Göteborg, 2021

Optimization of first-line anti-tuberculosis therapy in patients co-infected with HIV

Akademisk avhandling

Som för avläggande av farmacie doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, den 15 oktober, klockan 09:00

av Jesper Sundell

Fakultetsopponent: Professor Lena Friberg
Uppsala Universitet

Avhandlingen baseras på följande delarbeten

I. **Sundell J**, Bienvenu E, Birgersson S, Äbelö A, Ashton M, Hoffmann KJ. Simultaneous quantification of four first line antitubercular drugs and metabolites in human plasma by hydrophilic interaction chromatography and tandem mass spectrometry. *Journal of Chromatography B*. 2019 Jan 15;1105:129-135.

II. **Sundell J**, Bienvenu E, Janzén D, Birgersson S, Äbelö A, Ashton M. Population Pharmacokinetics and Pharmacogenetics of Ethambutol in Adult Patients Coinfected with Tuberculosis and HIV. *Antimicrobial Agents and Chemotherapy*. 2020 Jan 27;64(2):e01583-19.

III. **Sundell J**, Bienvenu E, Birgersson S, Äbelö A, Ashton M. Model-Based Assessment of Variability in Isoniazid Pharmacokinetics and Metabolism in Patients Co-Infected With Tuberculosis and HIV: Implications for a Novel Dosing Strategy. *Clinical Pharmacology and Therapeutics*. 2020 Jul;108(1):73-80.

IV. **Sundell J**, Bienvenu E, Äbelö A, Ashton M. Effect of efavirenz-based antiretroviral therapy on the pharmacokinetics of rifampicin and its primary metabolite in patients co-infected with tuberculosis and HIV. *Journal of Antimicrobial Chemotherapy*. 2021 Jul 31. *Online ahead of print*.

V. **Sundell J**, Wijk M, Bienvenu E, Äbelö A, Hoffmann KJ, Ashton M. Factors Affecting the Pharmacokinetics of Pyrazinamide and Its Metabolites in Patients Coinfected with HIV and Implications for Individualized Dosing. *Antimicrobial Agents and Chemotherapy*. 2021 Jun 17;65(7).

VI. **Sundell J**. Probability functions for susceptibility-guided precision dosing in antitubercular therapy. (*Submitted*)

VII. **Sundell J**, Bienvenu E, Birgersson S, Äbelö A, Ashton M. Non-linear pharmacokinetics and drug-drug interaction between rifampicin and isoniazid in patients co-infected with tuberculosis and HIV. (*Submitted*)

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Optimization of first-line anti-tuberculosis therapy in patients co-infected with HIV

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Abstract

Every year over one million people die from tuberculosis. People infected with HIV are significantly more vulnerable to tuberculosis, which is the leading cause of HIV-associated death. The first-line treatment for tuberculosis consists of rifampicin, isoniazid, pyrazinamide and ethambutol. Although the regimen is effective, the risk of treatment failure and acquired toxicity is unacceptably high. Due to the lack of effective alternative therapy against resistant tuberculosis, optimal use of the first-line combination is crucial. The aim of the studies presented within this thesis was to investigate potential for optimization of the first-line tuberculosis therapy in patients co-infected with HIV. A bioanalytical method for quantification of the four first-line antitubercular drugs and their primary metabolites in human plasma was developed and validated. Population pharmacokinetics of the drugs and their metabolites were described using non-linear mixed effects modelling. The effects of genetic polymorphism, concomitant HIV therapy and patient demographics on drug exposure were investigated. Individualized dosing based on patient characteristics to reduce high pharmacokinetic variability was proposed for isoniazid and pyrazinamide. Two drug-drug interactions of potential clinical relevance were described: an effect of HIV therapy on rifampicin pharmacokinetics and an effect of rifampicin on isoniazid pharmacokinetics. In addition, novel effects of polymorphism in cytochrome P450 on the pharmacokinetics of rifampicin and ethambutol were suggested. Lastly, a framework for determination of individual doses based on pathogen susceptibility was developed. Conclusively, new dose regimens for the first-line anti-tuberculosis drugs in patients co-infected with HIV are proposed. Such regimens may reduce the risk of treatment failure, resistance development and toxicity. The drug-drug interactions and pharmacogenetic effects described within this thesis may guide the design of future clinical studies.

Keywords: Tuberculosis, HIV, pharmacokinetics, pharmacogenetics, LC-MS/MS, individualized therapy

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