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Physiologically based pharmacokinetic modeling for assessing the clinical drug–drug interaction of alisporivir

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ABSTRACT

Alisporivir is a novel cyclophilin-binding molecule with potent anti-hepatitis C virus (HCV) activity. *In vitro* data from human liver microsomes suggest that alisporivir is a substrate and a time-dependent inhibitor (TDI) of CYP3A4. The aim of the current work was to develop a novel physiologically based pharmacokinetic (PBPK) model to quantitatively assess the magnitude of CYP3A4 mediated drug–drug interactions with alisporivir as the substrate or victim drug. Towards that, a Simcyp PBPK model was developed by integrating *in vitro* data with *in vivo* clinical findings to characterize the clinical pharmacokinetics of alisporivir and further assess the magnitude of drug–drug interactions. Incorporated with absorption, distribution, elimination, and TDI data, the model accurately predicted AUC, C_{max}, and t_{max} values after single or multiple doses of alisporivir with a prediction deviation within ±32%. The model predicted an alisporivir AUC increase by 9.4-fold and a decrease by 86% when alisporivir was co-administrated with ketoconazole (CYP3A4 inhibitor) or rifampin (CYP3A4 inducer), respectively. Predictions were within ±20% of the observed changes. In conclusion, the PBPK model successfully predicted the alisporivir PK and the magnitude of drug–drug interactions.

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1. Introduction

Allometry has long been used in predicting human pharmacokinetics (PK) utilizing data from preclinical species (Mahmood, 1999) However, due to notable interspecies differences, especially with metabolizing enzymes and drug transporters, alternative approaches have been proposed over the years to obtain improved predictions. Unlike allometry and other empirical pharmacokinetic models, physiologically based pharmacokinetic (PBPK) models provide mechanistic time-based profiles by integrating drug-dependent and physiology-dependent parameters, in the process of predicting human pharmacokinetics. In addition to allowing human PK predictions at the discovery stage, PBPK modeling is also useful in early and late development to predict drug exposure for various purposes including drug–drug interactions (DDIs), PK in organ dysfunction, different age and genotype populations (Sinha et al., 2012). The US FDA recommends the use of PBPK models to quantitatively predict the magnitude of DDIs in various clinical situations; furthermore, this approach may offer useful information to facilitate dedicated clinical study designs (US Food and Drug Administration, 2012).

Pharmacokinetic DDIs, an important issue in healthcare, mostly result from the modulations of the drug-metabolizing enzymes, particularly P450 enzymes, which are present in the liver and extra-hepatic tissues. CYP3A4 is the most abundantly expressed P450 enzyme in the liver and gut, and it is involved in the metabolism of more than half of the drugs used clinically (Wienkers and Heath, 2005). A number of important drugs have been identified as substrates, inducers, and/or inhibitors of CYP3A4, and the assessment of the potential for CYP3A4-mediated DDIs is an important part of the clinical development program for any new chemical entity. The Simcyp™ population based ADME simulator, which is commercially available software for PBPK modeling, integrates inter-individual variability into PBPK modeling for the prediction of drug disposition and DDIs in virtual populations. By combining information on physiology, genetic and demography/ethnicity with *in vitro* data, Simcyp™ simulator can perform extrapolation to *in vivo* situations and virtual populations (Jamei et al., 2009).

Abbreviations: CYP, cytochrome P450; DDI, drug–drug interactions; DPM, disintegrations per minute; HCV, hepatitis C virus; HLM, human liver microsomes; PBPK, Physiologically-based pharmacokinetics; PK, pharmacokinetics; TDI, time-dependent inhibitor.

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Alisporivir (alisporivir), a hepatitis C antiviral agent, is currently in phase III clinical development. Alisporivir, a structural analog of cyclosporine, has physicochemical properties similar to those of cyclosporine. *In vitro* data described in this manuscript suggested that alisporivir is a CYP3A4 substrate and a time-dependent inhibitor (TDI) of CYP3A4. Hence, there is a potential for clinically significant DDI when alisporivir is co-administered with inhibitors or inducers of CYP3A4 or other drugs that are substrates of CYP3A4. The objective of the present study is to develop a PBPK model to characterize PK of alisporivir following single and multiple oral administration and assess the DDI effects of a CYP3A4 inhibitor (ketoconazole) and a CYP3A4 inducer (rifampin) on its exposure. Specifically, the metabolic and DDI properties for alisporivir, observed in *in vitro* results, were incorporated in the model for quantitative prediction of mechanism-based drug disposition and interactions.

2. Materials and methods

2.1. Chemicals and reagents

Isotope labelled [^{14}C]alisporivir, [$^{2}H_9$]-1′-hydroxybufuralol, and [$^{13}C_6$]-4′-hydroxydiclofenac were synthesized by the DMPK Isotope Laboratory (Novartis, East Hanover, NJ) with chemical and radiochemical purity was greater than 99%. [$^{2}H_4$]-Acetaminophen and [$^{2}H_4$]-1′-hydroxymidazolam were obtained from Cerilliant (Round Rock, TX). Pooled human liver microsomes, S9, and cytosol from the same donor pool (*n* = 150 donors, mixed gender), recombinant human CYP enzymes, flavin monooxygenase enzymes, ketoconazole, diclofenac, acetaminophen, phenacetin, midazolam, 4′-hydroxydiclofenac and azamulin were purchased from BD Biosciences Co., Gentest (Woburn, Massachusetts). Potassium phosphate (mono- and di-basic), β-NADPH, $MgCl_2$, quinidine, ticlopidine, sulfaphenazole, and furafylline were obtained from Sigma–Aldrich (St. Louis, MO). Montelukast was purchased from Sequoia Research Products, Ltd. (Oxford, UK). Acetonitrile and formic acid were purchased from Fisher Scientific Co. (Pittsburgh, PA). Bovine serum albumin, fraction V (BSA) standard was purchased from Pierce (Rockford, IL). All other reagents and chemicals purchased were reagent grade.

2.2. In vitro studies

2.2.1. Permeability and transporter studies across Caco-2 cells

Caco-2 cells were seeded at a density of ~30,000 cells/cm^2 on permeable polyethylene terephthalate membranes (BD Falcon HTS Multiwell, 1.0 μm pore size, 0.31 cm^2 growth area) and cultured in a humidified atmosphere of 5% CO_2: 95% air at 37 °C for approximately 21 days prior to transport experiments. Prior to the transport experiments, the plate systems were protein saturated. Apical and basal compartments were saturated with BSA (20%) for 16 h at 37 °C and washed twice. Before dosing, the integrity of the equilibrated cell monolayers was ensured by measuring transepithelial electrical resistance values. The transcellular flux of [^{14}C]-alisporivir or alisporivir (0.40 μM, 3.5 μM, 10 μM) across Caco-2 cell monolayers was determined in both apical-to-basolateral (Ap → Bl) and basolateral-to-apical (Bl → Ap) directions with and without addition of transporter inhibitors of LY335979 (1 μM) and Ko143 (1 μM) in both compartments. Aliquot of samples were removed from the acceptor and donor chamber at 120 min or 240 min (10 μM). All Samples were analyzed using liquid scintillation counter or LC/MS/MS. The permeability and transporter studies at 0.4 and 3.5 μM was conducted in-house and the permeability study at 10 μM was conducted by a contract research Laboratory (Laboratoire d'Etude du Métabolisme des Médicaments, Cedex, France).

2.2.2. Alisporivir metabolic stability in human liver microsomes (HLM), S9 and cytosol)

The metabolism of [^{14}C] alisporivir was initially examined in pooled HLM, S9 and cytosol in the presence or absence of β-NADPH. Human liver microsomes, S9 or cytosol (1 mg protein·mL^{-1}) was incubated with β-NADPH (1 mM, final concentration) or water as a control in 100 mM potassium phosphate buffer (pH 7.4) containing 5 mM $MgCl_2$. The reactions were preincubated for 3 min at 37 °C and initiated by the addition of [^{14}C] alisporivir (24 μM, final concentration). The samples were incubated for 30 min at 37 °C and quenched with an equal volume of cold acetonitrile. The precipitated protein was removed by ultracentrifugation at ~4 °C. An aliquot (50 μL) of the supernatant from each sample was analyzed by HPLC with off-line radioactivity detection (see analytical methods in Supplemental materials). In addition, the metabolism activity of [^{14}C]alisporivir was found linear with microsomal protein concentration at (0.1–1.0) mg protein·mL^{-1} and time (5–15 min).

2.2.3. Effect of P450 inhibitors on the metabolism of [^{14}C]alisporivir in human liver microsomes (reaction phenotyping study)

To evaluate the contributions of specific cytochrome P450s to the metabolism of [^{14}C]alisporivir in human liver, inhibition of total [^{14}C]alisporivir metabolism in human liver microsomes was examined using selective CYP enzyme inhibitors at pre-selected concentration ranges encompassing reported apparent K_I values (median) for the inhibition of a specific CYP enzyme (Table 1). The inhibitors of azamulin, ticlopidine, or furafylline were pre-incubated with β-NADPH for 15 min at 37 °C. The incubation was then carried out by addition of [^{14}C]alisporivir at a concentration approximately at its K_m (1.2 μM, in-house data) value in human liver microsomes (0.1 mg protein·mL^{-1}) in combination with varying concentrations of the CYP inhibitors (inhibitors without pre-incubation) with a similar procedure described previously. An aliquot (50 μL) of the supernatant from each sample was analyzed by HPLC with off-line radioactivity detection. Control incubations were carried out without inhibitors. The percentage of impurity co-eluting with metabolites was accounted for in the reactions containing NADPH by subtraction of the percent impurity from the control reactions without NADPH. Inhibition of [^{14}C]

Table 1
Inhibition of [^{14}C]alisporivir metabolism by selective CYP inhibitors.

Substrate/inhibitor (main inhibited P450)	Concentration range used (μM)	IC_{50} (μM)	% Maximal inhibition[a]
Ketoconazole (3A)	0–1	0.012	100
Azamulin (3A)	0–5	0.018	100
Ticlopidine (2B6/2C19)	0–10	>10	8.60
Montelukast (2C8)	0–2	>2	12.3
Furafylline (1A2)	0–10	>10	4.71
Quinidine (2D6)	0–2	>2	23.5
Sulfaphenazole (2C9)	0–5	>5	12.4

[a] Percent maximal inhibition of total [^{14}C]alisporivir metabolism at the concentrations of inhibitor examined.

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