Pharmacokinetic Modeling of Simvastatin, Nelfinavir and Their Interaction in Humans

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Abstract*— Background: Simvastatin, a commonly used HMG-CoA reductase inhibitor, is extensively metabolized by CYP3A4. Therefore, co-administration of simvastatin and CYP3A4 inhibitor can affect simvastatin pharmacokinetics. Nelfinavir, a protease inhibitor, and its major metabolite (M8) are known to be potent CYP3A4 inhibitors. When simvastatin and nelfinavir are co-administered, simvastatin pharmacokinetics is significantly altered and may result in an increased risk of rhabdomyolysis. Objective: To develop a mathematical model describing a drug-drug interaction between simvastatin and nelfinavir in humans. Methods: Eligible pharmacokinetic studies were selected from Pubmed database and concentration time course data were digitally extracted and used for model development. Compartmental pharmacokinetic models for simvastatin and nelfinavir were developed separately. A drug-drug interaction model of simvastatin and nelfinavir was subsequently developed using the prior information. Finally, the final drug-drug interaction modeled was validated against observed simvastatin concentrations. Results: Three compartmental pharmacokinetic models were successfully developed. Simvastatin pharmacokinetics was best described by a one compartment model for simvastatin linked to its active form, simvastatin hydroxy acid. Nelfinavir pharmacokinetics could be adequately described by a one compartment parent-metabolite model. Our final drug-drug interaction model predicted an increase in simvastatin exposure which is in line with clinical observations linking the simvastatin-nelfinavir combination to an increased risk of rhabdomyolysis. Conclusion: Simvastatin-nelfinavir pharmacokinetic interaction can be explained by our final model. This model framework will be useful in further advanced developing other mechanism based drug-drug interaction model used to predict the risk of rhabdomyolysis occurrence in patients prescribed simvastatin and nelfinavir concurrently.

I. Introduction

Simvastatin, a member of HMG-CoA reductase inhibitors, is widely used in the management of dyslipidemia. The drug competitively inhibits the conversion of HMG-CoA to mevalonate, thereby, reducing the biosynthesis of cholesterol. Generally, statins are well tolerated with a known reversible elevation in transaminases. However, rhabdomyolysis, a rare but serious adverse drug reaction associated with simvastatin use has been reported. Rhabdomyolysis is characterized as a severe form of myopathy, typically with creatine kinase level > 10 times the upper limit of normal. The risk of rhabdomyolysis increases with the higher dose of simvastatin. Moreover, most of reported rhabdomyolysis cases may be caused by the drug interaction that inhibits cytochrom P-450 (CYP) 3A4, used for simvastatin metabolism [1-4]. Simvastatin is an inactive lactone form and has to be converted to its active form, simvastatin hydroxy acid, by esterases and even without enzymes in order to exert its therapeutic effect. Simvastatin hydroxy acid is also metabolized by CYP3A4 as well as CYP2C8 [5-6].

Nelfinavir is a selective inhibitor of protease, an enzyme responsible for post-translational processing of HIV propeptides. The use of protease inhibitors in combination with reverse transcriptase inhibitors has shown satisfactory reduction in morbidity and mortality in Human Immunodeficiency Virus (HIV) infected patients [7-8]. According to pharmacokinetic studies of nelfinavir, the drug could be metabolized by CYP3A4, 2C19, 2C9, and 2D6, where CYP3A4 accounts for about 50% of the metabolism. Following its metabolism, one major (hydroxyl-t-butylamide; M8) and several minor oxidative metabolites were found in plasma. The major metabolite has shown comparable in vitro activity with that of the parent drug. Additionally, like other protease inhibitors, nelfinavir is an inhibitor of CYP3A4, an enzyme responsible for metabolism of several drugs [9-11].

Metabolic complications including hyperlipidemia, diabetes mellitus, hypertension, osteopenia and lipodystrophy could be associated with HIV infection and treatment [12]. Therefore, simvastatin and nelfinavir are possibly co-prescribed. Given the overlap pathways of metabolism of both drugs, the drug-drug interaction between them might be expected. Pharmacokinetic interaction study between nelfinavir and simvastatin has shown an increase of 505% in the area under concentration time curve (AUC) and an increase of 517% in the maximum concentration (C_{max}) of simvastatin after the addition of nelfinavir in healthy volunteers [13]. Based on these results, it is of importance to explore possible mechanisms by which drug interaction occurs. Therefore, the objective of this work was to develop a semi-mechanistic drug-drug interaction model between simvastatin and nelfinavir at a level of CYP3A4.

II. Materials and Methods

This study was approved by Naresuan University Institutional Review Board and was conducted using data from selected published literatures [13] as follows:

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A. Study design and sample collection of the selected study used for drug-drug interaction model development [13]

This study was an open-label, sequential, multiple dose, single-center study to determine the pharmacokinetic interaction between nelfinavir and atorvastatin or nelfinavir and simvastatin in healthy volunteers. Medically normal subjects aged 18 to 55 were considered for inclusion. Exclusion criteria included: use of medications that might affect CYP3A4 activities, presence or recent history of alcohol consumption, illegal drug use or smoking, known history of HIV positive, hepatitis B, or hepatitis C. In period 1, subjects were administered simvastatin (Zocor®) 20 mg in the morning for 14 days. In period 2, same subjects received simvastatin 20 mg in the morning plus nelfinavir 1,250 mg twice daily for additional 14 days.

Simvastatin trough samples were collected prior to dosing on day 1, 5, 10, 20 and 25. Serial blood simvastatin concentrations were collected at pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 h post dose on days 14 and 28.

B. Drug-Drug interaction model of simvastatin and nelfinavir

Respective pharmacokinetic models of nelfinavir and simvastatin were developed separately using selected clinical studies [13-16]. A combined drug-drug interaction model was subsequently developed; the interaction model incorporated a basis of competitive inhibition at the level of CYP3A4. All of the computer coding and simulations were performed using ACSLX 3.0.2.2 Tox Sim (Aegis Technologies, Huntsville, AL, USA), a FORTRAN language-based computer program. A schematic diagram of simvastatin and nelfinavir pharmacokinetic interaction is shown in Figure 3.

C. Model evaluation

The drug-drug interaction model between simvastatin and nelfinavir was evaluated using a simulation approach. The pharmacokinetic parameters obtained from the final model were used to simulate simvastatin concentrations. The simulated concentrations were plotted against observed data from the selected clinical study.

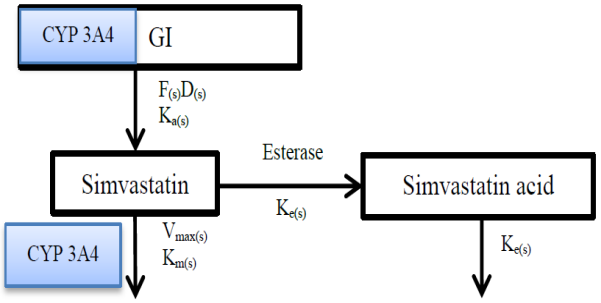

Figure 1. Schematic diagram of simvastatin pharmacokinetics

III. RESULTS AND DISCUSSION

A priori information from separate models for simvastatin and nelfinavir was used for conducting an interaction model. A one-compartment model with first order absorption, linked to its active form, simvastatin hydroxy acid, best described pharmacokinetics of simvastatin (Fig. 1). While, a pharmacokinetic model for nelfinavir was a one-compartment parent, one-compartment metabolite model (Fig. 2). Metabolic clearances of both simvastatin and nelfinavir were modeled as CYP-mediated biotransformation and were parameterized in terms of maximum rate of metabolism (V_{max}) and michaelis constant (K_m).

TABLE I. PHARMACOKINETIC PARAMETERS OF SIMVASTATIN AND NELFINAVIR USED IN SIMULATION PROCESSES

Drug	Pharmacokinetic	Result
Nelfinavir (N)	F	0.80
	$K_{a(N)}$ (h^{-1})	0.70
	$V_{D(N)}$ (L)	161.12
	$V_{D(NM)}$ (L)	438.37
	$V_{max(N)}$ (μM/h)	950.0
	$K_{m(N)}$ (μM)	21.6
	$K_{e(N)}$ (h^{-1})	0.04
	$K_{e(NM)}$ (h^{-1})	0.25
S + N	$K_{i(N)}$ (μM)	4.8
	$K_{i(NM)}$ (μM)	4.4
	$F_{(S)}$	0.4
Simvastatin (S)	F	0.05
	$K_{a(S)}$ (h^{-1})	0.85
	$V_{D(S)}$ (L)	150
	$V_{D(SM)}$ (L)	22.5
	$V_{max(S)}$ (μM/h)	6.0
	$K_{m(S)}$ (μM)	5.25
	$K_{e(S)}$ (h^{-1})	0.20
	$K_{e(SM)}$ (h^{-1})	0.90

N: nelfinavir, NM: nelfinavir metabolite, S: simvastatin, F: bioavailability, K_a: absorption rate constant, V_d: volume of distribution, V_{max}: maximum rate of metabolism, K_m: michaelis constant, K_e: elimination rate constant, K_i: inhibition constant

The pharmacokinetic interaction between nelfinavir and simvastatin was based on an inhibition of CYP3A4 in both gastrointestinal walls and hepatocytes. The major metabolite, M8, is also an inhibitor of CYP3A4. Based on the previous reported pharmacokinetic parameters of simvastatin after addition of nelfinavir with approximately 6 fold increase in C_{max} of simvastatin, we adjusted the bioavailability of simvastatin obtained from prior information of 0.05 to 0.4. The adjustment of bioavailability yielded a reasonable fit of simulated simvastatin concentrations to the data.

The proposed mathematical models for the inhibition of CYP3A4 in hepatocytes by nelfinavir were as follows:

Rate of simvastatin metabolism:

$$\text{Rate} = \left(K_{a(S)} \times AS_{GI}\right) - \frac{V_{max(S)} \times C_{(S)}}{K_{m(S)}\left(1 + \frac{C_N}{K_{i(N)}} + \frac{C_{NM}}{K_{i(NM)}}\right) + C_S} - \left(K_{e(S)} \times AS\right)$$

Where $K_{a(S)}$, $K_{e(S)}$, $K_{m(S)}$, and $V_{max(S)}$ are absorption rate constant, elimination rate constant, Michaelis constant, and maximum rate of metabolism of simvastatin, respectively. AS and AS_{GI} are the amount of simvastatin in central and gastrointestinal compartment, respectively. $C_{(S)}$, $C_{(N)}$ and $C_{(NM)}$ are the concentrations of simvastatin, nelfinavir and nelfinavir metabolite (M8), respectively. K_i is the inhibition constant of nelfinavir.

Fixing the nelfinavir model parameters at their prior information was essential for the model to estimate the inhibition effect of the drug. The pharmacokinetic parameters of the final drug-drug interaction model are summarized in Table 1.

The final drug-drug interaction model between simvastatin and nelfinavir was evaluated for its predictive power by simulation approach. Simvastatin concentrations were simulated and plotted alongside with the actual observed data. Figure 4 shows the results of the simulation. Overall, the drug-drug interaction model adequately described the observed concentrations. The higher predicted concentrations during absorption phase could be due to the effects of efflux transporters expressed in the gastrointestinal tracts [1].

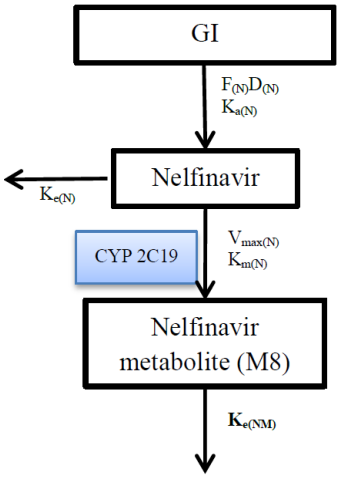

Figure 2. Schematic diagram of nelfinavir pharmacokinetics

Given that this drug-drug interaction model satisfactorily described observed simvastatin concentration levels, this model might be used to predict simvastatin concentration time course and respective AUC in patients prescribed simvastatin with nelfinavir. This predicted AUC, then, can be used for predicting the risk of rhabdomyolysis.

Our final model has some limitations. Those include: 1) it was developed based on data obtained from healthy volunteers, and; 2) it might not be able to extrapolate to other population. Therefore, confirmation of model

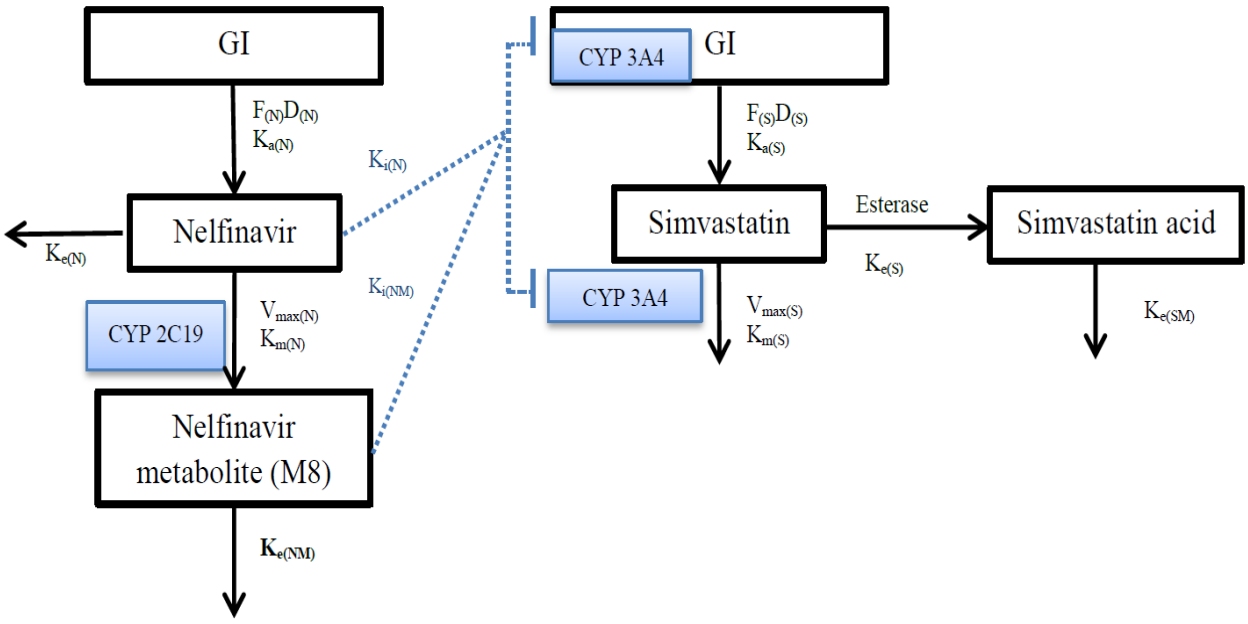

Figure 3. Schematic diagram of simvastatin and nelfinavir pharmacokinetic interaction

predictive ability with data that include HIV infected patients is important. Even though the model limitations are acknowledged, our model can still be used as an aid to further develop a more definitive model given that a more informative data set is available.

Physiologically based pharmacokinetic (PBPK) modeling is a powerful quantitative approach in incorporating any biological process into the models [17-19]. Therefore, to improve our current model, further development of a PBPK model of simvastatin and nelfinavir is warranted.

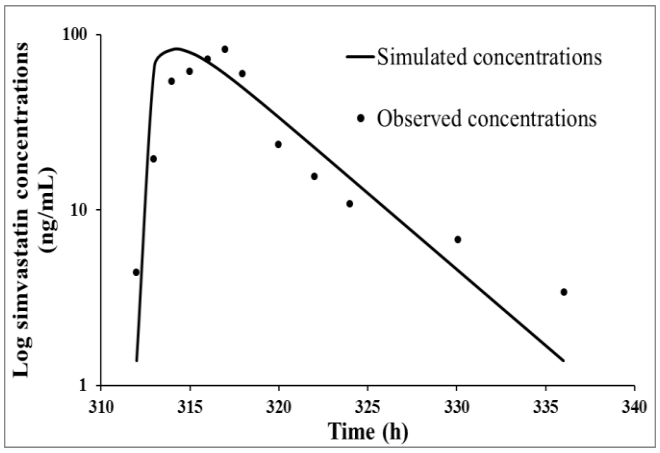

Figure 4. Simulated simvastatin concentrations (20 mg OD) co-administered with nelfinavir (1,250 mg bid) plotted against the actual extracted data from the literature.

IV. CONCLUSIONS

A drug-drug interaction model between simvastatin and nelfinavir has been developed and provides an adequate description of simvastatin clearance inhibition by nelfinavir. This generated model can be used as a useful tool for prediction of the risk of rhabdomyolysis occurrence in patients prescribed simvastatin whilst on nelfinavir, or vice versa.

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