Cytochrome P450 enzymes affected by artemisinin antimalarials

– *pharmacokinetic and pharmacogenetic aspects*

Akademisk avhandling

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av

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I. **Asimus S**, Gordi T. Retrospective analysis of artemisinin pharmacokinetics: application of a semiphysiological autoinduction model. *Br J Clin Pharmacol. 2007; 63(6):758-62.*

II. **Asimus S**, Elsherbiny D, Hai TN, Jansson B, Huong NV, Petzold MG, Simonsson US, Ashton M. Artemisinin antimalarials moderately affect cytochrome P450 enzyme activity in healthy subjects. *Fundam Clin Pharmacol. 2007; 21(3):307-16.*

III. **Asimus S**, Hai TN, Van Huong N, Ashton M. Artemisinin and CYP2A6 activity in healthy subjects. *Eur J Clin Pharmacol. 2008; 64(3):283-92.*

IV. Veiga MI, **Asimus S**, Ferreira PE, Martins JP, Cavaco I, Ribeiro V, Hai TN, Petzold MG, Björkman A, Ashton M, Gil JP. Pharmacogenomics of *CYP2A6, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5 and MDR1* in Vietnam. *Eur J Clin Pharmacol, Accepted, 2008*

V. **Asimus S**, Ashton M. Artemisinin - a possible CYP2B6 probe substrate? *Submitted, 2008*

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ABSTRACT

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With more than 500 million cases and at least 1 million deaths each year, malaria is a major global health problem. The main problem with malaria control is the emerging drug resistance among parasites causing the infection. Consequently, there is an urgent need for new drugs. The artemisinin endoperoxide antimalarials are highly effective, well tolerated and have become the most important class of drugs in the treatment of malaria. The parent compound, artemisinin, exhibits remarkable time-dependent pharmacokinetics, resulting from a pronounced capacity for auto-induction. Artemisinin has also been shown to influence the cytochrome P450 (CYP) mediated metabolism of other drugs, increasing the risk of drug–drug interactions. The artemisinin antimalarials are recommended to be used in combination treatment. It is therefore crucial to elucidate which principal CYP enzymes are affected by these drugs.

Using the cocktail approach it was demonstrated that several principal CYP enzymes were affected by the antimalarials artemisinin, dihydroartemisinin, artemether, arteether and artesunate in healthy volunteers. Metabolic changes were moderate but in several cases shared by all five endoperoxides studied, suggesting a class effect. At therapeutic doses artemisinin appeared to be associated with the strongest capacity for enzyme induction and inhibition. The time-dependent metabolism of artemisinin was described in both healthy volunteers and malaria patients by a previously developed pharmacokinetic auto-induction model. Further results indicate artemisinin to induce the activity of CYP2A6 in healthy subjects, but to which extent could not be demonstrated. Problems with studying induction of CYP2A6 using available probe compounds were highlighted. Pharmacogenetic data of genes coding for principal CYP enzymes involved in antimalarial treatment obtained in healthy Vietnamese volunteers, were in general agreement with reports from other Asian populations. Artemisinin is suggested to be an alternative marker to assess the activity of CYP2B6. Further studies are needed to investigate the metabolic fate of artemisinin, and evaluate its potential use as an *in vitro* and *in vivo* CYP2B6 probe.

In conclusion, this thesis has contributed with pharmacokinetic and metabolic information on the artemisinin antimalarials, useful in the development of new derivatives and combination treatments. The potential of these drugs to affect CYP enzymes has to be considered in order to reduce the risk of drug-drug interactions and achieve optimal treatments of malaria.

Keywords: artemisinin, autoinduction, cytochrome P450, induction, inhibition, malaria, metabolism, pharmacogenetics, pharmacokinetics, probe

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