Evaluation of the anti-Trypanosoma cruzi activity in vitro of the benznidazole combination with different classes of drugs.

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The chemotherapy drugs currently available for chagas disease, nifurtimox and benznidazole, are unsatisfactory due to toxicity and inadequate efficacy. As the prospects for the introduction of new compounds by the pharmaceutical industry are poor, an alternative strategy involves the identification of candidate drugs among those already available on the market that could be used in combination for a synergistic treatment plan. In order to improve the drug armamentarium against chagas' disease, in the present study we describe the activity of sulfone metabolite of fexinidazole and miltefosine in combination with benznidazole against amastigotes of *t. cruzi* y strain using h9c2 line as host cells. Pre-determined 50% effective concentrations (ed50) values were used to determine the top concentrations of the individual drugs to ensure that ed50 fell near the midpoint of a eight-point twofold dilutions series. Top concentrations used were 20μM for metabolite of fexinidazole and benznidazole and 30 μM for Miltefosine in a 72h assay. Fics and the sum of fics (σfics) were calculated and used to classify the nature of interaction. Interactions were classified as synergistic with mean Σfics of ≤0.5, as antagonistic with mean >4.0, and as indifferent (or additive) with mean Σfics between >0.5 and ≤4.0. The interaction of benznidazole with sulfone metabolite was classified as indifferent, i.e. simple additive effect, based on the mean σfics of 0.6 ±0.19μM at ed50 level and of 0,92 ±0.28 at ed90 level. The interaction of benznidazole with Miltefosine presented mean values of 1.66 ± 1.00 μM at the ed50 level and 1.57 ± 0.77 at the ed90 level. Although synergistic effect would be more desired, the additive effect, also named as indifferent interaction, can be considered a positive outcome, since *in vivo* biological interactions can contribute to favorable combined effect. In this way, the *in vitro* results indicate a potential beneficial effect of the benznidazole/sulfone metabolite and miltefosine combination and justify its evaluation *in vivo* using mice as an experimental model. Supported by Fapemig, DNDi and UFOP.

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