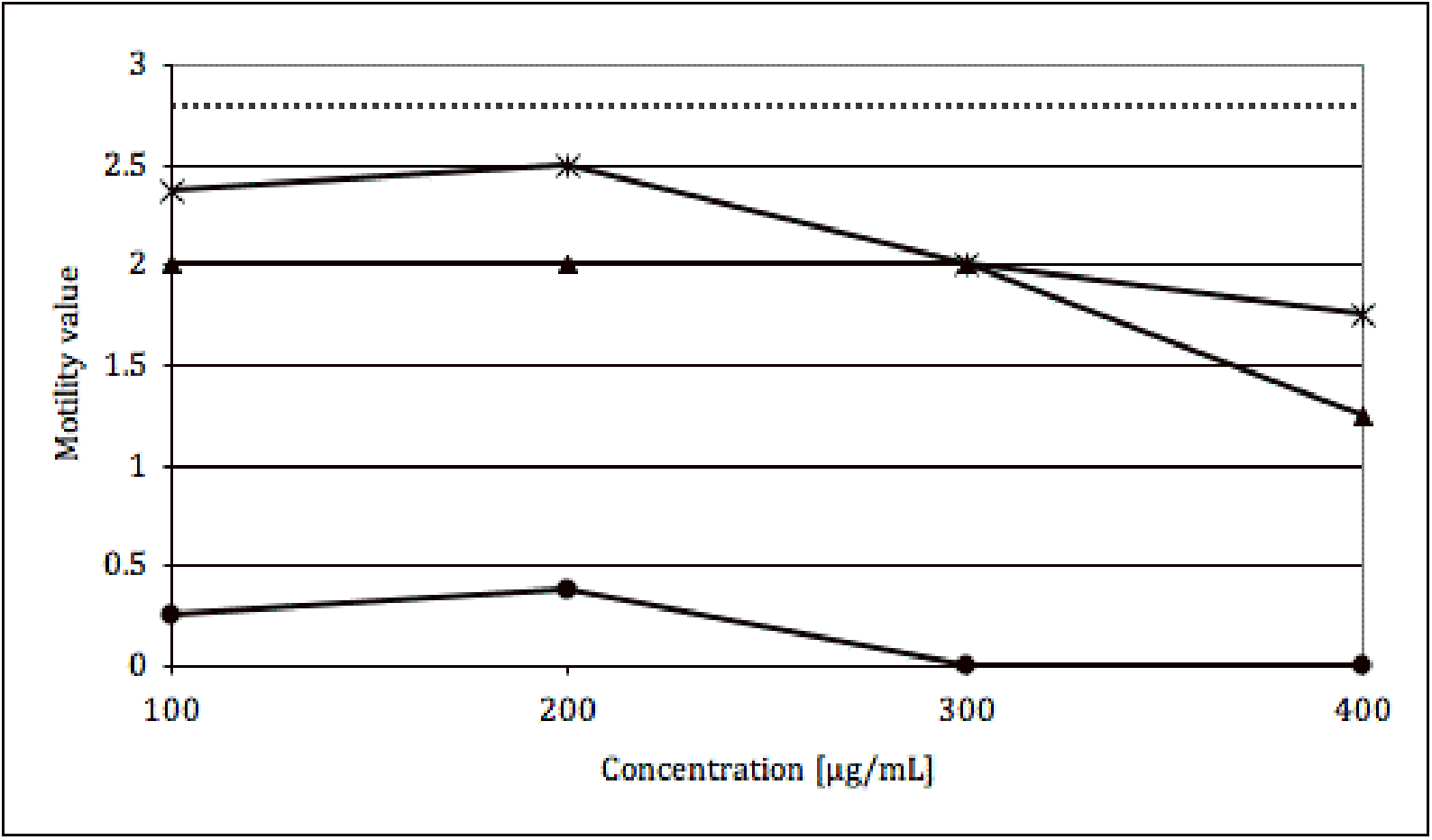
Activity of Praziquantel Enantiomers and Main Metabolites Against Schistosoma mansoni

Meister, Isabel; Ingram-Sieber, Katrin; Cowan, Noemi; Todd, Matthew H; Robertson, Murray N; Meli, Claudia; Patra, Malay; Gasser, Gilles; Keiser, Jennifer

Abstract: A racemic mixture of R and S enantiomers of praziquantel (PZQ) is currently the treatment of choice for schistosomiasis. Though the S enantiomer and the metabolites are presumed to contribute only a little to the activity of the drug, in-depth side-by-side studies are lacking. The aim of this study was to investigate the in vitro activities of PZQ and its main metabolites, namely, R- and S-cis- and R- and S-trans-4'-hydroxypraziquantel, against adult worms and newly transformed schistosomula (NTS). Additionally, we explored the in vivo activity and hepatic shift (i.e., the migration of the worms to the liver) produced by each PZQ enantiomer in mice. Fifty percent inhibitory concentrations of R-PZQ, S-PZQ, and R-trans- and R-cis-4'-hydroxypraziquantel of 0.02, 5.85, 4.08, and 2.42 g/ml, respectively, for adult S. mansoni were determined in vitro. S-trans- and S-cis-4'-hydroxypraziquantel were not active at 100 g/ml. These results are consistent with microcalorimetry data and studies with NTS. In vivo, single 400-mg/kg oral doses of R-PZQ and S-PZQ achieved worm burden reductions of 100 and 19%, respectively. Moreover, worms treated in vivo with S-PZQ displayed an only transient hepatic shift and returned to the mesenteric veins within 24 h. Our data confirm that R-PZQ is the main effector molecule, while S-PZQ and the metabolites do not play a significant role in the antischistosomal properties of PZQ.

DOI: https://doi.org/10.1128/AAC.02741-14


3
2.5
2
1.5
1
0.5
0
Motility value
100
200
300
400
Concentration [µg/mL]