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LIPID-BASED ANTIFUNGAL AGENTS: A CONCISE OVERVIEW

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Abstract: The development of lipid formulations of antifungal drugs has been a remarkable progress in the systemic antifungal arena. The lipid-based amphotericin B formulations; amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), and liposomal amphotericin B (L-AMB) have been in clinical use since the 1990s. They are significantly less nephrotoxic than the parent compound and can be safely used at higher doses. The primary cost of these formulations is significantly high and the extent of data related to their head-to-head comparison remains limited. The lipid formulation of nystatin, liposomal nystatin, is another lipid-based polyene under development. Available data concerning the *in vitro* activity, pharmacokinetic profile, *in vivo* efficacy, and safety of these formulations are summarized in this overview.

Key words: Amphotericin B Lipid Complex, Amphotericin B Colloidal Dispersion, Liposomal Amphotericin B, Liposomal Nystatin

The spectrum of human mycoses ranges from superficial and local to disseminated and life-threatening infections. Opportunistic fungal infections of the immunocompromised host are the most troublesome among all; they are difficult-to-diagnose and treat and result in significant mortality. Due to the divergent nature of the causative agents of these infections, antifungal drugs with a broad spectrum of activity, low rates of toxicity and acceptable efficacy are required for treatment.

LIPID-BASED AMPHOTERICIN B FORMULATIONS

Amphotericin B deoxycholate, a polyene antibiotic formulation and the mainstay of parenteral antifungal therapy for over 30 years, has a very broad spectrum

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covering various yeasts and moulds. However, its unacceptably toxic nature, particularly its nephrotoxicity, limits its use at high doses and frequently necessitates cessation of therapy. To overcome this major drawback, investigations have been initiated in the 1980s to develop lipid amphotericin B formulations and three lipid formulations of amphotericin B were approved for clinical use in the 1990s. These lipid amphotericin B formulations are amphotericin B lipid complex (ABLC; Abelcet®, Elan Pharmaceu.), amphotericin B colloidal dispersion (ABCD; Amphocil® or Amphotec®, Sequus Pharmaceu.), and liposomal amphotericin B (L-AMB; Ambisome®, Nexstar Pharmaceu.). The lipid configurations of ABLC, ABCD, and L-AMB are ribbon-like, disk-like, and unilamellar liposome vesicle, respectively [1, 2]. Beyond these, other lipid systems of amphotericin B have also been developed. Amphotericin B cochleate, amphotericin B incorporated with immunoliposomes or with long circulating liposomes are the major examples of these investigational formulations. Another lipid-based amphotericin B formulation, amphotericin B in lipid emulsion, is a pseudolipid formulation, prepared simply by suspending amphotericin B in commercially available lipid emulsions. The configuration of lipid in this formulation is undefined. It is a non-approved drug formulation and its use is limited to research facilities only [1].

The extent of data concerning several issues, including that about head-to-head comparison of these formulations is limited. Most studies have focused on the comparison of each individual formulation with the parent compound, amphotericin B. The data obtained so far point out the following results of primary importance [1-4]:

1. In vitro antifungal activity of the lipid-based preparations is due to the parent compound, and is thus similar to that of amphotericin B deoxycholate.
2. Similar to the parent compound, lipid formulations are administered intravenously. Aerosolized formulations of ABLC and L-AMB are under investigation.
3. Pharmacokinetic properties vary from one lipid formulation to another. L-AMB achieves higher plasma concentrations and remains in the circulation longer compared to the others.
4. Their spectrum of in vivo activity is similar to that of amphotericin B deoxycholate and covers systemic candidiasis, invasive aspergillosis, cryptococcosis, zygomycosis, fusariosis, endemic (true systemic) mycosis, leishmaniasis, and febrile neutropenia refractory to antibacterial therapy. However, they are not licensed for first-line therapy in any of the fungal infections. Lipid-based formulations are indicated only in case of failure or toxicity with amphotericin B deoxycholate.
5. Lipid-based amphotericin B formulations are at least as effective as the parent compound. They occasionally provide enhanced in vivo efficacy. The real mechanism underlying the enhanced therapeutic index remains unknown. They may achieve high tissue concentrations in the

- reticuloendothelial system and thus provide enhanced delivery to the site of infection.
6. The most striking advantage of these formulations is their significantly reduced nephrotoxicity and enhanced safety compared with amphotericin B deoxycholate.
 7. In general, infusion-related side effects (fever, chills, hypotension, dyspnea) of these preparations are also less serious than those of amphotericin B deoxycholate. However, the rate of these side effects may vary from one formulation to another and may also yield host-based variations. These side effects appear to be more common with ABCD compared to others.
 8. Amphotericin B deoxycholate is used at doses ranging from 0.3 to 1.5 mg/kg (most commonly, 0.6-0.8 mg/kg), and higher doses are not applicable due to serious toxicity. Given their reduced toxicity, lipid-based amphotericin B formulations can safely be used at doses as high as 3-7 mg/kg. The applicability of lipid formulations at higher doses compared with the parent compound may also attribute to enhanced efficacy of these formulations. Of note, the optimum daily or total dose of the lipid formulations has not been determined yet.
 9. Lipid-based amphotericin B formulations are considerably more expensive than amphotericin B deoxycholate. While the cost varies from one formulation to another, it is in general 10 to 20 times higher than amphotericin B deoxycholate per dose.

These results suggest that the development of lipid-based amphotericin B formulations has been a remarkable progress in antifungal therapy. However, and most importantly, the host factors and the status of the immune system are at least as effective as the efficacy of the antifungal formulation in determination of the clinical outcome of a systemic fungal infection.

LIPID-BASED NYSTATIN FORMULATION

Nystatin is a polyene antibiotic active against a broad spectrum of fungi, including various yeasts and moulds. While topical nystatin is in use for treatment of various superficial mycoses, the systemic use of nystatin has been irrelevant due to serious toxic reactions. To provide the systemic use of nystatin by reducing its toxic potential, an intravenous multilamellar liposomal nystatin formulation has been developed. This formulation contains dimyristoyl phosphatidyl choline and dimyristoyl phosphatidyl glycerol in a 7:3 ratio. Liposomal nystatin (Nyotran®, Aronex Pharmaceu.) is in late Phase III clinical trials. The data obtained so far suggest the relevance of the following information for liposomal nystatin [5]:

1. In vitro antifungal activity of liposomal nystatin is due to the parent compound, and is thus in general similar to that of nystatin.
2. Pharmacokinetic properties of a single dose of liposomal nystatin suggest a dose-dependent increase in area under the curve (AUC) at doses below 0.75

- mg/kg and a saturation at doses of ≥ 0.75 mg/kg. A rapid initial clearance from the blood is observed.
3. Liposomal nystatin is efficacious in treatment of candidiasis, aspergillosis and febrile neutropenia unresponsive to antibacterial therapy. Its in vivo efficacy may be superior compared to the parent compound, nystatin, due to the enhanced entrapment of the drug in the reticuloendothelial system and thus increased delivery to the site of infection.
 4. Liposomal nystatin is a safe and well-tolerated formulation. Hypokalemia is the most commonly observed side effect. Nephrotoxicity is dose-dependent and may be observed at doses above 6 mg/kg/day. Infusion-related side effects (fever, chills, dyspnea) are usually mild.
 5. Liposomal nystatin is not licensed yet. The current data suggest that, in case of its approval, liposomal nystatin may be a second- or third-line salvage agent, particularly in candidiasis and aspergillosis unresponsive to the currently available antifungal drugs.

OTHER LIPID-BASED ANTIFUNGAL AGENTS

Liposomal hamycin, liposomal miconazole, and liposomal ketoconazole have also been structured, but remain experimental [1].

REFERENCES

1. Arikan, S. and Rex, J.H. Lipid-based antifungal agents: Current status. **Curr. Pharmaceut. Des.** 7 (2001) 393-415.
2. Arikan, S. and Rex, J.H. New agents for treatment of systemic fungal infections-Current status. **Expert Opin. Emerg. Drugs** 7 (2002) 3-32.
3. Storm, G. and van Etten, E. Biopharmaceutical aspects of lipid formulations of amphotericin B. **Eur. J. Clin. Microbiol. Infect. Dis.** 16 (1997) 64-73.
4. Wasan, K.M. and Lopez-Berestein, G. Diversity of lipid-based polyene formulations and their behavior in biological systems. **Eur. J. Clin. Microbiol. Infect. Dis.** 16 (1997) 81-92.
5. Arikan, S. and Rex, J.H. Nystatin LF. **Curr. Opin. Invest. Drugs** 2 (2001) 488-495.