Lidocaine Reduces the Proliferation of *L. (L.) amazonensis* Promastigotes through Induction of Oxidative Stress, Damage to the Parasitic Membrane, and Cell Cycle Arrest

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Abstract

Due to the toxicity and increasing failure rates of conventional treatments for tegumentary leishmaniasis (TL), the search for new therapeutic approaches has been strongly encouraged. In this context, we recently investigated the antiparasitic effect of lidocaine (Lid), a local anesthetic of amide class, on *Leishmania (Leishmania) amazonensis* promastigotes and infected human macrophages. We observed a dose-dependent reduction in promastigote proliferation and in the macrophage infection index following treatment with Lid. Currently, we are exploring the mechanisms underlying the antiproliferative effect of Lid. To this end, L. (L.) amazonensis promastigotes were incubated with 0.625 mg/mL of Lid—the maximum non-cytotoxic concentration for human macrophages—for 24, 48, and 72 hours at 26 °C. After incubation, we assessed parasite viability by optical microscopy, as well as the production of reactive oxygen species (ROS), membrane integrity, and the distribution of promastigotes across cell cycle phases (SubG0/G1, G0/G1, S, and G2/M) using flow cytometry. Our results demonstrated that Lid prevented an increase in the number of viable parasites at all analyzed time points, confirming its antiproliferative effect. Furthermore, treated parasites exhibited a sustained increase in ROS production throughout incubation. We also observed a higher frequency of parasites with compromised membrane integrity at 48 and 72 hours. Finally, cell cycle analysis revealed that most promastigotes remained in the G0/G1 phase, suggesting that Lid blocks cell cycle progression. Thus, we conclude that the antiproliferative effect of Lid results from the induction of oxidative stress in the parasites, leading to reduced viability in part of the parasite population and inhibition of cell division in the remaining ones. These findings are promising and indicate that Lid may represent a potential therapeutic alternative for TL. However, additional studies are necessary to validate its efficacy and safety in *in vivo* models.

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