Anthelminthic activity of glibenclamide against experimental cystic echinococcosis

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Abstract (300 word limit)

Statement of the Problem: Cystic echinococcosis is a worldwide parasitic zoonosis caused by the larval stage of *Echinococcus granulosus*. Current chemotherapy against this disease is based on benzimidazoles (BZMs). However, BZM treatment results in a low cure rate and causes side effects. Therefore, new treatment options are needed. The antidiabetic drug glibenclamide (Glb) is a second-generation sulfonylurea receptor inhibitor that has been shown to be active against protozoan parasites. The purpose of this study is to investigate the *in vitro* and *in vivo* pharmacological effects of Glb against the larval stage of *E. granulosus*. Methodology & Theoretical Orientation: Viable protoscoleces and metacestodes were cultured *in vitro* with different concentrations of Glb and/or ABZSO and mortality was calculated daily. Subsequently, *E. granulosus*-infected mice were orally treated with Glb and/or ABZ daily for 60 days. The hydatid cysts collected from the animals were weighed and analyzed by SEM. Findings: The *in vitro* Glb activity on both protoscoleces and metacestodes was dependent on the concentration. In addition, the combination of Glb and ABZSO had a greater effect on metacestodes than each drug alone. Likewise, a reduction of the cyst weight was also found after administration of Glb to infected mice. However, Glb + ABZ combined treatment not shown to be more effective than Glb monotherapy. Our results also demonstrated mitochondrial membrane depolarization and increase of Ca^{+2} intracellular levels in Glb-treated protoscoleces. Moreover, the intracystic drug accumulation, the competition of Glb for 1-NPN binding site in protoscoleces, and the bioinformatic analysis using the available *E. granulosus* genome, suggest the presence of genes encoding receptor and transporters of sulfonylureas in the parasite. Conclusion & Significance: Glb shows anthelmintic effect on *E. granulosus* larval stage. Further studies are needed to fully investigate the mechanism involved in the therapeutic response of the parasite to this sulfonylurea.

Image

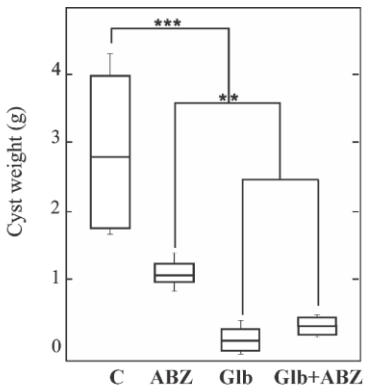


Fig 1. Therapeutic efficacy study in *E. granulosus* infected mice. (A) Box plots showing the comparative distribution of the weight (g) of cysts recovered from untreated mice (C) and treated with albendazole (ABZ, 5 mg/kg/d), glibenclamide (Glb, 5 mg/kg/d) and the combination of both drugs (Glb+ABZ) for 60 days. The weight of cysts was significantly decreased upon all treatments compared with the control (***$p < 0.05$), but the decrease was more prominent in the groups receiving Glb alone or the combined treatment than that with ABZ alone (**$p < 0.05$).

Recent Publications (minimum 5)

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2. Koh GC, Weehuizen TA, Breitbach K, Krause K, de Jong HK, Kager LM, *et al.* Glyburide reduces bacterial dissemination in a mouse model of melioidosis. PLoS Negl Trop Dis. 2013;7(10): e2500.
3. Loos JA, Dávila VA, Rodriguez Rodrigues C, Petrigh R, Zoppi JA, Crocenzi FA, et al. Metformin exhibits preventive and therapeutic efficacy against experimental cystic echinococcosis. PLoS Negl Trop Dis. 2017;11(2): e0005370.
4. Serrano-Martín X, Payares G, Mendoza-León A. Glibenclamide, a blocker of K^+ ATP channels, shows antileishmanial activity in experimental murine cutaneous leishmaniasis. Antimicrob Agents Chemother. 2006;50(12): 4214-4216.
5. Wojtovich AP, Burwell LS, Sherman TA, Nehrke KW, Brookes PS. The C. *elegans* mitochondrial K^+ ATP channel: a potential target for preconditioning. Biochem Biophys Res Commun. 2008;376(3): 625-628.



Biography (150 word limit)

Julia A Loos has a PhD in Biological Science (National University of Mar del Plata, 2017) and she is currently working as a postdoc under the direction of Prof. Dr. Andrea Cumino. She has been serving as assistant teacher for subjects such as Histology, General Microbiology and Farmacology, that are part of the Biology, Biochemistry and Medicine courses of study. She participates in several research projects on Parasitology and has published original articles. Currently, her research is focused on the study of intermediary metabolism and energy control in the larval stage of Echinococcus spp.

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