Enterohepatic Recirculation and Gender Differences of Roxithromycin in Humans Assessed via Population Pharmacokinetics

Soyoung Shin², Jürgen B. Bulitta¹, Martina Kinzig¹, Christoph Stelzer¹, Sven Hüttner¹, Tae Hwan Kim⁴, Beom Soo Shin⁵, Fritz Sörgel¹

¹IBMP - Institute for Biomedical and Pharmaceutical Research, Nürnberg-Heroldsberg, Germany; ²Department of Pharmacy, Wonkwang University, Iksan, Korea; ³College of Pharmacy, University of Florida, Orlando, FL, USA; ⁴School of Pharmacy, Sungkyunkwan University, Suwon, Korea; ⁵College of Pharmacy, Catholic University of Daegu, Gyeongsan, Korea

Objectives: Macrolide antibiotics undergo extensive enterohepatic recirculation (EHC) which affects their pharmacokinetics (PK). However, we are not aware of PK models to describe EHC for macrolides or for any other antibiotic. The aim of this study was to characterize the population PK and EHC of roxithromycin, a macrolide antibiotic, in humans over a range of doses and to assess potential gender differences.

Methods: We characterized the plasma concentration time profiles for roxithromycin given as a single oral dose of 50 mg (oral suspension), 150 or 300 mg (film-coated tablets) in healthy volunteers (in total: n=112). Roxithromycin plasma concentrations were determined by LC-MS/MS and simultaneously modeled using the S-ADAPT software.

Results: The model contained compartments for undissolved drug, gut, liver, hepatocytes, and bile, as well as the central and peripheral compartment. A bile-flow turnover model described a pulsatile release of drug from bile into gut. The model provided reasonably precise and unbiased curve fits. Transfer of drug from the hepatocyte into bile was described by Michaelis-Menten kinetics. Females had a 17% smaller maximum transfer rate compared to males (p<0.05) leading to more extensive metabolism in females. This explained why females had a higher apparent total clearance compared to males (i.e. 27% higher when clearance was expressed as L/h and 49% higher when it was expressed as L/h/kg) based on non-compartmental methods.

Conclusions: The developed model for EHC excellently described the time-course of roxithromycin plasma concentrations. The significantly higher clearances in females compared to males were well explained by a slower transfer of drug from hepatocytes into bile in agreement with previous literature reports on gender difference in P-glycoprotein.