Assessing Dose-Exposure-Response Relationships of Miltefosine in Adults and Children Using Physiologically-Based Pharmacokinetic Modeling Approach

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Objectives: Miltefosine is the first and only oral medication to be successfully utilized as an antileishmanial agent. However, the drug is associated with differences in exposure patterns and cure rates among different population groups e.g. ethnicity and age (i.e., children v adults) in clinical trials. In this work, mechanistic population-based PBPK models have been developed to study the dose-exposure-response relationship of miltefosine in *in silico* clinical trials and evaluate the differences in population groups, particularly children and adults.
Methods: The Simcyp population pharmacokinetics platform was employed to predict miltefosine exposure in plasma and peripheral blood mononuclear cells (PBMCs) in a virtual population under different dosing regimens. The cure rate of a simulation was based on the percentage of number of the individual virtual subjects with $AUC_{d0\text{-}28}$> 535 µg·day/mL in the virtual population.
Results: It is shown that both adult and paediatric PBPK models of miltefosine can be developed to predict the PK data of the clinical trials accurately. There was no significant difference in the predicted dose-exposure-response of the miltefosine treatment for different simulated ethnicities under the same dose regime and the dose-selection strategies determined the clinical outcome of the miltefosine treatment. A lower cure rate of the miltefosine treatment in paediatrics was predicted because a lower exposure of miltefosine was simulated in virtual paediatric in comparison with adult virtual populations when they received the same dose of the treatment.
Conclusions: The mechanistic PBPK model suggested that the higher fraction of unbound miltefosine in plasma was responsible for a higher probability of failure in paediatrics because of the difference in the distribution of plasma proteins between adults and paediatrics. The developed PBPK models could be used to determine an optimal miltefosine dose regime in future clinical trials.

Disclosure:
We thank the Engineering and Physical Sciences Research Council for funding through the GCRF scheme (EP/T020490/1). The authors also acknowledge Certara UK limited, for providing a free academic license of the Simcyp population-based simulator and support to conduct the PBPK model development.