IS01-2 **Physiologically-based pharmacokinetic (PBPK) modeling of digoxin as a P-glycoprotein (P-gp) transport victim drug**

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Background and Objectives: PBPK modeling is a powerful tool to explore and quantitatively predict the magnitude of drug-drug interactions (DDIs) and offers an alternative to dedicated clinical studies. Digoxin is recommended by the FDA as P-gp substrate for the use in clinical DDI studies [1]. Our objective was to establish a full body PBPK model of digoxin and to demonstrate its ability to predict the rifampicin-digoxin and the clarithromycin-digoxin DDIs.
Methods: PBPK models were built in PK-Sim® modeling software (Version 7.0.0). Digoxin drug-dependent parameters as well as plasma concentration-time profiles of 38 clinical studies were obtained from literature and used to establish a model accurately describing and predicting observed clinical data. The model was then coupled to previously established rifampicin [2] and clarithromycin models [3], clinical DDI studies were predicted and the results were compared to published observed data.
Results: The newly developed digoxin model features P-gp transport in various organs including gut, liver and kidney. Implementation of target binding to Na^+/K^+-ATPase was crucial to accurately describe the published plasma concentrations following intravenous and oral administration of digoxin. Simulation of different DDI scenarios with the coupled models generates digoxin plasma concentration-time profiles that are in very good agreement with observed data.
Conclusion: We provide a full body PBPK model of digoxin as a tool for the drug development process for dynamic evaluation of the DDI potential of investigational drugs that are P-gp inducers or inhibitors.

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[2] Hanke N, Frechen S, Britz H, Moj D, Kanacher T, Eissing T, Wendl T, Lehr T. Physiologically-based pharmacokinetic modeling of rifampin drug-drug interactions with midazolam and digoxin. PAGE 25 (2016) Abstr 5929.
[3] Moj D, Hanke N, Britz H, Frechen S, Kanacher T, Wendl T, Haefeli WE, Lehr T. Clarithromycin, midazolam, and digoxin: Application of PBPK modeling to gain new insights into drug-drug interactions and co-medication regimens. AAPS J (2017) 19(1): 298-312.