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Commercially available lipid formulations of amphotericin B: are they bioequivalent and therapeutically equivalent?

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Abstract. Amphotericin B is a polyene macrolide derived from *Streptomyces nodosus*. Introduced into therapy in 1957, for decades amphotericin B has been the "gold standard" for fighting systemic fungal infections. In order to facilitate its systemic use, much attention has been paid to the development of pharmaceutical forms that could reduce its toxicity, especially for the kidney. Because of its low solubility in water and excellent solubility in lipids, amphotericin B is an ideal candidate for lipid-based formulations. Three different lipid formulations for intravenous infusion are currently commercially available: liposomal amphotericin (AmBisome®), Amphotericin lipid complex (Abelcet®) and Amphotericin colloidal dispersion (Amphocil®). The three lipid formulations of amphotericin B show significantly different structural, physical, chemical, pharmacokinetic, pharmacodynamic and toxicological characteristics. Several lines of evidence indicate that the three formulations of amphotericin B are not therapeutically equivalent. First, they are not bioequivalent. Second, even though a complete picture of controlled clinical research designed to compare effectiveness and safety of the three lipid formulations is not available, all the clinical studies analyzed report clear differences in toxicity between the three formulations. AmBisome® appears to be clearly less toxic than the other two formulations, in terms of nephrotoxicity and of incidence of infusion-related adverse events. Third, the therapeutic non-equivalence of the three lipid formulations of amphotericin B is further supported by statements of Conferences and Scientific Societies that in their recommendations have awarded different grading to the three lipid formulations. (www.actabiomedica.it)

Key words: Amphotericin B, Lipid amphotericin formulations, AmBisome®, Abelcet®, Amphocil®

1. Introduction

Amphotericin B is a polyene macrolide derived from *Streptomyces nodosus*. Introduced into therapy in 1957, for decades amphotericin B has been the "gold standard" for fighting systemic fungal infections (1, 2).

This drug exerts a fungistatic or fungicidal effect according to the concentration reached in body fluids and the susceptibility of the fungus. In order to facilitate its use in the treatment of fungal infections, much attention has been paid to the development of pharmaceutical forms that could reduce its toxicity, especially for the kidney. Because of its low solubility in water and excellent solubility in lipids, amphotericin B is an ideal candidate for lipid-based formulations (3). There are currently four commercially available formulations of amphotericin B:

- Amphotericin deoxycholate (Fungizone®). In water it forms a colloidal suspension with particles of diameter less than 0.4 μm.
- Liposomal amphotericin (AmBisome®)
- Amphotericin lipid complex (Abelcet®)
- Amphotericin colloidal dispersion (Amphocil®)

AmBisome®, Abelcet® and Amphocil® are lipid formulations for intravenous infusion, whose preparation was possible due to the amphipathic nature of amphotericin B.

2. Physical and chemical properties

AmBisome® is a lyophilised formulation containing amphotericin B in combination with lipids in a molar ratio of about 10% (4). It is incorporated into unilamellar liposomes with a diameter of 60-70 nm, thus it may be considered as a kind of special colloidal system (Fig. 1). The liposomes are made up of hydrogenated soybean phosphatidylcholine, cholesterol and distearoyl phosphatidylglycerol in a ratio of 10:5:4 (5). The stability of the liposome is ensured by the fact that cholesterol and distearoyl phosphatidylglycerol exhibit a high transition temperature (55˚C), close to which the lipid preparation naturally tends to collapse, releasing its contents (3). The stability of the liposome is also guaranteed by its small size. Moreover, the negative charge of distearoyl phosphatidylglycerol can interact with the positive amino group of amphotericin B to form an ion complex in the lipid bilayer (4).

Abelcet® is a lipid complex of amphotericin B. It consists of two phospholipids in a molar ratio of 1:1 with the drug. The two phospholipids, L-α-dimyristoyl phosphatidylcholine and dimyristoyl phosphatidylglycerol, are present in a ratio of 7:3 (6). Unlike the liposomal formulation, Abelcet® has a ribbon-like appearance due to rupture of the lipid bilayer caused by amphotericin B, and to reorientation of the lipids and amphotericin B to form ribbon-like structures larger than 1600 nm (Fig. 1). Both phospholipids have a transition temperature of 23 ˚C, which is below body temperature; this means that the lipid complex may disintegrate before reaching the site of action.

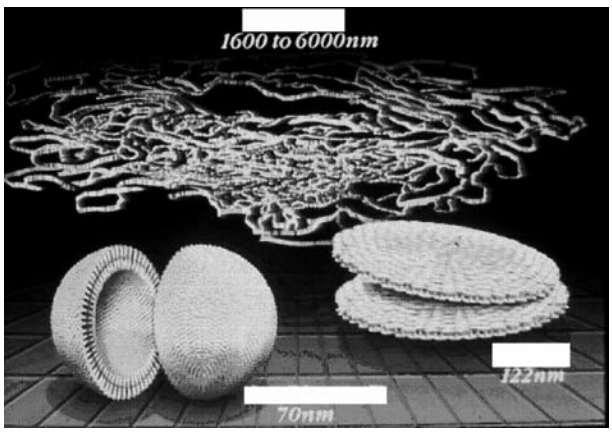

Figure 1.

Amphocil® is made up of amphotericin and sodium cholesteryl sulfate in a 1:1 ratio. It is a colloidal dispersion with a disc-like structure. Each disc has an approximate diameter of 122 nm and a thickness of 4 nm (Fig. 1) (7).

3. Pharmacokinetic properties AmBisome®

AmBisome® is made up of small, rigid and spherical liposomes, that are taken up slowly by the reticulo-endothelial system (8). Studies with single-dose AmBisome® in rats and mice have shown greater plasma concentration, a longer elimination half-life and a larger AUC than conventional amphotericin. Moreover, studies with multiple doses have highlighted that the active ingredient is concentrated more in the spleen and in the liver, whereas concentrations in the kidney and lungs (Table 1) are similar to those found after administration of Fungizone® (9). The uptake of intact liposomes by the liver is rather slow, leading to a slow decline in liposome blood levels (10).

Clinical trials have been carried out using AmBisome®. At a dose of 5 mg/kg, plasma concentration reaches a peak of 83 mg/l. This concentration, as shown in Table 2, is 25-200 times higher than that of Abelcet® and Amphocil® administered at the same dose. The C_{max} for amphotericin B after AmBisome® administration reaches mean values around 26 and 48 times higher than those obtained after administration of Abelcet® and Amphocil®, respectively (11, 12).

A phase IV study performed on healthy volunteers highlighted that AmBisome®, compared to Fungizone®, Amphocil®, Abelcet® leads to a higher plasma concentration and a lower Vd. (13). There was also a marked decrease in the excretion of unchanged amphotericin B in urine and feces (14). This could be the reason for the lower incidence of nephrotoxicity with AmBisome® (15).

The passage of amphotericin B into brain tissue also occurred in the presence of intact meninges, and

Table 1. Distribution of the three lipid formulations of amphotericin B

Formulation	Plasma C_{max} compared with conventional amphotericin	Tissue concentration of amphotericin compared with conventional amphotericin		
		Liver	Lungs	Kidneys
Abelcet®	Lower	Higher	Higher	Similar
AmBisome®	Higher	Higher	Similar	Similar
Amphocil®	Lower	Higher	Similar	Similar

From Metha J (10)

Table 2. Pharmacokinetic parameters of the three lipid formulations of amphotericin B

Formulation	Size (nm)	Structure	Dose (mg/Kg)	C_{max} (mg/l)	AUC (mg·h/l)	V_d (l/kg)
Amphotericin deoxycholate	0.035	Micelles	0.6	1.1	17.1	5.1
AmBisome®	<0.080	Liposomes	5	83	555	0.11
Abelcet®	1.6-11	Ribbon-like	5	1.7	9.5	131
Amphocil®	0.11-0.14	Disc-like	5	3.1	43	4.3

From Dupont B. *(11)*

tissue concentrations after administration of AmBisome® were found to be 6-10 times higher than those of Abelcet® and Amphocil®.

Finally, after a single intravenous administration, AmBisome® led to a far higher amphotericin B concentration in the aqueous humor of an inflamed eye than with Abelcet® and Fungizone®.

Abelcet®

Preclinical trials have shown that Abelcet® is taken up rapidly and in significant quantities by mononuclear phagocytes of the reticulo-endothelial system. This results in a concentration of amphotericin B in the systemic circulation in human subjects that is 5 times lower than when using Fungizone®, with plasma peaks of no more than 5 mg/ml when administered at therapeutic doses (1-10 mg/kg) (16, 17). Pharmacokinetic studies with Abelcet® have shown a lower AUC_{0-24} than for Fungizone®. The Vd and clearance are 3 and 7 times higher, respectively, than those for Fungizone® (10). Further studies, conducted using multiple doses in animals, showed a dose-dependent increase in the concentrations of amphotericin B in the liver, spleen and lungs (5).

In a study in mice with pulmonary aspergillosis, both AmBisome® and Abelcet® administered at doses of 1, 4, 8 or 12 mg/kg resulted in lung concentrations above therapeutic levels (3 g/g), but lung levels of Abelcet® were still high. In response to a dose of 12 mg/kg, both formulations produced a survival rate of 57%, but at higher doses (15-20 mg/kg) survival rates in animals treated with AmBisome® rose to 80-90%, while that of animals treated with Abelcet® were indistinguishable from that of the controls. At these doses, Abelcet® showed clear nephrotoxicity, while AmBisome® gave renal function parameters similar to those of controls (18).

Amphocil®

A study by Fielding et al., (16) showed that Amphocil®, administered to rats at a dose of 5 mg/kg, causes a lower peak plasma concentration and the AUC is 2 times less than for Fungizone®. The Vd and clearance, by contrast, are higher for Amphocil®. Amphocil® is rapidly cleared from plasma and taken up mainly by the tissues of the reticulo-endothelial system, with plasma peaks of no more than 5 mg/ml when administered at therapeutic doses (1-10 mg/kg)

(16, 17). AUC, C_{max} and V_d values appeared to be intermediate compared to those for AmBisome® and Abelcet® administered at the same doses (Table 2).

As far as distribution is concerned, the highest tissue concentrations were found in the liver, spleen and bone marrow. The high concentrations of Amphocil® in the liver were caused by the rapid and extensive uptake by the liver phagocytic cells. Therefore, it has been proposed that the liver may act as a reservoir of lipid-complexed amphotericin from which the active ingredient is slowly released (16). Moreover, its small size enables Amphocil® to cross the pulmonary vascular bed without accumulating there (19). The concentration of amphotericin in other organs, such as the kidney and heart, is comparable to those found after administration of Fungizone® (20). The concentrations observed in the kidney were three times higher after Amphocil® than after AmBisome® (21).

4. Pharmacodynamic properties and mechanism of action

The exact mechanism of action by which amphotericin B contained in AmBisome® penetrates the fungal cell has not yet been clarified. It has been suggested that amphotericin B activity is due to the high binding affinity of amphotericin B for ergosterol, the main component of the plasma membrane in fungi. Amphotericin B molecules form a rosette pattern around ergosterol, leading to a structural modification of the membrane, with pore formation. The pores lead to the formation of channels through which components of the fungal cell can leak, thus altering the osmotic integrity of the cell and causing its death. Inhibition of the proton ATPase in the fungal cell membrane and inhibition of lipid peroxidation are additional cytotoxic mechanisms of amphotericin B (22).

Amphotericin B has a concentration-dependent type activity, i.e. primarily related to the concentration at which it reaches the fungal cell. For a C_{max}/MIC ratio of 4, amphotericin B is already clearly effective, and its efficacy becomes optimal at a ratio of 10 (22, 23). Since the activity of amphotericin B is concentration-dependent, it should be administered once daily by infusion, whose duration (3-4 hours for deoxycholate and 2 hours for AmBisome®) is conditioned by the toxicity of the formulation used.

The concentration-dependent effect is also associated with a post-antifungal effect (PAFE), i.e. replication of the fungus remains suppressed even when the drug concentration has fallen below the MIC. Amphotericin B has a significant PAFE, higher than that of echinocandins; triazoles are not associated with PAFE (3). The onset of resistance to amphotericin B is unlikely (24).

In AmBisome®, amphotericin B is closely integrated with the liposome membranes forming a non-covalent complex between amphotericin B mycosamine (positively charged) and distearoyl phosphatidylglycerol (negatively charged), as well as by hydrophobic interactions with the cholesterol membrane (12). The stability of the formulation does not affect its efficacy. Experiments with the dye sulforhodamine have shown that liposomes accumulate at the site of infection by adhering to the surface of fungal cells even when they lack amphotericin B (25, 26). In fungal cells the liposome disintegrates and releases amphotericin B, which can thus exert its antifungal action at the site of infection (25).

The mechanism proposed for Abelcet® is different. In fact, it is assumed that fungal lipases play a crucial role by acting on the lipid formulation to induce release of Amphotericin B into the tissues (27). For Amphocil®, by contrast, it is suggested that the product is taken up by the phagocytic cells of the liver which then release processed amphotericin B into the circulation (20). In particular, macrophages can function as reservoirs of amphotericin B, due to their intracellular and extracellular antimicrobial activity. In this regard, Mehta et al. (10) showed that the improvement in the anti-candidiasis activity of AmBisome® is not due to the activation of macrophages. It seems that the improvement in anti-candidiasis activity depends on the increased uptake and retention of AmBisome® and its slow release by the macrophages. Indeed, AmBisome® is ingested by macrophages (28, 29) or monocytes and slowly processed and released to carry out its intra- ed extra-cellular antimicrobial activity. The speed with which AmBisome® is released by the macrophages is influenced by the stability of the complex (30).

5. Toxicity

Amphotericin B also shows affinity, although lower, for the cholesterol of human cell membranes; this property is at the basis of its potential toxicity.

Boswell et al. (12) reported that AmBisome® liposomes damage the membranes of erythrocytes to a far lesser extent than Amphocil® and Abelcet®. On in vitro erythrocytes, amphotericin B damages the membrane, releasing potassium and hemoglobin into the medium. The different formulations of amphotericin B were incubated with erythrocytes for 4 hours at 37°. The release of potassium into the medium was caused by low concentrations of Fungizone®. Amphocil® and Abelcet® required higher concentrations; AmBisome® required concentrations 3-4 times higher than those of Abelcet® and Amphocil® to cause leakage of potassium into the medium.

The fact that amphotericin B is retained by the liposomal dosage form until the site of infection is reached reduces the risk of nephrotoxicity related to high cholesterol content in renal tubular cells.

On the other hand, AmBisome® liposomes remain intact in the plasma for about 24 hours, allowing them to continuously affect the properties of the amphotericin B that they contain.

6. Clinical efficacy trials

In vitro, the order of antifungal activity is Fungizone® > Abelcet® > Amphocil® > AmBisome® (31, 32). Studies carried out in vitro do not take into account the different pharmacokinetic distribution of amphotericin B in the various formulations and do not correspond to the results obtained in vivo (33).

Ostrosky-Zeichner et al.(1) examined several clinical trials which highlighted that all of the new formulations of amphotericin B were more efficacious than Fungizone®. So the comparison between the efficacy of the different formulations of amphotericin B is subject to debate. In a very recent article, Bellmann (2) reports that AmBisome® was compared with Fungizone® in two randomized clinical trials and as empirical therapy for a multicenter randomized trial in 687 patients with persistent fever and neutropenia. The therapeutic efficacy of AmBisome® was similar to that of Fungizone®, while both nephrotoxicity and the incidence of infusion-related adverse events were significantly lower after administration of AmBisome® (34).

The treatment of fungal infections is not easy, as most of the organs generally appear to be infected and patients often have concurrent diseases.

In order to compare the activity of various formulations of amphotericin B, it would be interesting to evaluate the various pharmacokinetic characteristics of the lipid formulations related to their clinical efficacy. In this regard, it is important to focus attention on the target organs of amphotericin B, which are the main target of the pathogens.

In patients with disseminated candidiasis, it would be logical to state that AmBisome®, which has the highest elimination half-life (35), could be more efficacious than the other formulations of amphotericin B. In fact, Linder et al. (36) reported that clearance of fungemia was obtained in 83% of patients receiving AmBisome®, in 57% of subjects treated with Amphocil® and 68% of patients treated with Fungizone®.

Treatment with AmBisome® and Abelcet® shows that response rates in aspergillosis are much higher than with Fungizone® (1, 37, 38). The preferential localization of amphotericin B in the lungs and the high doses of Abelcet® and AmBisome® administered compared to those of Fungizone® may explain the difference in efficacy.

In Cryptococcus infections, in which the CNS is the primary site of infection, AmBisome® has a significantly greater effect than Fungizone® (39). Another study highlighted the greater efficacy of Abelcet® (86%) compared to Fungizone® (65%) (40).

Recently, AmBisome® was registered for the treatment of visceral leishmaniasis (in which the parasite localises preferentially at the level of the reticuloendothelial system), and a single dose of 5 mg/kg proved to be sufficient to treat 90% of patients in a clinical study performed in India (41, 42). Other lipid formulations of amphotericin B have been shown to have similar efficacy, although multiple doses are required (43, 44).

AmBisome® has been compared to Abelcet® for the empirical treatment of febrile neutropenia (45).

Although the two formulations have similar efficacy, AmBisome® was associated with significantly lower toxicity and therefore fewer patients receiving AmBisome® discontinued the therapy. Several studies report that Amphocil® has antifungal efficacy similar to that of Fungizone®, but that the toxicity of the latter was significantly higher than that of Amphocil® (2).

Lanternier and Lortholary (46) report the results of several retrospective studies on the survival of patients with zygomycosis treated with one of the three lipid formulations of amphotericin B. The survival rate was 69% with AmBisome®, 75% with Abelcet®, 60% with Amphocil®, and 61% with Fungizone®.

Finally, Moen et al. (47) report that liposomal amphotericin B remains the first-line option for empirical therapy in patients with febrile neutropenia and in those with disseminated histoplasmosis and an option for AIDS-associated cryptococcal meningitis and invasive Candida and Aspergillus infections. In comparison with other amphotericin B formulations, treatment with liposomal amphotericin B is associated with a lower incidence of infusion-related adverse reactions and with reduced nephrotoxicity in response to a standard dose of 3 mg/kg/day.

7. Tolerability and safety studies

The main problem of amphotericin B is its potential toxicity, in particular its nephrotoxicity, and infusion-related adverse reactions, such as chills, stiffness, fever and hypoxia. In this regard, several authors have argued that the choice of amphotericin B dosage form should be primarily based on its toxicological properties (48-50).

In 1995, Arning had already shown that AmBisome® infusion induces fewer adverse events than Abelcet® and Amphocil®, attributing this difference to the lower release by AmBisome® of cytokines. These formulations led to significant infusion-related adverse events, and resulted in a significant increase in plasma levels of IL-6 and IL-8, although to a lesser extent than IL-6 (51, 52).

Lipid formulations show less nephrotoxicity than Fungizone®. In a multicenter double-blind clinical study (34), 687 patients were randomized to receive either AmBisome® or Fungizone® as empirical therapy for persistent fever and neutropenia. Similar outcomes were observed in terms of survival and resolution of fever. But AmBisome® was associated with lower nephrotoxicity and fewer infusion-related adverse events. Probably, AmBisome® has less adverse events because the concentration of Amphotericin B in this formulation is lower (1). An important role in the induction of nephrotoxicity is the different state of aggregation of amphotericin B. The amphotericin B in Fungizone® is in an oligomeric state, which is the most cytotoxic, while the lipid formulations contain less toxic aggregates.

Furthermore, AmBisome® is less toxic than Abelcet® (11). In fact, a randomized double-blind study clarified that nephrotoxicity, assessed on the basis of a doubling of serum creatinine, is significantly higher for Abelcet® at both 3 and 5 mg/kg/day than for AmBisome® (53). Moreover, Abelcet®, unlike AmBisome®, causes a significant number of adverse events such as chills and shivering, fever, hypoxia and other infusion-related reactions (Table 3).

Various studies have shown that AmBisome® has a better profile in terms of reactions during the first

Table 3. Reactions related to the first day of infusion for Abelcet® and AmBisome®

Reactions	Percentage of patients			
	AmBisome® (3 mg/Kg)	AmBisome® (5 mg/Kg)	Abelcet® (5 mg/Kg)	P value
Chills/Shivering	18.8	23.5	79.5	<0.001
Fever (increase = 1°C)	23.5	19.8	57.7	<0.001
Hypoxia	0	1.2	11.5	<0.001
Other reactions	18.8	25.9	41.0	<0.001

From Dupont B. J Antimicrob Chemother 2002; 49, suppl S1: 31-36 (11)

day of infusion (11) . In a recent prospective study in immunocompromised patients conducted in 20 European centers (LEAD I), it was noted that the various formulations of amphotericin B exert a strong influence on nephrotoxicity, which was associated with longer duration of hospitalization (54) and higher mortality.

One study in 20 subjects died for failure of various organs showed concentrations in the kidney and lungs that were three times higher after Amphocil® than after AmBisome® (21). Pea (3) suggests that the risk of nephrotoxicity may be inversely related to accumulation of the drug in the kidney.

A dose-escalation study (55) with repeated administrations of up to 15 mg/kg of AmBisome® showed better tolerability by patients compared to Fungizone®, and when administered with other nephrotoxic drugs such as cyclosporins, AmBisome® does not significantly increase nephrotoxicity (56).

Furthermore, on the basis of its lower toxicity and its greater ability to penetrate the brain compared to the other lipid formulations, AmBisome® was approved as a drug that, at high doses and repeated administrations, can treat brain and other stubborn infections (fusariosis and zygomycosis).

The better tolerability of lipid formulations has been documented by a meta-analysis study in over 4500 patients (57). The paper reports that discontinuation of antifungal therapy due to toxicity problems is on average 5-15 times lower for the three lipid formulations, compared to Fungizone®. The three lipid formulations gave rise to much lower nephrotoxicity than that of Fungizone®. Of the three lipid preparations, AmBisome® had the lowest nephrotoxicity.

8. Guidelines and recommendations

Scientific Societies in the field have awarded differentiated grading to the various lipid formulations of amphotericin B.

The recommendations of the First European Conference on Infections in Leukaemia (ECIL-1), for empirical treatment in neutropenia patients, distinguish between AmBisome®, Abelcet® and Fungizone® (57).

Table 4. Candidemia in hematologic patients before species identification

	Overall population	Hematological pts
Micafungin	A I	B II
Anidulafungin	A I	B II
Caspofungin	A I	B II
AmBisome®	A I	B II
Other lipid-AmB	A II	B II
Fluconazole	A I *	C III
Voriconazole	A I **	B II

* Not in severely ill patients or in patients with previous azole prophylaxis
** Not in patients with previous azole prophylaxis

As regards treatment for invasive aspergillosis, the ECIL attributed level BI for AmBisome®, BII for Abelcet®, and DI for Fungizone® and Amphocil®.

On the other hand, for the treatment of invasive aspergillosis, the most recent guidelines of the Infectious Diseases Society of America (IDSA) report that "liposomal amphotericin B can be considered as alternative first-line therapy in some patients (A-I)" (58).

The recommendations from the Second ECIL Conference are also different for AmBisome® in relation to other lipid formulations of amphotericin B for treating candidemia in hematological patients prior to identifying the fungal species involved (Table 4).

Update ECIL-2 2007

It seems evident that the recommendations of authoritative scientific Societies make a clear distinction between the different lipid formulations of amphotericin B for the purposes of their use in therapy.

In 2009, the IDSA published an Update to the Guidelines for the treatment of candidiasis, compared with those previously published in January 2004.

The 2009 Guidelines mention the three different lipid formulations of amphotericin B: AmBisome®, Abelcet® and Amphocil®. In this regard, the Guidelines indicate that the three formulations have the same spectrum of activity as Fungizone®, but each of them presents different pharmacological properties and frequencies of treatment-related adverse events, and "should not be interchanged without careful consideration".

In a recent review article (46) the authors argue that liposomal amphotericin:

1. May be considered first-line treatment for HIV-positive patients with disseminated histoplasmosis and patients with cryptococcal meningitis, even in the presence of kidney damage or administration of nephrotoxic drugs.
2. In the case of zygomycosis, liposomal amphotericin B is a first-line treatment and high doses are recommended.
3. Liposomal amphotericin B may play a primary role in the empirical treatment of persistent febrile neutropenia.
4. For invasive aspergillosis, use is recommended in cases associated with risk of drug interactions and for patients with renal failure or azole intolerance.
5. Liposomal amphotericin B remains a viable therapeutic option for treating candidemia and a cornerstone for the treatment of certain visceral locations in systemic candidiasis, in particular in patients with renal impairment or for concomitant use of nephrotoxic drugs, as well as in cases of Candida meningitis or endocarditis.

9. Conclusions

Based on the above considerations and data from the literature, can it be argued that the three formulations of amphotericin B are bioequivalent and therapeutically equivalent to each other?

To answer this question, it must first be remembered that the concept of equivalence is based on three factors: pharmaceutical equivalence, bioequivalence and therapeutic equivalence. Two preparations are considered pharmaceutically equivalent if they have the same qualitative and quantitative composition of active ingredients and the same pharmaceutical form. Two pharmaceutical equivalents are defined as bioequivalent when, following administration of the same dose, their bioavailability do not differ statistically. If it is shown that two pharmaceutically equivalent forms are also bioequivalent, it can be assumed that they should be also therapeutically equivalent (theory of therapeutic equivalence).

The pharmacokinetic parameters of the lipid formulations of amphotericin B are markedly different from those of Fungizone®.

Indeed, AmBisome® is associated with a much higher amphotericin B AUC than Amphocil® and Abelcet® (3, 11). The C_{max} of AmBisome® appears to be much higher than that of the other two lipid formulations. In agreement with these data, the volume of distribution of AmBisome® is decidedly lower than that reported for the two other lipid formulations.

Moreover, the data in Table 2 show that the AUC of amphotericin B for Abelcet® is equal to 1.71% that of AmBisome®. On the other hand, the AUC for Amphocil® is equal to 7.74% of that of AmBisome®. In relation to C_{max}, Abelcet® reaches a C_{max} equivalent to 2.04% compared to AmBisome®, while Amphocil® reaches a C_{max} equivalent to 3.73% of that of AmBisome®.

Since the 90% confidence interval for AUC, and the C_{max} for the three lipid formulations are both outside the range 80-125% (59), the formulations cannot be considered bioequivalent.

Finally, the three different lipid formulations of amphotericin B (AmBisome®, Abelcet® and Amphocil®) cannot be considered therapeutically equivalent because:

1. They are not bioequivalent.
2. There is no complete picture of controlled clinical research designed to compare the effectiveness of three lipid formulations of amphotericin B and clinical trials available in the literature often document similar efficacies between the different lipid formulations of amphotericin B, and between lipid formulations and Fungizone®; only a few studies highlight greater activity of liposomal amphotericin B. On the other hand, all of the clinical studies analyzed report clear differences in toxicity between the various formulations of amphotericin B. AmBisome® appears to be clearly less toxic than the other two formulations, again in terms of nephrotoxicity and of incidence of infusion-related adverse events.
3. The therapeutic non-equivalence of the three lipid formulations of amphotericin B is further supported by the fact that in their recommen-

dations Conferences and Scientific Societies have awarded different grading to the three lipid formulations of amphotericin B.

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