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FREE AND LIPOSOMAL STIBOGLUCONATE: TISSUE LEVELS AND ANTIPARASITIC ACTIVITY IN THE MOUSE

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Pentavalent antimonials such as sodium stibogluconate, are the therapeutic mainstays for visceral leishmaniasis, a Leishmania donovani infection in which the amastigote form of the parasite resides within macrophages of the mononuclear phagocyte system. Vesicular formulations have been used to passively target the drug to the parasitised cells of the liver with up to 700-fold increases in drug efficacy in animals. However the antileishmanial effect of free or liposomal stibogluconate in murine models is influenced by factors such as; the tissue site of infection, the mouse strain used as host and the chronicity of the infection In addition, species differences, between mice and hamsters, are also apparent. These observations, which indicate the complexity of visceral leishmaniasis therapy, raise questions pertinent to the use of a carrier strategy, concerning the tissue distibution of free and liposomal sodium stibogluconate. We have initiated a study, in mice, aimed at correlating the parasite suppression observed with drug distribution at three major sites of infection.

Uninfected and infected BALB/c mice were treated via the tail vein with 0.2 mL volumes of free or liposomal drug preparation. Liposomes were prepared from dipalmitoyl phosphatidylcholine and cholesterol in the ratio 7:3, these components being lyophilised overnight from tert-butyl alcohol and hydrated with 300 mg mL^{-1} sodium stibogluconate solution under a constant stream of nitrogen for two hours at 50 °C. The liposomes were sonicated and free drug removed by dialysis. At various time intervals after drug administration, the animals were killed and impression smears of liver, spleen and bone marrow Giemsa stained to evaluate parasite burdens (no. of amastigotes per 10^3 host cell nuclei). At each of these infection sites, parasite suppression is the drug induced decrease of parasite burden relative to the burden in infected, untreated controls. Drug levels in these and other tissues were determined as antimony by hydride-generation atomic absorption spectrometry (sensitive to ppb Sb) of diluted nitric acid digests of the lyophilised tissues.

In uninfected mice, administration of even high doses of free stibogluconate resulted in transient, albeit high, Sb levels in the liver and much lower levels in spleen and bone marrow. Levels in these three major sites of infection can be ranked : liver> spleen> bone marrow. In infected mice, the dispositon of liposomal sodium stibogluconate was markedly altered compared to free drug, with higher drug levels in all tissues examined except the kidney, where the high Sb levels presumably reflect the rapid renal excretion of the drug. There was some correlation between tissue Sb levels and parasite suppression in that the liposomal formulation gave higher levels and greater suppression than the free drug. However for either formulation, free or liposomal, the correlation between tissue Sb levels and parasite suppression at the three major infection sites, liver, spleen and bone marrow was poor, e.g. higher Sb levels, yet lower suppression, in spleen than in liver.

Figure 1. Tissue Sb levels (1a) in liver (L), spleen (S), femur (F), heart (H) and kidney (K) after iv administration of liposomal and free stibogluconate in the mouse and the associated parasite burdens (1b) at the major sites, liver spleen and bone marrow, of infection.