Applied Population Pharmacokinetic / Pharmacodynamic Modeling of Antiretroviral and Antimalarial Drug Therapy

Akademisk avhandling
som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras
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av

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Avhandlingen baseras på följande delarbeten:


HIV/AIDS and malaria are two major global infectious diseases. Although better drugs against these conditions are becoming more available, dosages may not always be optimal with respect to effectiveness, safety, cost or convenience of administration. This thesis aims to quantitate the pharmacological relationship between dosing history, sources of variation between individuals, drug exposure and response to selected antiretroviral and antimalarial regimens.

Pharmacometric, i.e. pharmaco-statistical, models were fitted to observed data from five clinical studies, using the NONMEM software. Several polymorphic genes coding for drug metabolizing enzymes and transporters were found to have impact on the disposition of the non-nucleoside reverse transcriptase inhibitor efavirenz in healthy Ugandan subjects after single dose administration. Moreover, using simulation it was demonstrated that a 200 mg dose reduction in Zimbabwean HIV-patients with genetically decreased metabolic capacity would maintain efavirenz exposure within the therapeutic range during repeated administration. In a typical clinical trial large amounts of drug response data are collected. However, usually only limited amounts of the recorded data are actually used for investigating differences between regimens. Herein, a drug-disease model was developed to describe the time-course of repeatedly measured HIV-RNA levels in Scandinavian patients randomized to one of three commonly prescribed antiretroviral regimens. The initial analysis showed that an efavirenz-containing regimen appeared to be more efficacious compared to two protease inhibitor-containing regimens. Antimalarial artemisinin-based combination therapy bears many resemblances to antiretroviral treatment. The drugs exhibit variable and complex pharmacokinetics and the diseases themselves bring reasonable possibilities for pharmacodynamic assessment. Auto-induction of drug metabolism was described after multiple dosing with artemisinin in Vietnamese patients. The frequency of recrudescent malaria infection was as high as 37% but could not directly be linked to low artemisinin exposure. The elimination half-life of piperaquine, a suitable partner drug for artemisinin-based combination treatment, was estimated to 12 days with large between-subject variability.

The thesis demonstrates the utility of pharmacometric methodology in the analysis of clinical data originating from high-income countries as well as resource-limited settings. Ultimately it can be a tool for decision analysis and policy making.

Keywords: HIV, malaria, pharmacokinetics, pharmacodynamics, pharmacometrics, NONMEM