Prediction of Miltefosine Exposure in Mouse Model using Physiologically Based Pharmacokinetic Modelling (PBPK) Approach

Shadrack Joel Madu and Mingzhong Li

School of Pharmacy, De Montfort University, Leicester, UK

Leishmaniasis is an abandoned tropical/subtropical illness caused by the protozoan Leishmania parasites transmitted during blood meal by infected female Phlebotomus specie (sandflies) or to a lesser extent through accidental contact with infected human blood [1]. There are three main forms of the disease: cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (ML), and visceral leishmaniasis (VL). Among them, VL is the most severe form with higher chances of fatality without proper medical intervention. The available treatments for VL are limited, toxic, and expensive. Miltefosine is the first and only oral medication to be successfully utilised as antileishmanial agent and is found to be effective. However, administration of miltefosine is associated with many side effects, including gastrointestinal manifestations, hepatotoxicity and nephrotoxicity which requires monitoring thereby increasing the cost of therapy [2]. Miltefosine is also associated with high chances to develop resistance as a result of its long half-life of approximately seven days [3] .

Drug combinations have proved to be a successful strategy to shorten the course of therapy, reduce toxicities through lower dosage and reduce the selection of resistant mutations for several infectious diseases, most notably malaria and tuberculosis. Similarly miltefosine combination therapies, such as fluconazole and miltefosine [4], AmBisome and miltefosine [5], and ketoconazole and miltefosine [6], have demonstrated to have potential in delaying the development of resistance and shortening the duration of treatment for improving compliance and reducing cost. However, in order to develop an optimal miltefosine combination therapy and dosing regimens, extensive preclinical in vitro and animal tests must be conducted to show its efficacy, safety and benefits, which are expensive and time consuming.

Physiologically based pharmacokinetic (PBPK) modelling is widely used within the pharmaceutical industry to predict oral drug absorption [7]. It can be used to predict the plasma concentration–time profiles from preclinical in vitro and in vivo data, providing a valuable resource to support decisions at various stages of the drug development process. The aim of this work was to develop a PBPK model to predict the plasma concentrations of miltefosine under different dosing regimens in mice. Simcyp (Mouse Simulator Version 20) was employed in the work. As the first step of the model development, simulations of the oral mouse plasma concentration−time profiles of miltefosine were performed based on the relevant physicochemical, physiological, and pharmacokinetic input data of the drug which have been taken from the literature [8-12]. The PBPK model simulations were then compared to the in vivo plasma concentration−time profiles of miltefosine from animal experiments, which provided a means to refine the model parameters through the parameter sensitivity analysis and parameter fittings and to verify the PBPK model's predictive ability of the in vivo performance. Finally, the model validation was conducted using experimental data reported in the literature [10], indicating that the developed PBPK model can accurately predict the concentration-time profiles of miltefosine in mice following different single/multiple dose administration.

Disclosure:

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References:

1. Tiuman, T.S., et al., *Recent advances in leishmaniasis treatment.* International Journal of Infectious Diseases, 2011. **15**(8): p. e525-e532.
2. Alves, F., et al., *Recent Development of Visceral Leishmaniasis Treatments: Successes, Pitfalls, and Perspectives.* Clinical Microbiology Reviews, 2018. **31**(4): p. e00048-18.
3. Croft, S.L. and P. Olliaro, *Leishmaniasis chemotherapy—challenges and opportunities.* Clinical Microbiology and Infection, 2011. **17**(10): p. 1478-1483.
4. Shakya, N., S.A. Sane, and S. Gupta, *Antileishmanial efficacy of fluconazole and miltefosine in combination with an immunomodulator—picroliv.* Parasitology Research, 2011. **108**(4): p. 793-800.
5. Wasunna, M., et al., *Efficacy and Safety of AmBisome in Combination with Sodium Stibogluconate or Miltefosine and Miltefosine Monotherapy for African Visceral Leishmaniasis: Phase II Randomized Trial.* PLoS Negl Trop Dis, 2016. **10**(9): p. e0004880.
6. Shakya, N., et al., *Improved treatment of visceral leishmaniasis (kala-azar) by using combination of ketoconazole, miltefosine with an immunomodulator—Picroliv.* Acta Tropica, 2011. **119**(2): p. 188-193.
7. Jamei, M., et al., *Population-based mechanistic prediction of oral drug absorption.* The AAPS journal, 2009. **11**(2): p. 225-237.
8. Dorlo, T.P.C., et al., *Characterization and identification of suspected counterfeit miltefosine capsules.* Analyst, 2012. **137**(5): p. 1265-1274.
9. Alonso, L. and A. Alonso, *Hemolytic potential of miltefosine is dependent on cell concentration: Implications for in vitro cell cytotoxicity assays and pharmacokinetic data.* Biochimica et Biophysica Acta (BBA) - Biomembranes, 2016. **1858**(6): p. 1160-1164.
10. Voak, A.A., et al., *Pharmacokinetic / pharmacodynamic relationships of liposomal amphotericin B and miltefosine in experimental visceral leishmaniasis.* PLOS Neglected Tropical Diseases, 2021. **15**(3): p. e0009013.
11. Ménez, C., et al., *Intestinal absorption of miltefosine: contribution of passive paracellular transport.* Pharm Res, 2007. **24**(3): p. 546-54.
12. Jiménez-Antón, M.D., et al., *Pharmacokinetics and disposition of miltefosine in healthy mice and hamsters experimentally infected with Leishmania infantum.* European Journal of Pharmaceutical Sciences, 2018. **121**: p. 281-286.