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Comparison of the efficacy and pharmacology of formulations of amphotericin B used in treatment of leishmaniasis

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Purpose of the Review

Several lipid-based formulations of the anti-fungal and anti-parasitic drug Amphotericin B are now available on the market. The purpose of this review is to assess their efficacy against leishmaniasis in both experimental and clinical settings, and to point out new developments in the formulation of this antibiotic.

Recent Findings

The development of resistance to pentavalent antimony compounds has shifted the emphasis to amphotericin B for the treatment of visceral leishmaniasis in India. Lipid formulations show good efficacy but are expensive. However, the treatment period with lipid formulations is shorter, which reduces hospitalization costs. As a result, in developed countries where these costs are an important proportion of the treatment, lipid formulations are preferred, whereas they remain largely inaccessible in developing countries.

Lipid-associated amphotericin B has been found to be effective for secondary prophylaxis in HIV-positive patients, in studies carried out in European countries bordering the Mediterranean.

Summary

The reduced toxicity of lipid-based formulations of amphotericin B is no longer in doubt. In India, their efficacy against visceral leishmaniasis and shorter treatment periods compared with the conventional formulation with deoxycholate has to be counter-balanced against the very high cost. On the other hand, in developed countries around the Mediterranean, where leishmaniasis occurs mainly in immunocompromised subjects, lipid formulations have become the treatment of choice for visceral disease. On the other hand, the efficacy against cutaneous lesions is variable and in some reports oral miltefosine was active after failure of treatment with amphotericin B.

Key Words: Amphotericin B; HIV; leishmaniasis; lipid formulation; resistance

Abbreviations: AmB – Amphotericin B; GFP – green fluorescent protein; GM-CSF – Granulocyte-monocyte colony stimulating factor; HIV – human immunodeficiency virus.

Introduction

The profile of infection with *Leishmania* species is changing. Although the disease, in the visceral form known as kala azar, is endemic in India where it represents a major public health problem, it is also becoming increasingly prevalent as an opportunistic infection in Western countries, among individuals who are infected with the HIV virus or are immunocompromised for other reasons (1, 2**). In the latter group, cutaneous and mucocutaneous manifestations are often found. This dichotomy is reflected in the literature which has been published recently.

Immunological Factors

The outcome of Leishmaniasis infection is closely linked to the immunological status of the patient. A mechanistic study by Murray (3*) in various mouse strains lacking different components of the immune system demonstrated the importance of functional T cells (either CD8⁺ or CD4⁺) in preventing recrudescence in animals in which 90-95% of the parasites had been eliminated by treatment with amphotericin B (as a conventional formulation). Despite the particular immunomodulatory properties of AmB (4), the authors suggest that these observations can be transposed to other forms of antileishmanial chemotherapy.

Taking into account the importance of immunological status, recent clinical results will be discussed according to whether the patients were immunocompromised or not.

Immunocompetent Patients

Recent studies from India have concentrated on pin-pointing the most effective therapeutic regime in the immuno-competent population suffering from kala-azar. A review by Singh and Sivakumar (2**) shows that with the development of resistance to pentavalent antimony compounds the emphasis has shifted to AmB, as reported by two recent trials (5*, 6). The ability of lipid-based formulations of AmB to reduce the substantial toxicity of the conventional form containing deoxycholate is no longer in doubt (7), but the prohibitive cost of these new formulations, combined with the fact that it is not clear that they are as effective as the conventional formulation in curing visceral leishmaniasis, although higher doses can be given.

This question of conventional versus lipid formulations of AmB was addressed in a recent study by Sundar et al., (8**) on patients from Bihar state, India. Both a liposomal formulation (AmBisome®) and a lipid complex (Abelcet®) were tested. The cure rates were essentially similar and the lipid formulations provoked less infusion-related toxicity; however, their extremely high cost was only partly offset by the reduced hospitalisation necessary – 5 days at 2mg/kg as opposed to 30 days at 1 mg/kg for the conventional formulation. Several recent review articles underline the lack of toxicity and short treatment cycles of lipid formulations of AmB, while commenting on the cost (9-11**, 12-14). In a European situation, when cost is not such a preponderant issue, lipid-associated amphotericin B has become the treatment of choice, for example in Italy (9).

In developed countries, Leishmaniasis in adults is generally linked to an immunocompromised state. However, a few reports have described cases, both visceral and mucocutaneous in immunocompetent individuals (15-18). This emphasizes the importance of

awareness by general practitioners of this disease as a possible diagnosis in patients who travel for work or leisure, and the necessity for new diagnostic tools (see below).

A recent review has covered the neglected subject of treatment of visceral leishmaniasis in pregnancy (19). AmB is recommended as the first choice drug because of lower side-effects. In particular, lipid-associated AmB has been shown to have no adverse effects on the foetus (20).

As far as infantile visceral leishmaniasis is concerned, epidemiological features studied over a 5 year-period in a Brazilian endemic area showed this infection is mainly associated with underprivileged people with a tendency towards urban areas (21). In this region Glucantime is used in 98% of the cases. On the other hand, in the Mediterranean area (Greece, Italy and France) all the long-term studies have revealed that amphotericin B lipid formulations are safe and effective and improve the comfort of patients by reducing hospitalisation without increasing of the overall cost of treatment (22**, 23, 24). In Greece 4 mg/kg/day for 5 days, 4 mg/kg/day on day 1-5 and 9, 5 mg/kg/day for 4 days or 10mg/kg/day for 2 days with liposomal AmB are as effective as pentavalent antimony in all infants and are preferable to antimonate (20 mg/kg/day for 21 days) (22**). In Italy and in France six doses of 3mg/kg of liposomal AmB on days 1-5 and 10 have been the first-line treatments of infantile visceral leishmaniasis for 10 years. A two-day regimen with 10 mg/kg or even 20 mg/kg would have been preferable, although allergic reactions to the infusion forced the patients to be hospitalized for 7 days. These allergic reactions seem to be caused by the lipid. AmB lipid complexes have higher AmB/lipid ratios than AmB liposomes. It therefore might be worthwhile testing AmB lipid complexes at higher doses, to see whether cures can be achieved quickly without allergic reactions.

Immunocompromised Patients

The diagnosis and management of Leishmania/HIV co-infection is a major concern (25). In these immunocompromised patients, visceral disease may relapse as cutaneous manifestations (26). Recent results obtained with lipid-associated AmB in cases of co-infection have been variable.

In India, responses to AmB, in conventional or lipid formulations, as to antimony compounds, have been limited (25). On the other hand, treatment with oral miltefosine was promising. However, a case study (27) reported that AmB was effective in a triple infection with HIV, pulmonary tuberculosis and visceral leishmaniasis.

A case of cutaneous leishmaniasis in an African migrant infected with HIV did not respond to AmB in either the conventional or liposomal form, but was cured by oral miltefosine (28). On the other hand, a patient from Italy who developed cutaneous lesions after an initial visceral disease was cured by liposomal AmB (26). A report from Brazil has also shown the efficacy of lipid formulations of AmB in cutaneous disease (29). An HIV-positive patient was treated with Amphocil™, while another who had undergone a kidney transplant was treated with AmBisome®. The combination of liposomal AmB with GM-CSF to boost the immune system has been found beneficial in one study (30).

Two recent studies have investigated the use of lipid formulations of AmB for secondary prophylaxis in HIV-infected patients. A multicentre study in Spain and Portugal compared treatment with AmB lipid complex (Abelcet®, 3 mg/kg every 3 weeks for 51 weeks) with no

treatment in HIV-positive patients who had previously experienced at least one episode of leishmaniasis but were currently parasite-free. They concluded that the treatment with lipid-associated AmB was effective in preventing recurrence of visceral leishmaniasis and was well tolerated (31**). Another study, from Marseille, France, has investigated the use of liposomal AmB for prevent relapse of visceral leishmaniasis in HIV-infected patients (32). Although the number of evaluable patients was low, they concluded that a successful outcome depended on using a high initial dose (cumulative doses ranging from 60 to 86 mg/kg at day 30), higher than those recommended by the manufacturers, to avoid therapeutic escape.

As referred to above, kidney transplant patients are also at risk of developing leishmaniasis, which poses a diagnostic and therapeutic challenge to the clinician (33). In this category, liposomal AmB was found to be both better tolerated and more effective than AmB lipid complex. Visceral leishmaniasis has also been described as an opportunistic infection in bone-marrow-transplant patients (34) and in connective tissue disease (35).

Drug Resistance

The possibility of developing drug resistance to AmB is discussed by Ouellette et al, (36**) citing in-vitro work by Mbongo et al. (37). For this reason, it is recommended that dogs carrying *Leishmania* parasites in the Mediterranean area should not be treated systematically with AmB (38).

A recent study has looked at the drug sensitivity of Indian kala-azar field isolates in experimental models (mouse macrophages infected in vitro and hamsters, 39*). The sensitivity to pentavalent antimonials was retained after repeated passages in vitro and in vivo, showing that the unresponsive strains showed true resistance. These strains were sensitive to both AmB (used as the conventional formulation) and miltefosine.

New Perspectives

Maesabalide III, an olean triterpene saponin isolated from the Vietnamese plant *Maesa balansae* with antileishmanial activity has been evaluated in vivo against *Leishmania donovani* (MHOM/ET/67/L82)-infected golden hamsters after one single subcutaneous dose as compared with liposomal AmB as a reference (40*). Prophylactic and curative administration at 0.2 mg/kg and 0.8 mg/kg respectively were as efficient as AmBisome in reduction of liver amastigotes burdens. Multiple dose treatments should now be tested to determine whether a better clinical protection can be obtained with this interesting new drug.

In the search for new delivery systems for AmB, hydrophilic albumin microspheres of AmB were also evaluated in *Leishmania infantum* infected hamsters (41, 42). These formulations did not show any signs of toxicity for single injected doses up to 40mg/kg. They led to higher drug levels in spleen and liver as compared with free AmB and a greater reduction of the parasite burdens in these organs at both early and later stages of infection. These new delivery systems would be economical alternative to liposomes for the treatment of visceral leishmaniasis if they demonstrate their efficacy and their tolerance as compared with liposomal amphotericin B.

An article from the same group demonstrates how the physical state of AmB can influence toxicity and activity (43). A formulation which organized AmB as large aggregates (detected by spectrophotometric techniques) was less toxic than AmB complexed with cyclodextrin in a

monomolecular form, which released the drug rapidly. The multi-aggregate form was also slightly more effective against Leishmaniasis than the conventional formulation; however, no comparison was made with lipid formulations.

LicTXNPx, a recombinant protein conserved among different *Leishmania* species, was identified as a possible new marker for diagnosis and for monitoring the efficacy of treatment. In fact the results of a Portuguese study (44) showed that this protein presented the highest immunoreactivity and the evolution of the production of antibodies against *LicTXNPx* followed the evolution of the number of parasites even during the treatment with AmB or antimoniate. It is now necessary to determine whether these results, which were obtained with a group of 36 children, can be extended to a wider population.

Dube et al. (39*) have developed an interesting technique for the in-vitro evaluation of drug sensitivity. *Leishmania* parasites were transfected with the GFP gene. The green fluorescent labelling allowed their survival as amastigotes within mouse macrophages to be monitored easily. In general, the amastigote form of the parasite living within macrophages is considered to be a more relevant disease model for drug screening than the free-living promastigote form.

Conclusion

The use of lipid formulations of AmB to treat leishmaniasis is now more a question of economics than efficacy. There is still room for the development of new formulations which could reduce the cost of treatment. Apart from one report in 2003 (45), there have been no recent studies of formulations which could increase the efficacy of AmB by the oral route, although such a formulation would be a considerable breakthrough in treatment.

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