Clinical pharmacokinetics and pharmacodynamics of antimalarial combination therapy

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i Hörsal Ivan Östholm, LNC, Medicinaregatan 13, Göteborg, torsdagen den 14 maj 2009 kl 09.00

av

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The thesis is based on the following papers:

I **Hietala SF**, Bhattarai A, Msellem M, Röshammar D, Ali AS, Strömberg J, Hombhanje FW, Kaneko A, Björkman A, Ashton M. Population pharmacokinetics of amodiaquine and desethylamodiaquine in pediatric patients with uncomplicated falciparum malaria. *J Pharmacokinet Pharmacodyn.* 2007 Oct;34(5):669-86. Reprinted with kind permission from Springer Science and Business Media

II **Hietala SF**, Ahlin E and Ashton M. Binding of the antimalarial amodiaquine and its active metabolite N-desethylamodiaquine to albumin and α_1-acid glycoprotein *in vitro* explain their binding in human plasma. *In manuscript.*

III **Hietala SF**, Mårtensson A, Ngasala B, Dahlström S, Lindegårdh N, Annerberg A, Premji Z, Färnert A, Gil P, Björkman A, and Ashton M. Population pharmacokinetics and pharmacodynamics of artemether and lumefantrine in combination treatment of uncomplicated falciparum malaria in pediatric patients. *In manuscript.*

IV Hai TN, **Hietala SF**, Van Huong N, Ashton M. The influence of food on the pharmacokinetics of piperaquine in healthy Vietnamese volunteers. *Acta Tropica.* 2008 Aug;107(2):145-9. Reprinted with kind permission from Elsevier

UNIVERSITY OF GOTHENBURG

Clinical pharmacokinetics and pharmacodynamics of antimalarial combination therapy

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Abstract:

In the face of growing drug resistance, the World Health Organization (WHO) has issued recommendations strongly encouraging the use of combination therapies to combat uncomplicated malaria. Amongst the most effective treatments are those combining an artemisinin derivative with a longer acting component such as amodiaquine, lumefantrine or piperaquine. Despite the widespread use of these treatments there is a lack of understanding regarding both pharmacokinetics and pharmacodynamics of the combinations, particularly in pediatric patients. The aim of this thesis was to describe how the dosing of antimalarials during combination therapy correlates with the outcome of treatment and to investigate factors that may influence this relationship.

In order to evaluate the pharmacokinetics and pharmacodynamics of the combinations artesunate + amodiaquine and artemether + lumefantrine in pediatric patients, a group particularly vulnerable to malaria, studies were conducted during the implementation of these new treatment strategies in Tanzania. The population approach to analysing the pharmacokinetics and pharmacodynamics was used in these studies. This method allows the determination of the typical values of pharmacokinetic and pharmacodynamic parameters, as well as the description of the variability in these estimates in the population, from sparse data. Importantly, the method also allows the investigation of how covariates, such as demographics (weight, age) or food intake influences pharmacokinetics and/or pharmacodynamics. An *in vitro* study was conducted to characterize the plasma protein binding of amodiaquine and its primary metabolite N-desethylamodiaquine. The influence of concomitant intake of a typical Vietnamese meal on the absorption of piperaquine was investigated in healthy subjects.

There was a significant, albeit weak, correlation between the clinical outcome of the combination amodiaquine+artesunate and exposure to N-desethylamodiaquine. Amodiaquine and N-desethylamodiaquine were both shown to be extensively bound to plasma proteins *in vitro*, which may explain the difficulty in establishing a good concentration-effect relationship from total N-desethylamodiaquine concentrations. The proposed semi-mechanistic model of parasite dynamics adequately described the effect of artemether and its active metabolite DHA on the parasite density in malaria patients, with predicted median parasite clearance time corresponding well with the observed. To make full use of the model, however, stage-specific parasite counts should be obtained both prior to, and during, drug treatment. There was no significant impact on the exposure to piperaquine due to concomitant intake of a relatively low-fat meal. The 20-fold range in exposure in both fed and fasting subjects suggests that there are other factors contributing significantly to interindividual differences in piperaquine pharmacokinetics.

Keywords: pharmacokinetics, pharmacodynamics, antimalarials, artemisinins
ISBN: 978-91-628-7781-1