Clinical pharmacokinetics and pharmacodynamics of antimalarial combination therapy

Akademisk avhandling

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av

Sofia Friberg Hietala

Fakultetsopponent:
Dr. Peter J. de Vries

Division of Infectious Diseases, Tropical Medicine and AIDS,
Academic Medical Center, Amsterdam, The Netherlands

The thesis is based on the following papers:


II Hietala SF, Ahlin E and Ashton M. Binding of the antimalarial amodiaquine and its active metabolite N-desethylamodiaquine to albumin and α1-acid glycoprotein *in vitro* explain their binding in human plasma. *In manuscript.*


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Sofia Friberg Hietala
Department of Pharmacology, Institute of Neuroscience and Physiology
The Sahlgrenska Academy, University of Gothenburg, Sweden 2009

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