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

Akademisk avhandling
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av

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Avhandlingen baseras på följande delarbeten:

I. Mukonzo J, Röshammar D, Waako P, Andersson M, Fukasawa T, Milani L, Svensson J-O, Ogwal-Okeng J, Gustafsson LL, Aklillu E (2008) A novel polymorphism in MDR1 gene, CYP2B6*6 and sex predict single dose efavirenz population pharmacokinetics in Ugandans. Submitted

II. Nyakutira C, Röshammar D, Chigutsa E, Chnozi P, Ashton M, Nhachi C, Masimirembwa C (2008) High prevalence of the CYP2B6 516GT(*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe. Eur J Clin Pharm 64: 357-365

III. Röshammar D, Josephson F, Simonsson USH, Ekvall H, Flamholc L, Ormaasen V, Sönnerborg A, Wallmark E, Ashton M, Gisslén M (2009) Assessment of antiretroviral drug efficacy in the NORTHIV study by non-linear mixed effects modeling. Manuscript

IV. Röshammar D, Hai TN, Thanh NV, Huong DX, Huong NV, Thu NB, Ashton M (2007) Modeling of the time-dependent population pharmacokinetics and exposure-response relationship of the antimalarial artemisinin based on sparsely sampled saliva. Manuscript

V. Röshammar D, Hai TN, Friberg Hietala S, Huong NV, Ashton M (2006) Pharmacokinetics of piperaquine after repeated oral administration of CV8 in 12 healthy male subjects. Eur J Clin Pharm 62: 335-41

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ABSTRACT

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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

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