Inherent paromomycin susceptibility and induction of resistance of SSG-sensitive and SSG-resistant Nepalese Leishmania donovani strains

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An understanding of how drug resistance occurs may allow development of novel treatments where parasite insensitivity could be reversed by co-treating with an inhibitor of the drug resistance mediator. This understanding may also allow monitoring of field isolates, so that drug use could be managed more effectively in the clinic, resulting in an extension of their clinical life. Resistance to antimonial drugs is reducing the number of clinical options for the treatment of leishmaniasis, and paromomycin (PMM) is one of the alternative drugs that could be used. In this study, the effect of exposure of promastigotes to increasing concentrations of PMM on the induction of PMM resistance was determined on strains showing different sodium stibogluconate (SSG) susceptibilities, in order to determine if the background of SSG susceptibility could influence the development of PMM resistance. Three Nepalese Leishmania donovani strains (BPK 282/0 cl4: SSG-sensitive; BPK 087/0 cl11: SSG-intermediate resistant and BPK 275/0 cl18: SSG-resistant) were exposed to increasing concentrations of PMM in a stepwise manner. Twenty six weeks were required to build up resistance up to 97μM of PMM. Adopting a high throughput in vitro assay to select for PMM resistance, SSG-S promastigotes were the least susceptible to PMM (IC50 = 661μM) whereas SSG-I and SSG-R promastigotes showed similar sensitivities to PMM (IC50 between 49 and 58μM). Preliminary studies using the intracellular amastigote stage indicate a similar PPM resistance profile with SSG-S strain being less susceptible to PMM (IC50 = 174μM) compared to the SSG-I and SSG-R strains (IC50 between 65 and 69μM).