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Human: Influence of time between substrate and inducer administration

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The induction of cytochrome P450 enzymes (CYPs) is an important source of drug-drug interaction (DDI) and can result in pronounced pharmacokinetic (PK) changes. Rifampicin (RIF) is a potent inducer of CYP3A4 and also acts as a competitive inhibitor which can partially mask the induction. The objective of this study was to determine a clinical DDI study design for RIF resulting in maximum CYP3A4 induction. A physiologically based pharmacokinetic (PBPK) model was developed to project the dynamics and magnitude of CYP3A4 induction *in vivo* from *in vitro* data generated with primary human hepatocytes. The interaction model included both inductive and inhibitory effects of RIF on CYP3A4 in gut and liver. The model has been verified for 4 CYP3A4substrates: Midazolam, triazolam, alfentanil and nifedipine using plasma concentration data from 20 clinical study designs with intravenous and oral administrations. The influence of the time between RIF and substrate administration was explored. The model integrating *in vitro* induction parameters correctly predicted intravenous induction but underestimated oral induction. The use of a 1.6-fold higher value for the maximum induction effect (Emax) improved significantly the accuracy and precision of oral induction with 82% of simulated concentrations within 2-fold of observed data. Our simulations suggested that a concomitant administration of RIF and midazolam resulted in significant competitive inhibition limited to intestinal enzyme. Accordingly, a maximum induction effect could be achieved with a RIF pre-treatment of 600 mg/day during 5 days and a substrate administration at least 2 h after the last RIF dose.

Biography

Guillaume Baneyx has completed his PharmD from University of Paris Descartes and PhD studies from University of Aix-Marseille. His research works were dedicated to prediction of drug-drug interactions and assessment of tumor penetration of anticancer agents. He is Modeling and Simulation Scientist in oncology at Novartis, Basel.

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