Different dosing protocols for old drugs for treating *Trypanosoma cruzi* infection in mice.

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Nowadays, is growing the studies to search for new regimens for older drugs to treat Chagas disease, such as benznidazole and nifurtimox. This study was designed to evaluate a new reading of the therapeutic regimes for benznidazol and nifurtimox. We used an experimental mouse model of *T. cruzi* infection with Y and Colombian strains (partially and full drug resistant) for the evaluation of the time and concentration dependence of benznidazole and nifurtimox treatments. For time dependence, Y strain infected mice received 1, 3, 7, 10, 20 e 40 doses daily of benznidazol. The 3 to10-days treatments were effective in cleared the parasitemia and suppressing the mortality, but the parasitological cure has not achieved, as parasite or its DNA was detected in blood sample of all mice after the treatment. The extending treatments from 20 to 40 days clearly improve the benznidazole efficacy. The 20-days treatment induced cure in 57.14% of Y strain infection and failure to cure Colombian strain infection, while 40-days treatment was able to cure 100% of Y and 50% of Colombian infected mice. The increased cure rates among *T. cruzi* infected animals that received nifurtimox for 40 days confirm the relationship between the length of treatment and its efficacy. Following we evaluated a range of oral doses of benznidazole (25 to 300mg/kg administered orally or intraperitoneally) to determine the minimal effective dose in curing the experimental infection. Consistently an improvement in the efficacy may be observed with increasing drug concentration. The complete cure was verified only among the animals treated with doses higher that 75mg/kg of bodyweight by oral route, in a ascendant rate: 28.57% (75mg/kg), 57.14% (100mg/kg) and 80% (300mg/kg). Additionally, the influence of the administration route have been demonstrated, being a highest cure index detected among orally, in relation intraperitoneally, treated mice at the same dose. Overall, these data provide evidence that the optimal effect of benznidazole treatment in nonclinical study is dose and time dependent, with the increased treatment period related to highest cure rate in animals infected with Y (a drug partially resistant) and Colombian (a full drug resistant) *T. cruzi* strains.

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