Antihistaminic drugs: antileishmanial activity and cellular alteration in *Leishmania (L.) infantum*

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Leishmaniasis is a complex of antropozoonotic infection disease caused by protozoan parasites *Leishmania* and transmitted by sandflies. It is considered a major public health problem and represents a group of disease with clinical and epidemiological diversity spectrum. Due to restricted therapeutic arsenal, toxicity, poor efficacy, resistance, cost and inconvenience of the treatment regimens there is an urgent need to identify new therapies. Drug repositioning is a therapeutic approach that has shown satisfactory results in the treatment of Leishmaniasis. Recently, our group described for the first time the in vitro and in vivo activity of histamine H1-antagonists against *Leishmania infantum*. In this way, this work aimed to investigate whether the in vitro antileishmanial activity of this therapeutic class would be shared by other antihistaminic drugs and identify the cellular alterations. The drugs fexofenadine (FXF), cetirizine (CTZ), cinarizine (CNZ), cyproheptadine (CPH) and meclizine (MCZ) were incubated with promastigotes of *L. infantum* and the viability was determined by MTT assay. These drugs were also evaluated against intracellular amastigotes by optical microscopy. The mammalian cytotoxicity was determined in NCTC cells by MTT assay. Cellular alterations were assessed using fluorescent probes. CNZ, CPH and MCZ showed activity against promastigotes with 50% inhibitory concentration (IC50) values between 10-28 μM. These drugs were also active against amastigotes with IC50 values between 20-35 μM. CTZ and FXF did not show antileishmanial activity against both *Leishmania* forms. The 50% cytotoxic concentration (CC50) of CPH and CNZ was about 130 μM, similar to the drug miltefosine for clinical use. MCZ, FXF and CTZ showed no cytotoxic activity at the highest tested concentration of 200 μM. The permeability of the plasma membrane was evaluated using SYTOX® Green. Considering the IC99, CNZ and MCZ demonstrated interference in plasma membrane permeability of promastigotes, resulting in 19% and 5% of permeation at 60 min and 25% and 15% at 120 min, respectively, compared to control cells. CPH demonstrated no interference in plasma membrane permeability. The alteration in production of reactive oxygen species was evaluated using H2DCFDA, considering IC50 and IC99, all active drugs showed a discrete reduction in fluorescence signal, but it did not show statistically significant difference. The mitochondrial membrane potential was indicated by the Rhodamine 123. Considering the IC99 value, the drugs cause a significant reduction in the potential, which is a concentration-dependent. CPH caused complete depolarization of mitochondrial membrane potential. CNZ and MCZ also showed reduction in 81% and 59%, respectively. In conclusion, these antihistaminic drugs are effective as in vitro antileishmanial agents and are novel candidates for further experimental studies.