In vitro and *in vivo* studies of artemisinin endoperoxides

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av
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This thesis is based on the following studies:

I. **Ericsson T**, Masimirembwa C, Abelo A, Ashton M. The evaluation of CYP2B6 inhibition by artemisinin antimalarials in recombinant enzymes and human liver microsomes. Drug Metab Lett. 2012;6(4):247-57

II. **Ericsson T**, Sundell J, Torkelsson A, Hoffmann KJ, Ashton M. Effects of artemisinin antimalarials on Cytochrome P450 enzymes *in vitro* using recombinant enzymes and human liver microsomes: potential implications for combination therapies. *Xenobiotica*. 2014:Jul;44(7):615-26

III. Birgersson S, **Ericsson T**, Blank A, von Hagens C, Ashton M, Hoffmann KJ. A high-throughput liquid chromatographic-tandem mass spectrometric method for quantification of artesunate and its metabolite dihydroartemisinin in human plasma and saliva. *Bioanalysis*. 2014:doi:10.4155/BIO.14.116 (*In press*)

IV. Blank A, **Ericsson T**, Walter Sack I, Markert C, Burhenne J, von Hagens C, Ashton M, Edler L, Haefeli WE, Mikus G. Pharmacokinetics of artesunate and its active metabolite dihydroartemisinin in prolonged use in patients with metastatic breast cancer. (*Submitted*)

V. **Ericsson T**, Blank A, von Hagens C, Ashton M, Abelo A. Population pharmacokinetics of artesunate and dihydroartemisinin during long-term oral administration of artesunate to patients with metastatic breast cancer. (*Submitted*)

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UNIVERSITY OF GOTHENBURG

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ABSTRACT

Artemisinin and its semi-synthetic derivatives (eg. Artemether/ARM, artesunate/ARS, dihydroartemisinin/DHA) play an important role in combating malaria, and treatments containing an artemisinin derivative (artemisinin-based combination therapies, ACTs) are today the standard treatment worldwide for *Plasmodium falciparum* malaria. In addition to their antimalarial effect, artemisinin endoperoxides have been demonstrated to exert cytotoxic effects, making them interesting candidates for oncologic indications.

This thesis specifically aimed to (1) investigate *in vitro* effects of artemisinin endoperoxides on human liver Cytochrome P450 (CYP) enzyme activity, and to (2) study the pharmacokinetics of ARS and DHA in plasma and saliva during long-term oral ARS treatment in patients with breast cancer. *In vitro* experimental assays using recombinant and microsomal CYP enzymes were conducted to assess potential inhibitory effects of artemisinin, ARM, ARS and DHA (**Papers I** and **II**). Results were extrapolated to evaluate the risk of drug-drug interactions (DDIs) *in vivo*. An LC-MS/MS method was optimized and validated for the quantification of ARS and DHA in human plasma and saliva (**Paper III**). Drug concentration-time profile data was analyzed by non-compartmental analysis (**Paper IV**) and population pharmacokinetic modelling (**Paper V**) to characterize the pharmacokinetic properties of the two compounds in patients with breast cancer, and to evaluate the relationship between salivary and plasma DHA concentrations.

In conclusion, artemisinin endoperoxides exerts inhibitory effects on the activity of CYP enzymes *in vitro*, which could result in clinically significant DDIs. This could be a concern in both malaria and cancer therapies, which often include concomitant administration of multiple drugs. Also, for the first time, the presented bioanalytical method offers the possibility to quantify ARS and DHA in saliva. Therefore, based on both plasma and saliva data, the pharmacokinetics of the two compounds have been characterized during long-term oral ARS treatment in patients with breast cancer. Prior knowledge regarding the pharmacokinetics of these antimalarial drugs is based on single dose or short-term (up to7 days) regimens in healthy volunteers or in malaria patients, making the results presented here significant.

Keywords: artemisinin, artesunate, breast cancer, Cytochrome P450, dihydroartemisinin, inhibition, LC-MS/MS, pharmacokinetics, plasma, saliva

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