Pharmacokinetics of artemisinin derivatives in rats, healthy volunteers and patients.

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet, Göteborg kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg

Fredagen den 25 september 2015, kl. 09.00

Av
Sofia Birgersson

Fakultetsopponent:

Professor Kevin Batty,

Head of School of Pharmacy, Curtain University,
Perth, Australia

Avhandlingen baseras på följande delarbeten:

I. **Sofia Birgersson**, Therese Ericsson, Antje Blank, Cornelia von Hagens, Michael Ashton, & Kurt-Jürgen Hoffmann. A high-throughput LC–MS/MS assay for quantification of artesunate and its metabolite dihydroartemisinin in human plasma and saliva. Bioanalysis. 2014 Sep;6(18):2357-69.

II. **Sofia Birgersson**, Joel Tarning, Kurt-Jürgen Hoffmann, Michael Ashton, Angela Abelö. Pharmacokinetics of artesunate after intravenous and oral administration in pregnant and non-pregnant rats. In manuscript

III. **Sofia Birgersson**, Pham Van Toi, Nguyen Thanh Truong, Nguyen Thi Dung, Michael Ashton, Tran Tinh Hien, Angela Abelö, Joel Tarning. Population pharmacokinetic properties of artemisinin in healthy male Vietnamese volunteers. Submitted

IV. **Sofia Birgersson**, Innocent Valea, Halidou Tinto, Maminata Traore, Laeticia C. Toe, Jean-Pierre Van Geertruyden, Geraint R. Davies, Stephen A. Ward, Umberto D'Alessandro, Angela Abelö, Joel Tarning. Population pharmacokinetics of artesunate in pregnant and non-pregnant women with uncomplicated Plasmodium falciparum malaria in Burkina Faso. In manuscript

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SAHLGRENSKA AKADEMIN

Pharmacokinetics of artemisinin derivatives in rats, healthy volunteers and patients.

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Göteborg, Sweden 2015

ABSTRACT

Malaria is still a major health problem, killing approximately 1,600 people each day. The most vulnerable patient groups are children under the age of five and pregnant women. Artemisinin-based combination therapy is recommended by the World Health Organization as first-line treatment of uncomplicated *P. falciparum* malaria. The aim of this thesis was to investigate the pharmacokinetic properties of artemisinin derivatives with particular focus on pregnancy. As part of the thesis, a sensitive and accurate bioanalytical method for the quantification of artesunate and dihydroartemisinin in plasma and saliva using tandem mass spectrometry was developed. Furthermore, the population pharmacokinetic properties of artemisinin, artesunate and dihydroartemisinin were characterized in pregnant and non-pregnant rats, healthy volunteers and in pregnant and non-pregnant patients, using nonlinear mixed-effects modelling. In conclusion, a bioanalytical method has been developed for non-invasive saliva sampling in order to support high-quality pharmacokinetic field studies and in populations where invasive sampling is unethical or difficult, e.g. pediatric and pregnant studies. Furthermore, this thesis advances our pharmacokinetic understanding of antimalarial drugs. The pharmacokinetic effects of pregnancy in rats were similar to those seen in humans which imply that this animal model could be useful in translational studies in early pregnancy. The developed pharmacokinetic model in healthy volunteers was validated and could be of use in future drug development studies. A lower antimalarial drug exposure was demonstrated in pregnant women with malaria indicating the need for dose adjustment in this vulnerable patient group.

Keywords: malaria, artemisinin, artesunate, dihydroartemisinin, LC-MS/MS, pharmacometrics, pregnancy
ISBN: 978-91-628-9531-0