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Physiologically based pharmacokinetic modeling of disposition and drug–drug interactions for atorvastatin and its metabolites

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ABSTRACT

Atorvastatin is the most commonly used of all statins to lower cholesterol. Atorvastatin is extensively metabolized in both gut and liver to produce several active metabolites. The purpose of the present study is to develop a physiologically based pharmacokinetic (PBPK) model for atorvastatin and its two primary metabolites, 2-hydroxy-atorvastatin acid and atorvastatin lactone, using *in vitro* and *in vivo* data. The model was used to predict the pharmacokinetic profiles and drug–drug interaction (DDI) effect for atorvastatin and its metabolites in different DDI scenarios. The predictive performance of the model was assessed by comparing predicted results to observed data after coadministration of atorvastatin with different medications such as itraconazole, clarithromycin, cimetidine, rifampin and phenytoin. This population based PBPK model was able to describe the concentration–time profiles of atorvastatin and its two metabolites reasonably well in the absence or presence of those drugs at different dose regimens. The predicted maximum concentration (Cmax), area under the concentration–time curve (AUC) values and between-phase ratios were in good agreement with clinically observed data. The model has also revealed the importance of different metabolic pathways on the disposition of atorvastatin metabolites. This PBPK model can be utilized to assess the safety and efficacy of atorvastatin in the clinic. This study demonstrated the feasibility of applying PBPK approach to predict the DDI potential of drugs undergoing complex metabolism.

1. Introduction

Coronary heart diseases are the number one cause of death worldwide. In the United States, coronary heart disease and cardiovascular disease account for nearly 40% of all deaths each year (Smith et al., 2009). High levels of cholesterol, or hypercholesterolemia, is a major risk factor leading to the development of atherosclerotic diseases, such as coronary heart disease, carotid artery disease and chronic kidney disease. The 3-hydroxy-3-methylglutaryl-coenzyme (HMG–CoA) reductase inhibitors, also known as statins, are the first-line agents and the most effective class of drugs for lowering serum low-density lipoprotein cholesterol concentrations (Smith et al., 2009). Atorvastatin is the most commonly prescribed statins in the United States. Although it is generally considered as a safe and effective drug, adverse effects have been observed (Shin et al., 2011). It has been reported that 3–8% of patients taking atorvastatin experienced muscle-related adverse effects such as myopathy and rhabdomyolysis (Sipe et al., 2003; Thompson et al., 2003; Joy and Hegele, 2009; Shin et al., 2011). Statin-associated myopathy is related to the systemic exposure of the drug, and its incidence increases about fivefold when statins are coadministered with medications that share their metabolic pathways and/or increase their systemic exposure (Hodel, 2002; Jacobson, 2004).

Atorvastatin is administered orally as calcium salt of the active hydroxyl acid form. It is well absorbed but has a low oral bioavailability (F), which is approximately 14% due to substantial first-pass metabolism (Lennernas, 2003). The pharmacologically active atorvastatin (acid) is biotransformed to its corresponding lactone form via a coenzyme A–dependent or an acyl glucuronide intermediate pathway (Kearney et al., 1993; Prueksaritanont et al., 2002). Both atorvastatin and atorvastatin lactone are further metabolized to form hydroxylated metabolites, primarily via cytochrome P450 (CYP) 3A4 enzyme mediated metabolic pathway (Jacobsen et al., 2000). The lactone forms of atorvastatin and its metabolites can also be hydrolyzed back into their corresponding acid forms

Abbreviations: AUC, area under the concentration–time curve; CL, clearance; Cmax, maximum concentration; CYP, cytochrome P450; DDI, drug–drug interaction; F, bioavailability; HMG–CoA, 3-hydroxy-3-methylglutaryl–coenzyme A; Jmax, maximum rate of transporter-mediated efflux; Km, Michaelis–Menten constant; OATP, organic anion transporting polypeptide; PBPK, physiologically based pharmacokinetic; P-gp, P-glycoprotein; UGT, UDP-glucuronosyltransferase; Vmax, maximum rate; Vss, volume of distribution.

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nonenzymatically or by esterases and paraoxonases (Kearney et al., 1993; Billecke et al., 2000; Prueksaritanont et al., 2002). Atorvastatin has also shown to be a substrate of the efflux transporter P-glycoprotein (P-gp) and organic anion transporting polypeptide (OATP1B1) (Konig et al., 2000; Wu et al., 2000). The polymorphism of OATP1B1 can affect the pharmacokinetic profiles and exposure of atorvastatin (Pasanen et al., 2007). The major hydroxylated metabolites, 2-hydroxy-atorvastatin acid and 4-hydroxy-atorvastatin acid, are pharmacologically equipotent to parent atorvastatin and significantly contribute to the inhibitory activity on HMG–CoA reductase during treatment (Lennernas, 2003). The pharmacologically inactive lactone forms, atorvastatin lactone, 2-hydroxy-atorvastatin lactone and 4-hydroxy -atorvastatin lactone, have been suggested to be associated with the adverse events of muscle toxicity and cause statin-induced myopathy (SIM) and rhabdomyolysis (Hermann et al., 2006).

Although the pharmacokinetics of atorvastatin metabolites, in addition to the parent atorvastatin, is equally important for assessing the safety and therapeutic efficacy, it has been poorly investigated. Many clinical drug–drug interaction (DDI) studies only measured the concentrations of atorvastatin, or sometimes together with the equivalent concentrations of metabolites, probably due to the lack of good quantitation methods (Lennernas, 2003). Since administration of statins usually constitute part of a multidrug regimen (Williams and Feely, 2002; Neuvonen et al., 2006), reliable prediction of the parent and metabolite pharmacokinetic profiles in the presence of other drugs is of significant value in the clinic.

Physiologically-based pharmacokinetics (PBPK) modeling and simulation approach is a very useful mechanistic tool to quantitatively predict complicated DDIs. It provides many advantages over static models. PBPK model incorporates both drug-specific properties and system-specific factors in a dynamic way. The inter-individual variability of the physiological and anatomical parameters can be integrated to account for the differences of population subgroup related to age, sex, ethnicity and disease impact. Recently, PBPK models have been increasingly used in pharmaceutical research and drug development, and gained acceptance in regulatory decision-making process (Huang, 2012; Huang and Rowland, 2012; Leong et al., 2012; Zhao et al., 2012; Sinha et al., 2014). A few PBPK models have been established for the statins such as simvastatin, pravastatin and rosuvastatin, which are proved to useful to predict the drug disposition in humans (Watanabe et al., 2009; Lippert et al., 2012; Jamei et al., 2014; Rose et al., 2014).

The aim of the present work is to develop a mechanistic PBPK model for atorvastatin and its major metabolites 2-hydroxy-atorvastatin acid and atorvastatin lactone. The model incorporated the physicochemical and pharmacokinetic properties of the compounds based on the findings from *in vitro* and *in vivo* studies. The PBPK model was qualified by comparing the predicted concentration–time profiles and pharmacokinetic parameters to corresponding literature reported values at different DDI scenarios. The simulation results of atorvastatin coadministered with CYP3A4 inhibitor (itraconazole, clarithromycin, or cimetidine), or CYP3A4 inducer (rifampin or phenytoin) have been assessed. To the best of our knowledge, such a predictive PBPK model encompassing both parent and metabolites for the statins has not been established. In addition, the hepatic transporter OATP1B1 mediated uptake of atorvastatin was added and validated with the observed data after coadministration of a single dose of rifampin. This validated model for atorvastatin and its metabolites provide insightful information to help characterize the formation and metabolism of atorvastatin metabolites, which would never be assessed by *in vivo* studies.

2. Materials and methods

2.1. Model development for atorvastatin, 2-hdyroxy-atorvastatin acid and atorvastatin lactone

A PBPK model consisting of atorvastatin and the two metabolites, 2-hydroxy-atorvastatin acid and atorvastatin lactone was constructed with the Simcyp™ population-based ADME simulator (V14; Simcyp Limited, Sheffield, UK). Briefly, for atorvastatin, its absorption was described with the advanced dissolution, absorption and metabolism (ADAM) model, distribution was described using a whole-body PBPK model with tissue partition coefficients predicted by the Poulin, Theil and Berezhkovskiy method (Poulin and Theil, 2002; Berezhkovskiy, 2004), and elimination process was characterized using enzyme kinetics of CYP3A4, CYP2C8, UDP-glucuronosyltransferase (UGT)1A1, UGT1A3. The formation of 2-hydoxy-atorvastatin acid was described as a result of atorvastatin metabolism mediated by CYP3A4, its distribution was described with a minimal PBPK model and the elimination process was characterized with the enzyme kinetics model involved CYP3A4 and other unspecified pathways. For atorvastatin lactone, its formation was assumed as the result of atorvastatin metabolism mediated by UGT1A1 and UGT1A3, its distribution was modeled with the minimal PBPK model and elimination was described with enzyme kinetics model involved CYP3A4. The details of PBPK model inputs for atorvastatin and metabolites are shown in Tables 1–3.

2.1.1. Drug-specific parameters for atorvastatin

The physicochemical properties of atorvastatin, including molecular weight, log*P*, p*K*a, blood-to-plasma ratio and fraction unbound in plasma were obtained from literature as listed in Table 1. The ADAM model was used to describe the absorption process. The ADAM model has incorporated various features, which can handle different formulations, fasted or fed states, transporter-mediated efflux, and metabolism in the GI tract. Since CYP3A4 is the major enzyme responsible for atorvastatin metabolism, and CYP3A4 is present in the small intestine, the ADAM model can incorporate the intestinal CYP3A4 contribution to the model. The effective permeability in human was predicted using the Caco-2 permeability measured in the previous study (Li et al., 2011). The full PBPK model was used to describe the distribution. The volume of distribution (Vss) and tissue-to-plasma partitioning coefficients (Kp) were estimated using *in silico* method developed by Poulin, Theil and Berezhkovskiy (Poulin and Theil, 2002; Berezhkovskiy, 2004). The Kp scalar of 2.0 was estimated by optimizing with the *in vivo* observed concentration–time profiles. The enzyme kinetic elimination model was used to describe the elimination process, which can predict the DDI effect upon coadministration with a perpetrator of specific enzyme. First, the *in vivo* clearance (CL) of atorvastatin was applied based on the value obtained following intravenous infusion in human (Lennernas, 2003) and then finetuned based on observed oral data. Then the CL of atorvastatin was attributed to metabolism mediated by CYP3A4, CYP2C8, UGT1A1 and UGT1A3, and renal excretion (<1%). The maximum rate of metabolite formation (Vmax) and Michaelis–Menten constant (km) for CYP3A4, CYP2C8, UGT1A1 and UGT1A3 were obtained from *in vitro* studies (Jacobsen et al., 2000; Prueksaritanont et al., 2002; Lennernas, 2003). The Inter System Extrapolation Factors (ISEFs) were utilized for these enzymes to obtain the best simulation results compared to observed data. Atorvastatin has been shown as a substrate of the P-glycoprotein (P-gp) transporter (Wu et al., 2000). The *in vitro* maximum rate of transporter-mediated efflux (Jmax) and km