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Repurposing Memantine: A Novel Therapeutic Strategy for Leishmaniasis

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Abstract

Leishmaniasis is a neglected tropical disease caused by Leishmania spp. Its treatment comprises a limited selection of drugs, often associated with therapeutic failure, high toxicity, elevated costs, and the emergence of resistance. To overcome these challenges, combination therapy and drug repurposing have emerged as promising alternatives. In this context, this study evaluated the efficacy of memantine (MEM), a drug currently used to treat Alzheimer's disease, for drug repurposing as a monotherapy and in combination with reference drugs for leishmaniasis treatment, and its potential immunomodulatory effects. *Leishmania infantum* promastigotes were incubated to varying MEM concentrations for 24 and 72 h, leading to a concentration-dependent inhibition of cell viability. Against intracellular amastigotes, MEM reduced the infection index in a concentration-dependent manner after 72 h, with an IC_{50} of 5.49 µM, while exhibiting no toxicity to macrophages. When combined with miltefosine, MEM demonstrated an additive effect in both evolutionary forms, with a fractional inhibitory concentration index (FICI) of 1.67 and 1.38 for promastigotes and intracellular amastigotes, respectively. In a murine model of visceral leishmaniasis, BALB/c mice were infected with *L. infantum* promastigotes for 7 days and subsequently treated for 5 days with different doses of MEM, meglumine antimoniate, or vehicle control. Two experimental approaches were employed: mice were euthanized either immediately after treatment (short-term) or 18 days later (long-term). MEM reduced liver parasite load by 99.9% in both experimental approaches compared to the control group. Serological toxicity markers showed no significant alterations, suggesting MEM's safety. Additionally, immunological assays revealed its immunomodulatory potential. These results suggest memantine as a promising candidate for drug repurposing in leishmaniasis chemotherapy.

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