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 Akademin vid Göteborgs universitet
kommer att offentligen försvaras i hörsal Ivan Östholm, Medicinaregatan 13, Göteborg,
fredagen den 14 juni 2013 kl. 09.00

Av
Carl Johansson

Fakultetsopponent:
Professor Meindert Danhof
Universiteit Leiden, Leiden, Nederländerna

Avhandlingen baseras på följande delarbeten:

I. Cloete TT, **Johansson CC**, N'Da DD, Vodnala SK, Rottenberg ME, Breytenbach JC, Ashton M. Mono-, di- and trisubstituted derivatives of eflornithine: synthesis for *in vivo* delivery of DL-alpha-difluoromethylornithine in plasma. *Arzneimittelforschung*. 2011;61(5):317-25.

II. **Johansson CC**, Cloete TT, N'Da DD, Breytenbach JC, Svensson R, Jansson-Löfmark R, Ashton M. *In vitro* and *In vivo* Pharmacokinetic Evaluation of Eflornithine Based Prodrugs for Oral Treatment of Human African Trypanosomiasis. (*Submitted*)

III. **Johansson CC**, Gennemark P, Artursson P, Äbelö A, Ashton M, Jansson-Löfmark R. Population pharmacokinetic modeling and deconvolution of enantioselective absorption of eflornithine in the rat. *Journal of pharmacokinetics and pharmacodynamics* 2013;40(1):117–128

IV. **Johansson CC**, Ashton M, Jansson-Löfmark R, Äbelö A. Eflornithine elicits stereoselective extent of absorption: simultaneous population modeling of IV and oral pharmacokinetics in the rat and permeability in a modified Ussing chamber. (*Submitted*)

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*)

GÖTEBORGS UNIVERSITET
SAHLGRENSKA AKADEMIN

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

Carl Johansson

Department of Pharmacology, Institute of Neuroscience and Physiology
at the Sahlgrenska Academy, University of Gothenburg, Sweden 2013

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
ISBN: 978-91-628-8625-7