Population Pharmacokinetic-Pharmacodynamic Modelling of Antimalarial Treatment

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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