Quantitative Clinical Pharmacological Studies on Efavirenz and Atazanavir in The Treatment of HIV-1 Infection

Akademisk avhandling

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av

Dinko Rekić

Fakultetsopponent:
Professor Mats O Karlsson
Institutionen för farmaceutisk biovetenskap, Uppsala Universitet, Uppsala.

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**Quantitative Clinical Pharmacological Studies on Efavirenz and Atazanavir in The Treatment of HIV-1 Infection**

Dinko Rekić  
Department of Pharmacology, Institute of neuroscience and Physiology  
The Sahlgrenska Academy, University of Gothenburg, Sweden 2012

**ABSTRACT**

There are 34 million people infected with the HIV-1 virus in the world today. Due to increased access to antiretroviral therapy, AIDS related death has dropped by 30% since 2005. Optimizing the pharmacotherapy of the HIV-1 infection is of great importance to reduce adverse effects, reduce viral resistance development and increase the patients’ survival as well as quality of life. This thesis presents pharmacometric applications to optimize pharmacotherapy of the HIV-1 infection as well as to expedite the clinical drug development of new drugs.

Methods to extrapolate *in vitro* data to *in vivo* settings have been applied to predict the level of the drug-drug interaction between efavirenz and rifampicin as well as to evaluate the current dosage recommendations. Nonlinear mixed effects (NLME) models, as implemented in the software NONMEM, have been fitted to data from clinical studies to investigate the disease effect of HIV-1 on efavirenz pharmacokinetics. Further, NLME modeling and simulation was used to evaluate and validate bilirubin as a marker of exposure and adherence in HIV-1 infected patients. Simulation of a mechanistic viral dynamics model, describing the interplay between virus and CD4 cells, was used to optimize the design and analysis of clinical trials in antiretroviral drug development. Model based techniques for hypothesis testing were shown to be superior in terms of power compared to traditional statistical hypothesis testing.

In conclusion, model based drug development techniques can be used to optimize HIV-1 therapy as well as expedite drug development of novel compounds.

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