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ORAL EFLORNITHINE TREATMENT OF LATE-STAGE HUMAN AFRICAN TRYPANOSOMIASIS

Akademisk avhandling

Som för avläggande av farmacie doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i sal Europa, Konferenscentrum Wallenberg, Medicinaregatan 20A, den 16 december, klockan 13:00

av Mikael Boberg

Fakultetsopponent:
Professor Charlotte Kloft
Freie Universität Berlin, Tyskland

Avhandlingen baseras på följande delarbeten:

I. **Boberg M**, Jonson AC, Leek H, Jansson-Löfmark R, Ashton M. Chiral chromatographic isolation on milligram scale of the human African trypanosomiasis treatment D- and L-eflornithine. *ACS Omega*, 2020; 5(37): 23885-91

II. **Boberg M**, Cal M, Kaiser M, Jansson-Löfmark R, Mäser P, Ashton M. Enantiospecific antitrypanosomal *in vitro* activity of eflornithine. *PLoS Neglected Tropical Diseases*, 2021; 15(7): e0009583

III. Amilon C*, **Boberg M***, Tärning J, Äbelö A, Ashton M, Jansson-Löfmark R. Population pharmacodynamic modeling of eflornithine-based treatments against late-stage *gambiense* human African trypanosomiasis and efficacy predictions of L-eflornithine-based therapy. *AAPS J*. 2022; 24(3): 48
* Authors contributed equally

IV. **Boberg M**, Akhondipour Salehabad Y, Oladetoun-Ageh E, Vallöf D, Jansson-Löfmark R, Ashton M. Enantiospecific pharmacokinetics after enantiopure and racemic dosing of eflornithine in the rat. *In manuscript*

V. **Boberg M**, Jansson-Löfmark R, Na-Bangchang K, Ashton M. Pharmacokinetics of racemic eflornithine in human plasma and cerebrospinal fluid: Clinical perspectives for L-eflornithine against human African trypanosomiasis. *In manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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ORAL EFLORNITHINE TREATMENT OF LATE-STAGE HUMAN AFRICAN TRYPANOSOMIASIS

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Abstract

Human African trypanosomiasis is a fatal disease unless treated. It is a parasitic vector borne disease endemic in sub-Saharan African countries. Eflornithine is a recommended treatment for *gambiense* human African trypanosomiasis (g-HAT) in the later disease stage when the parasites have infected the central nervous system. Eflornithine is currently dosed as a racemic mixture of D- and L-eflornithine via repeated intravenous infusions, which comes with several disadvantages. The work in this thesis aimed to assess the feasibility of an oral eflornithine treatment. A chiral liquid chromatography method was developed for separation and preparation of the D- and L-eflornithine enantiomers from the racemic mixture. The acquired enantiopure material was used to determine that L-eflornithine had higher antiparasitic *in vitro* potency compared to D-eflornithine. The *in vitro* findings were used with a mathematical modeling approach to predict survival in late-stage g-HAT patients treated with L-eflornithine using pharmacodynamic time-to-event modeling. The *in vivo* pharmacokinetics in the rat after oral or intravenous doses of enantiopure L-eflornithine was characterized using nonlinear mixed effects modeling and compared to the racemic mixture. Moreover, the distribution of D- and L-eflornithine to the third brain ventricle from the systemic circulation was examined using *in vivo* microdialysis. Clinical pharmacokinetics in plasma and cerebrospinal fluid for L-eflornithine was modeled using literature data. The pharmacokinetic model was used to predict drug exposure and estimate the probability of target attainment for oral L-eflornithine-based treatments against late-stage g-HAT. L-eflornithine administered as monotherapy dosed at 750 mg/kg/day four or twelve times daily could serve as efficacious regimens. In combination with nifurtimox, dose regimens of L-eflornithine at 375 mg/kg/day dosed two, four or twelve times daily could be efficacious. These results are based on *in vitro* and preclinical *in vivo* data as well as clinical data using a translational modeling and simulation approach. Future clinical pharmacokinetic studies are warranted to assess the feasibility of an oral L-eflornithine-based treatment and to establish optimal treatment strategies against late-stage g-HAT.

Keywords: Sleeping Sickness; Neglected Tropical Diseases; Enantiomers; Nonlinear Mixed Effects Modeling; Pharmacokinetics; Pharmacodynamics

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