Failure of Albendazole as an Alternative Treatment of Cutaneous Leishmaniasis in the Hamster Model

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Search for better anti-leishmanial drugs is still imperative, since the current treatment with antimonials is toxic, expensive, and requires prolonged intramuscular administration (EM Netto et al. 1990 Transactions 84: 367). All these features are serious obstacles to compliance in endemically exposed populations.

Evaluation of antiparasitic drugs that are already marketed and used for other infectious diseases should be regarded as a viable, and expeditious alternative to the costly development of new compounds. Albendazole has been shown to inhibit the growth of various protozoal parasites in vitro, and was successfully used for treating immunocompromised individuals infected with microsporidial infections (R Weber et al. 1994 Clin Microbiol Rev 7: 426). Since these organisms are intracellular parasites it was speculated that an aggressive treatment schedule similar to that used in AIDS patients, could also be active against Leishmania, another intracellular protozoan parasite. To explore this possibility we used the golden hamster (Mesocricetus auratus), which has been shown to be an adequate model for studying anti-Leishmania therapy (WL Hanson et al. 1991 J Parasitol 77: 780, BL Travi et al. 1993 Transactions 87: 567).

A subline of MHA inbred hamsters (n=14) was inoculated s.c. in the hindfoot with 1x10⁴ promastigotes of L. (V.) panamensis (MHOM/COL/84/1099). Thirty days postinfection seven hamsters were treated orally with albendazole (Zentel, SmithKline Beecham) (40mg/kg/twice a day) during six weeks, while the remaining seven animals were used as untreated controls. The clinical evolution of the lesion was monitored by measuring the infected and contralateral uninfected foot at weekly intervals until the end of treatment. Para site burden at the lesion site was roughly estimated by microscopy (1,000 X) in Giemsa-stained impression smears. Dissemination to reticuloendothelial tissues was determined by culturing in Senekjie’s medium samples from lymph nodes draining the lesion, distant lymph nodes, spleen and liver.

Although the inflammatory signs of the lesions of treated hamsters were less conspicuous, the parasite burden was similar to that of untreated animals (mean 4.8 vs 6.1 amastigotes/100 cells, respectively). Although cutaneous metastasis was significantly less frequent in the treated group (2.4 vs 17%; P=0.025), no difference in internal amastigote dissemination was found.

This experiment showed that albendazole, even at large doses, had a negligible anti-leishmanial effect in hamsters infected with L. panamensis, as compared with antimonials (Travi et al. 1993 loc. cit.). The low intestinal absorption of the drug could explain in part the treatment failure, although it was postulated that the high and prolonged administration of albendazole should have compensated for this pharmacokinetic drawback. The reason as to why cutaneous metastases in treated animals were significantly reduced is not clear; this phenomenon might have been related to the amelioration of the inflammatory response. It is worth noting that inflammation has already been associated with the expression of metastasis in the hamster model (BL Travi et al. 1996 J Parasitol 82: 454). Also, in an unpublished experiment, we have observed a significant reduction of cutaneous metastases (33.3 vs 7.1%, P< 0.005) in hamsters infected with L. panamensis and subsequently treated with the anti-inflammatory drug indomethacine (Upjohn). Despite the negative results with albendazole, preclinical trials should continue to be carried out whenever additional, less toxic benzimidazoles with higher intestinal absorption, and proven antiprotozoal activity become available.

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