Population Pharmacokinetic-Pharmacodynamic Modelling of Antimalarial Treatment

Akademisk avhandling

som för avläggande av farmacie doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet, Göteborg kommer att offentligen försvaras i hörsal Ivan Östholm, Medicinaregatan 13, Göteborg

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Av
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Fakultetsopponent:

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Avhandlingen baseras på följande delarbeten:

I. **Hoglund RM**, Adam I, Hanpithakpong W, Ashton M, Lindegardh N, Day NP, White NJ, Nosten F, Tarning J. A population pharmacokinetic model of piperaquine in pregnant and non-pregnant women with uncomplicated *Plasmodium falciparum* malaria in Sudan. *Malaria Journal. 2012 Nov 29;11(1):398.*

II. **Hoglund RM**, WWARN pooled analysis group, Tarning J. Meta-analysis of the population pharmacokinetics of piperaquine; a revised dose regimen. (*In manuscript*)

III. **Hoglund RM**, Amaratunga C, Song L, Sreng S, Lim P, Suon S, Day NP, White NJ, Fairhurst R, Tarning J. Population pharmacokinetics and pharmacodynamics of piperaquine in Cambodian patients with drug-resistant *P. falciparum* malaria. (*In manuscript*)

IV. **Hoglund RM**, Byakika-Kibwika P, Lamorde M, Merry C, Ashton M, Hanpithakpong W, Day NP, White NJ, Äbelö A, Tarning J. Artemether-lumefantrine coadministration with antiretrovirals; population pharmacokinetics and dosing implications. *British Journal of Clinical Pharmacology. 2014 Oct 8*

V. **Hoglund RM**, Byakika-Kibwika P, Lamorde M, Merry C, Ashton M, Hanpithakpong W, Day NP, White NJ, Äbelö A, Tarning J. The impact of artemether-lumefantrine therapy on the population pharmacokinetics of efavirenz and nevirapine (*In manuscript*)

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ABSTRACT

Malaria is one of the most important tropical diseases, with hundreds of millions of cases every year. The current recommended treatment is an artemisinin based combination therapy (ACT), which has shown good efficacy. However, differences in exposure have been observed in children and pregnant women for some antimalarial drugs. Interactions might also change the outcome of the treatment. Recently resistance development has been noted, which further underlines the importance to optimise these treatments. In this thesis, a nonlinear mixed-effects modelling approach has been used to optimise the treatment with ACT. The aims were to optimise the treatment with piperaquine, and to investigate the interactions between the antimalarial drug combination artemether-lumefantrine and antiretroviral therapy. The pharmacokinetics of piperaquine during pregnancy was investigated, and no difference in exposure was found. However, a difference in exposure was found in children, and a new optimised dose regimen for children and adults were derived. A significant difference in clinical outcome was found between three sites in Cambodia. Potential interactions between antimalarials and antiretrovirals were investigated and a significant difference in the exposure of lumefantrine was found when combined with the three antiretroviral drugs efavirenz, nevirapine or lopinavir, and new doses for artemether-lumefantrine were simulated. Exposure of nevirapine was also found to differ when combined with artemether-lumefantrine, and a new dose suggestion was simulated. In conclusion, this thesis has optimised the treatment of piperaquine and the co-treatment of artemether-lumefantrine and efavirenz, nevirapine and ritonavir boosted lopinavir.

Keywords: Malaria, pharmacometrics, HIV, drug-drug interactions, pediatrics, pregnancy, dose optimisation

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