapsed or failed to respond (responses graded using a previously published clinical scoring system for mycoses). The relatively low dosages of ABCD used in this non-comparative trial reflect the fact that it was conducted very early in the clinical development of ABCD.

4.2 Comparative Study with Conventional Amphotericin B

ABCD 4 mg/kg/day has been compared with C-AmB 0.8 mg/kg/day in a multicentre randomised double-blind pilot study involving 193 evaluable patients with neutropenia (absolute neutrophil

Table VIII. Efficacy of amphotericin B colloidal dispersion (ABCD) in patients with proven or suspected fungal infection after bone marrow transplantation (BMT)

No. evaluable patients	Dosage (mg/kg/day) [duration in weeks]	Response (%)			Survival rate (%)	Reference
		complete[a]	partial[b]	failure		
54 (allogeneic BMT)	4 (median) [2.28, median]		56[d]	44	28	48[c]
19 (autologous BMT)			68[d]	32	58	
61	0.5 - 8 (dose escalation study) [not stated]	51	13	36		38

a Where defined, complete response was clearance of positive blood cultures after 48 hours of treatment for fungaemia, complete resolution of computed tomography (CT) evidence of infection or partial resolution and no evidence of recurrence while off therapy for ≥3 months for visceral disease and clearance of clinical symptoms and negative examination of stool for fungal elements for enteritis.

b Defined only for visceral infection; stabilisation or improvement but not complete resolution of CT evidence of infection.

c Available only as an abstract.

d Total response rate (complete/partial).

count $\leq 0.5 \times 10^9$/L) and persistent fever.[40] In this study, published only as an abstract, a successful outcome (defined as survival for ≥7 days after the last dose, absence of suspected or documented fungal infection, absence of fever and no adverse events necessitating treatment withdrawal) was achieved in 48% of patients treated with ABCD and in 43% of C-AmB recipients.

4.3 Prophylaxis

Fungal infections are an important cause of morbidity and mortality in patients with haematological malignancies[51] and in those who are severely immunosuppressed or neutropenic.[52,53] Strategies to prevent fungal infections, most importantly those caused by *Candida* and *Aspergillus* species, include those aimed at decreasing fungal colonisation through use of oral or systemic antifungal agents (against *Candida* species) and reduction of environmental exposure to aspergilli and improving host immune response by prophylactic administration of granulocyte transfusions and colony-stimulating factors.[51]

Studies of the prophylactic efficacy of conventional amphotericin B have reported both success and failure to reduce the incidence of fungal infection in immunocompromised patients.[52,54] There are no placebo-controlled studies of prophylactic ABCD.

None of 16 patients with acute leukaemia undergoing bone marrow transplant or high-dose chemotherapy without stem cell support who received pretreatment with ABCD [0.5 to 3 (median 1) mg/kg/day] developed an invasive fungal infection.[55] However, these preliminary data from small numbers of patients do not permit conclusions about the efficacy of ABCD in this situation.

4.4 Visceral Leishmaniasis

The pentavalent antimonial compounds sodium stibogluconate and meglumine antimonate administered for a minimum of 28 days are standard treatments for symptomatic visceral leishmaniasis (kala azar). Conventional amphotericin B is also an effective treatment for visceral leishmaniasis but has not been widely used because of its toxicity.

Three groups of 10 Brazilian patients with parasitologically demonstrated kala azar were treated with ABCD 2 mg/kg/day for periods of 10, 7 or 5 days.[56-58] Follow-up for ≤12 months after treatment revealed no clinical manifestations of the disease in all but one patient treated with the shortest regimen.[58] This patient, who relapsed after 5 months, was successfully retreated with meglumine antimonate. There was no evidence of *Leishmania* amastigotes in bone marrow aspirates from any patient 2 weeks after treatment with each regimen and spleen size regressed by a mean of 79% 2 months after treatment.[57]

5. Tolerability

The adverse event profile of ABCD is derived mainly from the experience of 572 patients with systemic fungal infections treated with mean dosages of 3 to 6 (range 0.5 to 8.0) mg/kg/day for 1 to 409 days (mean 25). Adverse events that occurred in ≥5% of patients that were considered to be probably or possibly associated with ABCD included chills (50%), fever (33%), increased serum creatinine level (12%), tachycardia (10%), hypotension (10%), nausea (8%), hypokalaemia (8%), hypertension (7%), nausea and vomiting (7%), thrombocytopenia (6%), vomiting (6%), dyspnoea (5%), hypoxia (5%) and headache (5%). The overall incidence of adverse effects was similar in patients with pre-existing renal impairment and in patients with normal renal function.[41] There was a tendency for adverse events to occur more often with ABCD dosages >4 mg/kg/day than with dosages ≤4 mg/kg/day.[41]

Infusion-related adverse events occurred in association with ≥1 infusion in 65.2% of patients, most often with the first infusion. These events necessitated withdrawal of ABCD treatment in 5.4% of patients and were the most frequent cause of treatment withdrawal in the 12.2% of patients in whom treatment was discontinued because of adverse events (fig. 2).[41]

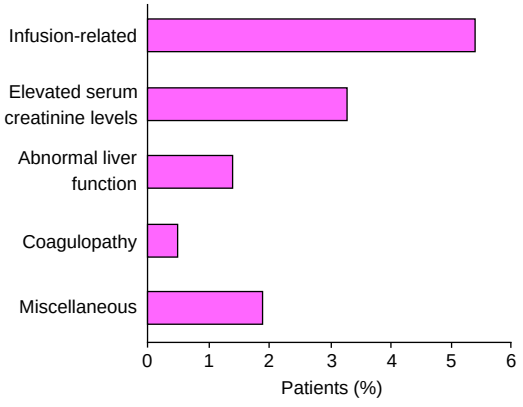

Fig. 2. Proportion of 572 patients with proven or suspected fungal infection treated with amphotericin B colloidal dispersion (mostly 3 to 6 mg/kg/day) [mean duration 25 days; range 1 to 409] who experienced adverse events that necessitated discontinuation of the drug.[41]

Thrombocytopenia, which developed in 11% of 572 patients, occurred more frequently in patients with pre-existing renal impairment (16.4%) or those with dosages >4 mg/kg/day than in patients with normal renal function or those on lower dosages.[41] However, in only 8.7% of patients who received ABCD >4 mg/kg/day was thrombocytopenia attributable to the drug; most patients had underlying diseases or were receiving drug therapy thought to be contributory. Neutropenia developed in 2.8% of patients and anaemia in 2.5% of patients treated with ABCD.[41]

5.1 Nephrotoxicity

Amphotericin B-induced renal toxicity limits the usefulness of the drug when administered as the conventional formulation[59-61] and is manifested as disturbances in both glomerular and tubular function. When administered as the colloidal dispersion formulation, drug distribution to the kidneys is reduced (section 3), which may contribute to the lower incidence of nephrotoxicity reported with ABCD.

Of 572 patients treated with ABCD in phase I or II clinical trials, 193 had renal impairment due to previous treatment with C-AmB and a further 140 had renal dysfunction due to other causes. Treatment with ABCD (0.5 to 8 mg/kg/day) did not alter mean serum creatinine levels: in 474 patients for whom data were available, mean serum creatinine levels were 189 μmol/L both before and after ABCD treatment.[41] Similarly, mean creatinine levels were unaltered in a subset of patients who received cumulative ABCD doses >10g (n = 96, mean total dose 18g, mean duration of treatment 61 days).[62] However, some patients have developed increased creatinine levels during ABCD therapy:[37] 17 of 126 patients whose serum creatinine was <221 μmol/L at baseline had levels >221 μmol/L after ABCD treatment.

Among patients undergoing chemotherapy for neoplastic disease who were randomised to ABCD 4 mg/kg/day or C-AmB 0.8 mg/kg/day, ABCD recipients were significantly less likely to develop renal toxicity (defined as a doubling, or an increase of ≥188 μmol/L, of serum creatinine or a ≥50% decrease in creatinine clearance from baseline) [17 *vs* 47%; $p < 0.001$].[40] More than 90% of patients in both arms of this study received potassium replacement therapy,[63] and both groups received approximately equal amounts of potassium supplementation;[64] however, 7 *vs* 23% of patients receiving ABCD and C-AmB treatment, respectively, experienced serum potassium levels <3 mmol/L ($p < 0.005$).[64]

Patients who develop nephrotoxicity while receiving C-AmB may benefit from a switch to ABCD therapy.[46] Of 9 patients who developed dose-limiting nephrotoxicity during C-AmB therapy, substitution of ABCD for the conventional formulation resulted in decreased serum creatinine levels in 7 (mean reduction 106 μmol/L); in 2 patients renal function continued to deteriorate despite the change in therapy.

Patients receiving ABCD plus cyclosporin or tacrolimus demonstrated a lower rate of renal toxicity than patients receiving C-AmB plus cyclosporin or tacrolimus. Data from an unpublished randomised comparison of ABCD with C-AmB in adult and paediatric patients also receiving cyclosporin or tacrolimus indicated that 31% (16/51) of ABCD 4 mg/kg/day recipients compared with

68% (34/50) of C-AmB 0.8 mg/kg/day recipients developed renal toxicity (defined as a doubling or an increase of ≥76 μmol/L from baseline serum creatinine levels or a ≥50% decrease from baseline calculated creatinine clearance).[64] An additional, nonrandomised study conducted in 28 centres in 133 patients with invasive fungal infection and impaired renal function indicated that ABCD is well tolerated in this population, including patients receiving cyclosporin, tacrolimus or other medications with nephrotoxic potential.[65]

5.2 Liver Function

Biochemical values reflecting liver function were generally little affected by treatment with ABCD. Values at baseline and end of treatment were respectively, 54.5 and 57 U/L for aspartate aminotransferase, 227.6 and 235.6 U/L for alkaline phosphatase and 74.5 and 79.3 μmol/L for total bilirubin.[41] In a study involving 168 patients treated with ABCD because of nephrotoxicity associated with C-AmB or pre-existing renal impairment from other causes, aspartate aminotransferase levels were elevated at the end of treatment in 15 patients with normal values at baseline; levels normalised at the end of treatment in 14 patients in whom values were initially elevated. Similarly, alanine aminotransferase levels were elevated in 22 patients with initially normal levels and normalised in 19 patients with initially elevated levels.[37]

6. Dosage and Administration

The recommended initial dosage of ABCD in adults and children is 3 to 4 mg/kg/day by intravenous infusion at a rate of 1 mg/kg/hour.[64] Higher dosages have been studied (section 4). A test dose of 10ml of the infusion solution is advisable before starting a new course of treatment with ABCD. The duration of treatment is variable and will be affected by the type and site of infection, as well as the patient's clinical response and immune status.

ABCD should be reconstituted by addition of sterile water to provide a solution containing 5 mg/ml. For infusion, this solution should be further diluted with 5% dextrose for injection to a final concentration of about 0.6 mg/ml.[64]

There have been no formal drug interaction studies with ABCD, but the potential for renal toxicity may be enhanced by concomitant administration of antineoplastic agents, cyclosporin, tacrolimus and other nephrotoxic medications such as aminoglycosides and pentamidine.[64]

ABCD-induced hypokalaemia may enhance digitalis toxicity and the curariform effect of skeletal muscle relaxants (e.g.tubocurarine) and may be potentiated by concomitant administration of systemic corticosteroids and corticotrophin (ACTH).[64] Concurrent administration of flucytosine with amphotericin B may increase the toxicity of flucytosine.[64]

7. Place of Amphotericin B Colloidal Dispersion in the Management of Systemic Mycoses and Visceral Leishmaniasis

Amphotericin B has been available since the 1950s and remains the treatment of choice for most serious systemic fungal infections.[1] This drug has been the standard with which all other therapies for systemic fungal infection have been compared.[66] In the last decade there have been a substantial number of clinical trials with azole compounds in which efficacy similar to that reported with intravenous conventional amphotericin B has been demonstrated.[66] Azoles are now used as initial therapy for mild or moderate systemic mycoses, but intravenous C-AmB is still used as initial therapy in severe systemic mycoses. For future clinical trials of new drugs for the treatment of invasive aspergillosis, severe candidaemia, coccidioidal meningitis or zygomycosis, C-AmB should be the comparative agent.[66] Despite its status as the treatment of choice, the toxicity of the conventional formulation often necessitates a reduction in dosage to a tolerable level sometimes resulting in suboptimal or inadequate clinical efficacy. Incorporation of amphotericin B into liposomes or attachment to other lipid carriers clearly increases the therapeutic ratio of the new formulations, re-

sulting, particularly, in reduced renal toxicity. The new formulations, despite altered pharmacokinetic properties resulting in greater uptake of the new formulations by organs rich in reticuloendothelial cells, exhibit efficacy in animal models of systemic fungal infections comparable to that of the conventional formulation.

Aspergillosis has become an increasingly common cause of opportunistic fungal infection in neutropenic patients, although there are many instances of invasive aspergillosis occurring in non-immunocompromised patients. The incidence of invasive aspergillosis is increasing rapidly in Western countries while that of aspergilloma is decreasing.[67] The rate of progression of invasive aspergillosis varies, but in patients who have undergone liver or bone marrow transplantation and have profound neutropenia the course of the disease from clinical or radiological abnormality to death is usually 10 to 14 days. The diagnosis is often difficult to establish and several days can elapse between consideration of the diagnosis and partial or complete confirmation. Thus, it is important that treatment is started early. Intravenous C-AmB is the standard treatment for invasive aspergillosis in patients in whom oral treatment (i.e. itraconazole[68]) is unsuitable. In patients with renal impairment or in whom it is likely to become a problem, as in patients receiving cyclosporin, a lipid-based formulation may be appropriate. In a retrospective study, ABCD was associated with higher response rates, significantly lower mortality rates and improved renal tolerability compared with C-AmB in patients with proven or suspected invasive aspergillosis. Nevertheless, it cannot be concluded from such a study that ABCD is more effective than C-AmB. Therefore, the clinical efficacy of ABCD relative to that of the conventional formulation has not been adequately demonstrated.

Candidaemia is a difficult-to-treat infection for which, until recently, there have been few effective antifungal agents. *Candida* species continue to be important causes of systemic infection, not only in patients with cancer, those undergoing organ transplantation and those with AIDS or with major burns,[69] but also other critically ill hospitalised patients as well as the newborn.[70] Results of a prospective randomised comparison of empirical C-AmB and fluconazole[71] in patients without neutropenia, and of a matched cohort study comparing C-AmB and fluconazole in patients with haematogenous candidiasis,[72] indicated that the two drugs were similarly effective. Consequently, fluconazole is now considered a better tolerated alternative to C-AmB in treating candidaemia in patients without neutropenia.[69,73] However, the lack of efficacy of fluconazole against *C. krusei* remains a concern,[69] as does the development of fluconazole-resistant strains of *C. glabrata*.[74] The lipid-based formulation of amphotericin B may be considered an option against candidaemia caused by these organisms in patients unable to tolerate C-AmB.

As the lipid-based formulations of amphotericin B appear to be preferentially accumulated in the organs of the reticuloendothelial system, where *Leishmania* reside, these formulations would be predicted to be effective in the treatment of visceral leishmaniasis.[75] Indeed, these agents are effective when administered for 5 to 10 days and may be indicated particularly in the treatment of visceral leishmaniasis that is resistant to standard treatment with pentavalent antimonial compounds such as stibogluconate and meglumine antimonate.[75] The high incidence of infusion-related adverse effects associated with ABCD treatment in young children with visceral leishmaniasis[57,58] may limit the potential of this drug. The effective dosage regimen may differ between countries and patients should be treated with a formulation and regimen that have been reported to cure the disease in the region where it was acquired. To date, ABCD has been studied only in Brazil where it is probable that the antimonial compounds remain effective.[75]

Preliminary data suggest that ABCD may be useful in preventing systemic fungal infection in patients with leukaemia undergoing bone marrow transplantation. However, like other high-cost lipid-based formulations, ABCD is unlikely to be used prophylactically unless randomised studies demonstrate that it significantly reduces the risk of

fungal infection. At present, fluconazole is the most widely studied drug for prophylaxis in immunocompromised patients.[70]

The increasingly high rate of invasive fungal infection in patients with neutropenia and the frequent difficulty in diagnosis have led to the empirical use of C-AmB in the setting of neutropenia with persistent fever and no identifiable cause.[76] To date, this is the only clinical setting in which ABCD has been prospectively compared with C-AmB in a randomised double-blind trial. Preliminary data from this pilot trial do not permit conclusions about the relative efficacy of the 2 formulations.

The acquisition cost of the lipid-based formulations of amphotericin B is considerably higher that than of the conventional formulation. However, the increased cost of these formulations in comparison with that of C-AmB must be weighed against their improved therapeutic indices. Formal cost-effectiveness analyses of the new formulations in specific clinical settings would aid decision makers.

Randomised comparative trials of ABCD, liposomal amphotericin B and amphotericin B lipid complex are needed to assess their comparative clinical efficacy and clearly establish their respective roles in the management of severe systemic mycoses and visceral leishmaniasis.

In summary, in the absence of prospective comparisons ABCD appears to be an effective alternative to C-AmB in the treatment of invasive aspergillosis in immunocompromised patients and of visceral leishmaniasis in immunocompetent patients. Promising initial results were achieved in the treatment of suspected or documented fungal infection after bone marrow transplantation. Similarly, ABCD demonstrated potential as treatment of proven or suspected systemic mycoses in patients intolerant of C-AmB, with pre-existing renal impairment or who had failed to adequately respond to the conventional formulation. Preliminary results from an ongoing double-blind comparison of ABCD and C-AmB in patients with neutropenia and persistent fever reported a successful outcome in a similar proportion of patients treated with either formulation. The efficacy of ABCD relative to that of the conventional formulation has yet to be adequately demonstrated, and the role of ABCD in managing invasive fungal infections remains to be determined. However, the improved renal tolerability of ABCD compared with the conventional formulation is likely to be an important therapeutic advantage.

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