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Novel forms of oral melarsoprol cure CNS stage *Trypanosoma brucei brucei* infection in a murine model of human African trypanosomiasis

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Human African trypanosomiasis (HAT) is a parasitic disease caused by the protozoan parasites *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. Following infection the disease progresses in two stages and without treatment is invariably fatal. Pentamidine and Suramin are effective against early stage *T.b. gambiense* and *T.b. rhodesiense* respectively but once the disease progresses to the CNS stage chemotherapy is mainly dependent on the melaminophenyl arsenical melarsoprol. Melarsoprol therapy is associated with a 5% fatality rate and resistance is now widespread in the field. There is therefore an urgent need for new trypanocides.

Cyclodextrins are naturally occuring cyclic oligosaccharides widely utilised by the pharmaceutical industry for solubilising and stabilising drugs. A variety of melarsoprol-cyclodextrin inclusion were created, of which mel/RAMCD (randomly methylated cyclodextrin) and mel/HPCD (hydroxypropyl-cyclodextin) displayed the highest stability and solubilisation enhancement, indicating these substances as possible candidates for further development. To assess the *in-vivo* activity and toxicity of the compounds female CD-1 mice were infected with *T.b. brucei* GVR35/C1.9. Drugs were administered at 21 days post-infection. At this point parasites are known to be established in the CNS. Mel/HPCD or mel/RAMCD was administered at doses of 0.0125, 0.025, 0.05, 0.1 and 0.2 mmol/kg daily for 7 consecutive days. On completion of chemotherapy blood samples were examined on a weekly basis for the presence of trypanosomes. Animals remaining aparasitaemic after a 60 day observation period were killed, the brain divided and half homogenised in phosphate buffered glucose saline and injected intraperitoneally into normal recipient mice. Recipient mice were then parasitaemically monitored on a weekly basis for a further 60 days. Homogenates failing to establish parasitaemia in the recipient mice were considered to have come from animals following a successful chemotherapy regimen.

Histological examination of liver tissue shows that mel/RAMCD, when administered at a dose equivalent to 0.2 mmol/kg melarsoprol to uninfected mice, induces pathological changes, including cellular infiltration and areas of necrosis. However, mel/HPCD and mel/RAMCD can successfully cure CNS stage trypanosome infection when administered at 0.05 mmol/kg. Mel/HPCD and mel/RAMCD, if proven to be toxologically safe, have great potential as oral therapies for the treatment of human trypanosomiasis, thus eliminating the current problems associated with parenteral administration of melarsoprol.

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