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AMPHODEPOT®: A NOVEL SINGLE DOSE INTRALESIONAL TREATMENT OF CUTANEOUS LEISHMANIASIS

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Abstract

Intralesional (IL) meglumine antimoniate is the gold standard for the treatment of uncomplicated cutaneous leishmaniasis (CL) in Brazil. However, due to the rapid absorption to the circulation, repeated doses are necessary. Thus, we proposed a new AmB formulation that could be effective with a single IL dose. First, biodegradable polymeric microparticles of PLGA loaded with AmB were designed for both phagocytosis and sustained extracellular drug release. They were effective but the drug load was low (0.7%), mainly due to the amphoterous AmB nature that makes polymeric encapsulation difficult. Here, we proposed to increase the drug loading using a modified emulsion and solvent evaporation method. Microparticles with smooth and spherical surface and average size of 3 µm were synthesized, showing 9 times higher drug load (7% AmB). Such AmB/PLGA formulation was registered as AmphoDepot®. For anti-parasitic activity, *Leishmania amazonensis* promastigotes were cultured with different concentrations (0.01-100 µg/mL) of AmphoDepot® or free AmB for 72 h. Cell viability assayed by resazurin showed that both AmB forms were similarly active (IC_{50} = 0.01 and 0.02 µg/mL, respectively). For cytotoxicity, bone marrow-derived macrophages ($2x10^5$/well) were treated with 1.23 – 300 µg AmB/mL for 48h. AmphoDepot® were less than 6-fold cytotoxic than free AmB (CC_{50} = 4.6 and 0.8 µg/mL, respectively). For in vivo studies, BALB/c mice were infected in the ear with *L. amazonensis* ($2x10^6$), and 21 days later they were given a single dose of 10 µg of AmB in AmphoDepot® or in the free form (Anforicin®). On day 56 of infection, parasites were measured in the ear by limiting dilution assay. AmphoDepot® was able to reduce the parasite load by 86% (without deoxycholate) whereas Anforicin® reduced only 32% in comparison with vehicle alone. In conclusion, AmphoDepot® is the first single-dose formulation of AmB that is safe and may greatly simplify CL treatment.

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