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BACKGROUND:

The leishmaniases are a complex of neglected tropical diseases caused by more than 20 Leishmania parasite species, for which available therapeutic arsenal is scarce and unsatisfactory. Pentavalent antimonials (SbV) are currently the first-line pharmacologic therapy for leishmaniasis worldwide, but resistance to these compounds is increasingly reported. Alkyl-lysophospoholipid analogs (ALPs) constitute a family of compounds with antileishmanial activity, and one of its members, miltefosine, has been approved as the first oral treatment for visceral and cutaneous leishmaniasis. However, its clinical use can be challenged by less impressive efficiency in patients infected with some Leishmania species, including L. braziliensis and L. mexicana, and by proneness to develop drug resistance in vitro.

METHODOLOGY/PRINCIPAL FINDINGS:

We found that ALPs ranked edelfosine>perifosine>miltefosine>erucylphosphocholine for their antileishmanial activity and capacity to promote apoptosis-like parasitic cell death in promastigote and amastigote forms of distinct Leishmania spp., as assessed by proliferation and flow cytometry assays. Effective antileishmanial ALP concentrations were dependent on both the parasite species and their development stage. Edelfosine accumulated in and killed intracellular Leishmania parasites within macrophages. In vivo antileishmanial activity was demonstrated following oral treatment with edelfosine of mice and hamsters infected with L. major, L. panamensis or L. braziliensis, without any significant side-effect. Edelfosine also killed SbV-resistant Leishmania parasites in in vitro and in vivo assays, and required longer incubation times than miltefosine to generate drug resistance.

CONCLUSIONS/SIGNIFICANCE:

Our data reveal that edelfosine is the most potent ALP in killing different Leishmania spp., and it is less prone to lead to drug resistance development than miltefosine. Edelfosine is effective in killing Leishmania in culture and within macrophages, as well as in animal models infected with different Leishmania spp. and SbV-resistant parasites. Our results indicate that edelfosine is a promising orally administered antileishmanial drug for clinical evaluation.