Physiologically-based pharmacokinetic (PBPK) model to describe the disposition of pyronaridine

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Objectives: Pyronaridine has long been used for the treatment of malaria. Currently, the potential utility of pyronaridine against Ebola and Chagas disease is being investigated which has led to the need for better understanding of its pharmacokinetics. The objective of this study was to develop a PBPK model capable of describing the disposition of pyronaridine in rats.

Methods: Pharmacokinetic data was extracted from the literature \cite{1} using WebPlotDigitizer \cite{2}. Sprague-Dawley rats were administered a single oral dose of \textsuperscript{14}C-pyronaridine tetraphosphate (10mg/kg) and sacrificed at 1, 4, 8, 24, 48, 96, 144, 192, and 240h for quantification in whole blood, plasma, lungs, heart, kidneys, liver, spleen, stomach, small intestine, large intestine, urine, and feces \cite{1}. Model development was conducted using a pooled approach with maximum likelihood estimation using ADAPT5 \cite{3}. Physiological parameters were obtained from Brown et al. \cite{4}.

Results: Based on model discrimination, a gastrointestinal tract (GIT) compartment combining the stomach, small intestine, and large intestine resulted in improved model fits and estimates. The final PBPK model (Figure 1) described the concentration-time profiles of \textsuperscript{14}C-pyronaridine in whole blood, plasma, lungs, heart, kidneys, liver, spleen, and GIT and its excretion into urine and feces well. Pyronaridine highly distributes into tissues; tissue-to-blood partition coefficient estimates were 141.1, 31.7, 206.6, 255.7, 577.4, and 205.8, respectively (<4\%SE). The blood-to-plasma partition coefficient estimate was 1.36 (3.1\%SE). CL\textsubscript{ur} and CL\textsubscript{fe} estimates were 73.4 (2.5\%SE) and 4.1 mL/h (2.6\%SE). Metabolism was assumed to be negligible \cite{5}.

Conclusions: The developed PBPK model captures the disposition of pyronaridine in rats. The model will be used to assist in the design of future animal experiments evaluating the PK/PD of pyronaridine for the treatment of Ebola and Chagas disease.

References:
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