REFINING PRECLINICAL EVALUATION IN CHAGAS DISEASE: PROLONGED TREATMENT MODEL FOR FEXINIDAZOLE

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Therapeutic failures observed in clinical studies with drug candidates for Chagas disease highlight the need to refine preclinical evaluation strategies to identify models with greater translational value. Fexinidazole, a candidate with excellent antiparasitic activity and tolerability demonstrated in preclinical models of *T. cruzi* infection, resulted in alarming rates of hepatotoxicity and neutropenia in up to 30% of patients when evaluated for the treatment of chronic Chagas disease. In this context, this study aimed to assess the toxicity profile of fexinidazole and benznidazole (reference drug) in prolonged *in vitro* treatment models. HepG2 cells were incubated for 192 hours in the presence of 0.25mM to 2mM of benznidazole (Bz) and fexinidazole (Fx-sulfone). The culture medium was refreshed every 48 hours, and after 96 and 192 hours of incubation with the drugs, the cells were quantified by flow cytometry. The proliferation of treated and control cells (incubated with DMSO) was measured by calculating the CPD (cumulative population doubling). Results showed that cell proliferation was maintained during the first 96 hours of treatment, although significantly reduced in the presence of Fx-sulfone starting at 1mM and Bz starting at 0.5mM. However, a pronounced reduction (Fx-sulfone at 1mM and Bz at 0.5mM) or complete interruption of proliferation (Fx-sulfone at 2mM and Bz at 1mM and 2mM) was observed at 192 hours. These findings highlight the importance of exploring alternative models for evaluating the cytotoxicity of trypanocidal drugs.

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