ABSTRACT

Phenyl substitution of furamidine markedly potentiates its anti-parasitic activity against Trypanosoma cruzi and Leishmania amazonensis.

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Furamidine (DB75) and related unfused aromatic diamidines have proven useful for the treatment of parasitic infections. These compounds were primarily developed to combat infections by Pneumocystis carinii and African trypanosomes but they are also active against other parasites. Here we have investigated the in vitro effects of DB75 and its phenyl-substituted analog DB569 on two kinetoplastid haemoflagellates Trypanosomatidae: Trypanosoma cruzi and Leishmania (L) amazonensis. The phenyl-amidine compound DB569 has equivalent DNA binding properties compared to DB75 but it was selected on the basis of its distinct tumor cell distribution properties. We found that DB569 is significantly more potent than DB75 at reducing the proliferation of the parasites, using either isolated parasites in cultures or with cardiomyocyte and macrophage host cells. DB569 is effective towards the intracellular forms of T. cruzi (IC(50) in the low-micromolar range) and it exhibits trypanocidal dose-dependent effects against trypomastigote forms of T. cruzi parasites obtained from the Y strain and Dm28c clone, which belong to two different biodemes. Fluorescence microscopy experiments indicated that both diamidines were mostly localized in the nucleus of the mammalian host cells and within the nuclei and kinetoplast of the parasites. Electron microscopy studies showed that the treatment of the parasites with DB75 and DB569 induces important alterations of the parasite nucleus and kinetoplast, at sites where their DNA target is localized. Altogether, the data suggest that the phenyl-substituted furamidine analogue DB569 is a potential new candidate for the treatment of the Chagas' disease and Leishmaniasis.