Characterisation and semi-mechanistic modelling of eflornithine pharmacokinetics and evaluation of prodrugs in oral treatment against late-stage human African trypanosomiasis

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademien vid Göteborgs universitet kommer att offentligen försvaras i hörsal Ivan Östholm, Medicinaregatan 13, Göteborg, fredagen den 14 juni 2013 kl. 09.00

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Avhandlingen baseras på följande delarbeten:


V. Johansson CC, Äbelö A, Jansson-Löfmark R, A retrospective time-to-event analysis of three eflornithine based treatments to evaluate effectiveness of oral eflornithine for treatment of late-stage T.b. gambiense infection. (In manuscript)

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Characterisation and semi-mechanistic modelling of eflornithine pharmacokinetics and evaluation of prodrugs in oral treatment against late-stage human African trypanosomiasis

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ABSTRACT

The present thesis explores the hypothesis that treatment of human African trypanosomiasis can be improved by characterising the enantioselective pharmacokinetics of eflornithine, and investigating the oral eflornithine absorption. Eflornithine pharmacokinetics after oral single dose or intravenous administration in the rat was well described by a three-compartment model with saturable distribution to one peripheral, binding, compartment. Enantiospecific oral bioavailability was estimated at 32 and 59% for L- and D-eflornithine, respectively. Although eflornithine enantiomers display similar rates of absorption their extents of absorption differed. This may be caused by a chemical complex in the gut rendering less L-eflornithine available for absorption. In an attempt to improve oral bioavailability, prodrug candidates were synthesised and administered orally to the rat. The candidates were found to be metabolically too stable and did not deliver eflornithine in vivo. Furthermore, in vitro permeability, potency and metabolic stability for the prodrugs were investigated. The pharmacodynamics in man was mathematically modelled in a time-to-event approach and three different eflornithine based treatments were compared. The three-fold difference in potency between oral and intravenous eflornithine monotherapy may suggest that it is mainly the L-eflornithine enantiomer that elicits the anti-trypanosomal effect, since the oral bioavailability for the L-enantiomer is reported to be about 30% in vivo. Further investigation into the separate eflornithine enantiomers is motivated since the potency differs and combination with nifurtimox further improves efficacy which could enable an oral eflornithine based dosage regimen.

Keywords: Eflornithine, enantioselective, absorption, pharmacokinetics, prodrug, time-to-event