On the Stereoselective Pharmacokinetics of Eflornithine and Prediction of Drug Tissue to Plasma Concentration Ratios

Akademisk avhandling
som för grundläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras i Konferenscentrum Wallenberg, Lyktan, Medicinaregatan 20A, Göteborg,
torsdagen den 8 oktober kl. 09:00

av Rasmus Jansson Löfmark

Fakultetsopponent: Professor Geoffrey T. Tucker
University of Sheffield, Storbritannien

The thesis is based on the following papers:

I. **Jansson R**., Bredberg U., Ashton M. Prediction of drug tissue to plasma concentration ratios using a measured volume of distribution in combination with lipophilicity. *Journal of Pharmaceutical Sciences*, 2008 Jun;97(6):2324-39

II. **Jansson R**., Malm M., Roth C., Ashton M. Enantioselective and nonlinear intestinal absorption of eflornithine in the rat. *Antimicrobial Agents and Chemotherapy,* 2008 Aug;52 (8):2842-8.

III. **Jansson-Löfmark R**., Römsing S., Albers E., Ashton M. Determination of eflornithine enantiomers in plasma, by precolumn derivatization with o-phtaladehyde-N-acetyl-L-cysteine and liquid chromatography with UV-detection. *Submitted*

IV. **Jansson-Löfmark R**., Johansson C-C., Hubatsch I., Artursson P., Ashton M. Investigations of the enantioselective absorption and pharmacokinetics of eflornithine in the rat and bidirectional permeabilities in Caco-2 cells. *In manuscript*

V. **Jansson-Löfmark R**., Björkman S., Na-Bangchang K., Doua F., Ashton M. Enantiospecific reassessment of the pharmacokinetics and pharmacodynamics of oral eflornithine against late-stage *T.b. gambiense* sleeping sickness. *In manuscript*

UNIVERSITY OF GOTHENBURG

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Abstract:

Eflornithine is one of two registered drugs for the treatment of late-stage human African trypanosomiasis, a uniformly fatal neglected disease with sixty million people are at risk of being infected. Eflornithine is efficacious but the cumbersome intravenous administration leaves numerous patients untreated. A simplified mode of administration, preferably oral, would enable more patients having access to treatment. The trypanostatic agent eflornithine is administered as a racemate where the L – form has a several-fold greater *in vitro* potency compared to the D – enantiomer. Despite the difference in potency of the enantiomers, the stereoselective pharmacokinetics of eflornithine has not been considered.

This thesis aimed to study L – and D – eflornithine pharmacokinetics in the rat, in Caco-2 cells and in late-stage human African trypanosomiasis patients. A secondary aim was also to develop a general method for predicting drug tissue to plasma concentration ratios.

In the rat, eflornithine displayed stereoselective absorption where the more potent L – form had an approximately 50% lower fraction absorbed compared to D – eflornithine. The stereoselective mechanism was not detected in the present Caco-2 cell assay. Late-stage HAT patients, treated with racemic oral eflornithine, had an approximate 50% lower exposure of L – compared to D – eflornithine, similar to those in rat. The findings suggested that previous attempts to develop an oral eflornithine dosage regimen have failed due to unfavorable stereoselective absorption. High plasma exposure for both L – and D – eflornithine were significantly correlated to the probability of being cured.

For the secondary aim of this thesis, the novel method to predict drug tissue distribution, based on a measured volume of distribution in combination with drug lipophilicity performed reasonably well. Predicted drug tissue to plasma concentration ratios agreed reasonably well with experimentally determined values with 85% being within a factor of ±3 to experimental values (n=148).

In conclusion, this thesis present the stereoselective pharmacokinetics of eflornithine that can give information on whether a much needed oral eflornithine can be developed or not. In addition, the thesis also presents a general method to predict drug tissue to plasma concentration ratios.

Keywords: Human African trypanosomiasis, HAT, pharmacokinetics, NONMEM, stereoselectivity, eflornithine, tissue distribution

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