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Physiologically based pharmacokinetic modeling of CYP3A4 induction by rifampicin in human: Influence of time between substrate and inducer administration

Guillaume Baneyx [a,*], Neil Parrott [a], Christophe Meille [a], Athanassios Iliadis [b], Thierry Lavé [a]

[a] F. Hoffmann-La Roche AG, pRED, Pharma Research and Early Development, Non-Clinical Safety, Basel, Switzerland
[b] Aix Marseille University, Inserm, CRO2, UMR_S 911, 13385 Marseille, France

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ABSTRACT

The induction of cytochrome P450 enzymes (CYPs) is an important source of drug–drug interaction (DDI) and can result in pronounced changes in pharmacokinetics (PK). 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 and accounting for the observed RIF auto-induction. The model has been verified for 4 CYP3A4 substrates: midazolam, triazolam, alfentanil and nifedipine using plasma concentration data from 20 clinical study designs with intravenous ($n = 7$) and oral ($n = 13$) administrations. Finally, the influence of the time between RIF and substrate administration was explored for the interaction between midazolam and RIF.

The model integrating *in vitro* induction parameters correctly predicted intravenous induction but underestimated oral induction with 30% of simulated concentrations more than 2-fold higher than of observed data. The use of a 1.6-fold higher value for the maximum induction effect (E_{max}) improved significantly the accuracy and precision of oral induction with 82% of simulated concentrations and all predicted PK parameters 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 pretreatment of 600 mg/day during 5 days and a substrate administration at least 2 h after the last RIF dose. A period of 2 weeks after RIF removal was found sufficient to allow return to baseline levels of enzyme.

1. Introduction

The induction of cytochrome P450 enzymes (CYPs) is an important source of drug–drug interaction (DDI) and can result in pronounced changes in drug pharmacokinetics (PK). CYP3A4 is involved in the metabolism of numerous drugs (Guengerich, 2006) and CYP3A4 induction is a major concern in clinical practice (Lin, 2006). Substantial clinical consequences include reduction in therapeutic effect due to decreased drug exposure (Backman et al., 1996; Hebert et al., 1999), potentiation of therapeutic effect due to higher conversion of a pro-drug to a pharmacologically active form (Judge et al., 2010) or induction of toxicity due to higher levels of reactive metabolites (Laine et al., 2009). Consequently, the prediction of potential CYP3A4 induction during drug discovery is a critical step in selection of development candidates (Lin, 2004; Smith, 2000) and a set of *in vitro* assays has been established to characterize CYP3A4 induction potency (EC_{50}) and magnitude (E_{max}). Primary cultures of human hepatocytes are the most accepted system (Chung et al., 2006) since, with adequate experimental conditions, it is possible to scale *in vitro* induction to the *in vivo* situation in terms of magnitude and specificity (LeCluyse et al., 2000).

Over the last decade, model-based approaches have been increasingly used to predict *in vivo* CYP3A4 induction based on *in vitro* data (Almond et al., 2009; Einolf, 2007). Initially, empirical models were applied to rank the induction risk (Kato et al., 2005; Ripp et al., 2006). Subsequently, mathematical models were developed to predict steady state induction using average (Templeton et al., 2011) or maximal (Fahmi et al., 2008; Shou et al., 2008) inducer plasma concentration. These static models included

* Corresponding author. Tel.: +33 682345738.
E-mail address: guillaume.baneyx@gmail.com (G. Baneyx).

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mechanistic information such as systemic clearance, fraction of substrate metabolized by the induced enzyme and plasma protein binding of inducer as well as an empirical *in vitro–in vivo* extrapolation factor for induction magnitude. However, static models are restricted to predicting the ratio of substrate exposures before and after inducer treatment and cannot simulate the induction time course. Indeed, induction of CYPs is concentration dependent (Sahi et al., 2000) and time dependent (Fromm et al., 1996). Accordingly, a dynamic model simulating the inducer PK profile in portal vein has been proposed to predict DDI before and after steady-state (Kozawa et al., 2009). Although generating interesting results, this model disregarded the impact of CYP3A4 induction on oral bioavailability. More recently, the development of physiologically-based pharmacokinetic (PBPK) models has extended the DDI capabilities of dynamic approaches (Baneyx et al., 2012; Zhao et al., 2011) with the ability to simulate time-varying substrate and inducer kinetics at interaction sites (Guo et al., 2013; Xu et al., 2011). Recent DDI guidelines from the Food and Drug Agency (FDA) and the European Medicines Agency (EMA) encourage sponsors to use PBPK modeling to select and improve the design of DDI clinical studies to capture the maximal interaction effect (EMA, 2010; FDA, 2012).

Rifampicin (RIF) is a potent inducer of numerous CYPs, phase 2 enzymes and transporters (Niemi et al., 2003) and is recommended by health authorities for clinical DDI studies evaluating the impact of CYP3A4 induction on PK of new drug candidates (FDA, 2006). RIF dose selection for a maximal CYP3A4 induction effect has been explored with a PBPK model (Xu et al., 2011) and resulted in administration of 450–600 mg once a day (QD) or of 200–300 mg twice a day (BID) for approximately 7 days. However, the influence of the dosing interval between RIF and substrate was not explored. This aspect has to be considered since a competitive inhibition of CYP3A4 enzyme by RIF has been characterized *in vitro* (Kajosaari et al., 2005).

The objective of this work was to use PBPK modeling and simulation to determine a design for clinical DDI studies with RIF resulting in maximum CYP3A4 induction. As inhibitory effect of RIF may partially mask the inductive effect, the influence of the dosing interval between RIF and substrate was explored for the midazolam–RIF interaction and an optimal time interval was recommended. To build confidence in the interaction model, DDI predictions for 4 probe CYP3A4 substrates, namely midazolam (MDZ), triazolam (TRZ), alfentanil (ALF) and nifedipine (NIF) were simulated and verified against clinical studies with intravenous and oral administrations.

2. Materials and methods

2.1. CYP3A4 substrates

MDZ, TRZ, NIF and ALF were selected because of their well characterized PK properties, ADME processes and physico-chemical parameters as well as extensive published clinical studies showing pronounced interactions with RIF. These substrates are mainly metabolized by CYP3A4 and active transport does not contribute to their PK. Therefore the interaction with RIF can be assumed to be solely due to a modification of the CYP3A4 metabolism. These substrates all have similar PK with total plasma clearance ranging from 0.2 to 0.5 L/h/kg, terminal half-live ranging from 1.1 to 4.2 h and volume of distribution from 0.7 to 2 L/kg (Echizen and Eichelbaum, 1986; Garzone and Kroboth, 1989; Scholz et al., 1996). These drugs also have good solubility and permeability, resulting in rapid and complete absorption from the gastro intestinal tract. However, first pass effect can be significant and absolute bioavailability ranges from 34% to 68%.

2.2. DDI studies with rifampicin

DDI clinical studies with RIF were collected in March 2012 from the University of Washington drug interaction database (http://www.druginteractioninfo.org). Twenty DDI study designs from eleven clinical studies were found to verify PBPK simulations and DDI predictions for MDZ, TRZ, NIF and ALF (Table 1). Only studies with fasted healthy volunteers and with information on dosing schedule, drug formulation and concentration–time profiles were selected. Studies reporting PK profiles with standard deviations were preferred over those with only a mean profile. The number of DDI study design was 13 for MDZ, 1 for TRZ, 2 for NIF and 4 for ALF. Intravenous and oral administrations were available for all substrates, except TRZ where only the oral route was found. Accordingly, the intravenous profile of TRZ was extracted from (Kroboth et al., 1995) to verify the PBPK model. These DDI studies explored the induction at steady state with a prior ($n = 1$), concomitant ($n = 1$) or delayed ($n = 16$) substrate administration relative to the last dose of RIF. The de-induction was explored via the recovery of MDZ pharmacokinetics during 4 weeks after the last dose of RIF (Reitman et al., 2011).

Clinical practice in terms of RIF pretreatment duration and dosing interval between RIF and substrate was determined for the typical RIF dose (600 mg QD) by a literature review based on the following criteria: (i) published later than 2000, (ii) assessment of CYP3A4 induction with a single administration of substrate before and after multiple doses of RIF and (iii) decrease of substrate exposure over 20%. Over the 77 DDI studies found, the duration of RIF pretreatment was 5 days (31%), 6 days (13%), 7 days (22%) or more than 7 days (34%) with a maximum of 28 days (Reitman et al., 2011). The interval between the last RIF administration and substrate dosing was 0 h (13%), 12 h (32%), more than 12 h (17%) or not reported (34%). In two studies, the substrate was administered 2 h prior and 1 h after the RIF dose.

2.3. CYP3A4 induction parameters

The *in vitro* CYP3A4 induction parameters (E_{50} and E_{max}) for RIF were characterized by Templeton et al. (2011) with primary human hepatocytes data from 14 donors. They found mean values of 0.8 μM and 9-fold for E_{50} and E_{max}, respectively. They applied a static "E_{max} model" to relate variations in CYP3A4 activity to variations in RIF levels and an *in vivo* E_{max} value was estimated by minimizing the geometric mean fold error between predicted and observed clinical DDI for their *in vivo* intravenous dataset including MDZ, ALF and NIF. They found an *in vivo* E_{max} value of 14.6-fold. In our work, DDI predictions were done with both *in vitro* and *in vivo* E_{max} values to explore utility of an *in vitro–in vivo* extrapolation factor.

2.4. Model structures

The human PBPK disposition model included 14 tissue compartments (adipose, red bone marrow, yellow bone marrow, brain, gut, heart, kidney, liver, lung, muscle, reproductive organs, rest of body, skin and spleen) connected by the arterial and venous blood flows (Appendix A.1). The drug absorption, distribution, metabolism and excretion processes were described by a set of differential equations available in the GastroPlus software version 8.0 (Simulations Plus Inc.). The physiological characteristics of each tissue (blood flow, volume, pH, enzyme expression level, tissue composition) and drug specific properties (lipophilicity, solubility, ionization, permeability and metabolism) were used as input parameters. Equations describing induction of metabolism are presented in the next section.