A Pharmacokinetic Drug-Drug Interaction Model of Simvastatin and Clarithromycin in Humans

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***Abstract*— Background: Simvastatin is a HMG-CoA reductase Inhibitor and a substrate of CYP3A4. Clarithromycin is a commonly used macrolide antibiotics and a potent inhibitor of CYP3A4. When co-administered with simvastatin, clarithromycin can significantly increase simvastatin plasma concentration levels, thereby, increase the risk of rhabdomyolysis. At present, pharmacokinetic data of the interaction between both drugs are available. However, they are being used for semi-quantitative application only, not for quantitative prediction. We aimed to develop a mathematical model describing a drug-drug interaction between simvastatin and clarithromycin in humans. Methods: Selected pharmacokinetic interaction study was obtained from PubMed search. Concentration-time course data were subsequently extracted and used for model development. Compartmental pharmacokinetic interaction model was developed using Advanced Continuous Simulating Language Extreme (ACSLX), a FORTRAN language-based computer program. Results: The drug-drug interaction between simvastatin and clarithromycin was modeled simultaneously with a parent-metabolite model for clarithromycin and a one-compartment model for simvastatin linked to its active form, simvastatin hydroxy acid. The simulated simvastatin concentrations obtained from the final model displayed satisfactory goodness of fit to the data from the literature. Conclusion: Our model could successfully describe concentration-time course of simvastatin-clarithromycin interaction. The resulting interaction model can be able to use for further development of a quantitative model predicting rhabdomyolysis occurrence in patients concurrently receiving simvastatin and clarithromycin.**

I. Introduction

Simvastatin is a HMG-CoA reductase inhibitor widely used to lower LDL cholesterol and to reduce cardiovascular risk. One of the serious side effects associated with statin use is rhabdomyolysis, a syndrome characterized by the leaking of myoglobin and other intracellular proteins and electrolytes into circulation. The incidence of this adverse drug reaction increases about five folds when certain statins are co-administered with medications known to inhibit statin metabolism including fibrates, calcium channel blockers, macrolide antibiotics, imidazole antifungal agents or protease inhibitors [1-4]. Simvastatin undergoes extensive metabolism via cytochrome P450 (CYP) 3A4. Its active form (simvastatin hydroxy acid) is also metabolized by CYP 3A4 and CYP2C8 [5-7].

Clarithromycin, structurally related to erythromycin, is a macrolide antibacterial with a 14-membered ring. The methylation of the hydroxyl group at position 6 on the lactone ring makes it being acid-stable drug. Clarithromycin undergoes extensive metabolism by hydroxylation and oxidative N-demethylation resulted in at least 8 metabolites, where 14-hydroxy clarithromycin is the major metabolite recovered in plasma and urine [8]. *In vitro* study has shown that CYP3A is the major enzyme responsible for clarithromycin metabolism [8]. It has been reported that clarithromycin metabolism is saturable and its elimination may be a dose-dependent process as shown by a 13-fold increase in area under concentration time curve (AUC), prolonged elimination half-life ($t_{1/2}$), and a decrease in total body clearance (CL/F) when the dose was increased from 250 to 1200 mg [8-10]. Another dose- ranging study of 100, 200, 400, 600, 800 and 1200 mg of clarithromycin has confirmed the dose-dependent elimination of clarithromycin as evidenced by the increase in elimination half-life. Additionally, it has been reported that clarithromycin is an inhibitor of CYP3A4 which can increase both AUC and steady state concentrations (C_{ss}) of drugs that are primarily metabolized by this enzyme [9, 11].

Jacobson *et al.* reported an increase in maximum concentration (C_{max}) and AUC of simvastatin by 609% and 885%, respectively, when co-administered with clarithromycin [12]. Given these results, the increase risk of rhabdomyolysis in patients concurrently receiving clarithromycin and simvastatin should be of concern. Therefore, the objective of this study was to develop a pharmacokinetic interaction model between simvastatin and clarithromycin in humans.

II. Materials and Methods

This study was approved by Naresuan University Institutional Review Board and was performed using clinical data acquired from selected papers [12] as follows:

A. Study design and sample collection of the study used for drug-drug interaction model development [12]

The design of the selected study was a 4 small, short-term parallel-group studies that evaluated the effects of CYP3A4 inhibitors (verapamil, mibefradil, itraconazole, and clarithromycin) on the multiple-dose pharmacokinetics of statins (pravastatin, simvastatin, or atorvastatin) in 4 groups of healthy subjects. Forty-five healthy men and women aged 18-60 years who were not currently using agents metabolized

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by CYP3A4 were enrolled in this study. Subjects were randomly assigned to open-label administration of pravastatin 40 mg (n = 15), simvastatin 40 mg (n = 15), or atorvastatin 80 mg (n = 15). The subjects were administered statins once daily after breakfast on study days 1 to 7 and days 10 to 17. Clarithromycin 500 mg was administered on days 10 to 18 in the morning and evening. Serum simvastatin concentration levels were obtained on days 7 and 17. The samples were analyzed by liquid chromatography/tandem mass spectrometry.

B. Drug-Drug interaction model of simvastatin and clarithromycin

ACSLX 3.0.2.2 Tox Sim (Aegis Technologies, Huntsville, AL, USA), a FORTRAN language-based computer program was used for model development. The model development process was conducted by, first, developing separate models for simvastatin and clarithromycin using pharmacokinetic data from selected studies [13-17]. The drug-drug interaction model of simvastatin and clarithromycin was subsequently developed. Pharmacokinetic effects of clarithromycin on simvastatin were explored.

C. Model evaluation

The final drug-drug interaction model between simvastatin and clarithromycin was evaluated by means of simulation using ACSLx 3.0.2.2 Tox Sim (Aegis Technologies, Huntsville, AL, USA). Serum simvastatin and simvastatin hydroxy acid concentrations were simulated and plotted against the actual data obtained from the literature.

III. RESULTS AND DISCUSSION

Separate models for simvastatin and clarithromycin were successfully developed and used as a priori information for conducting an interaction model.

The pharmacokinetics of simvastatin was best described by a one compartment model with first order absorption, linked to its active form, simvastatin hydroxy acid. The pharmacokinetics of clarithromycin was also best described by a one-compartment model with first order absorption linked to a metabolite compartment, 14-hydroxy clarithromycin. In addition, the auto-inhibition of clarithromycin on CYP3A4 was incorporated in the model. Both simvastatin and clarithromycin metabolisms were modeled using Michaelis-Menten equation. The estimated model parameters for simvastatin and clarithromycin are presented in Table 1.

A pharmacokinetic interaction model was developed based on the hypothesis that clarithromycin can competitively inhibit CYP3A4 responsible for simvastatin metabolism at both gastrointestinal walls and hepatocytes. However, the major metabolite, 14-hydroxy clarithromycin is not subject to CYP3A4 inhibition. Figure 1 represents a schematic diagram of simvastatin and clarithromycin pharmacokinetic interaction (Note: all parameters' descriptions and their values are shown in table 1).

The inhibition of CYP3A4 on gastrointestinal walls would result in an increase bioavailability of simvastatin. According to the nine fold increased in AUC of simvastatin when co-administered with clarithromycin, we increased the bioavailability of simvastatin from 0.04 to 0.375 when conducted an interaction model. The clarithromycin model parameters were fixed at their estimates obtained from the previous step. The pharmacokinetic parameters of the drug-drug interaction model are summarized in Table 1.

For the effect of clarithromycin inhibition of CYP3A4 responsible for simvastatin metabolism in hepatocytes, the following equations were used:

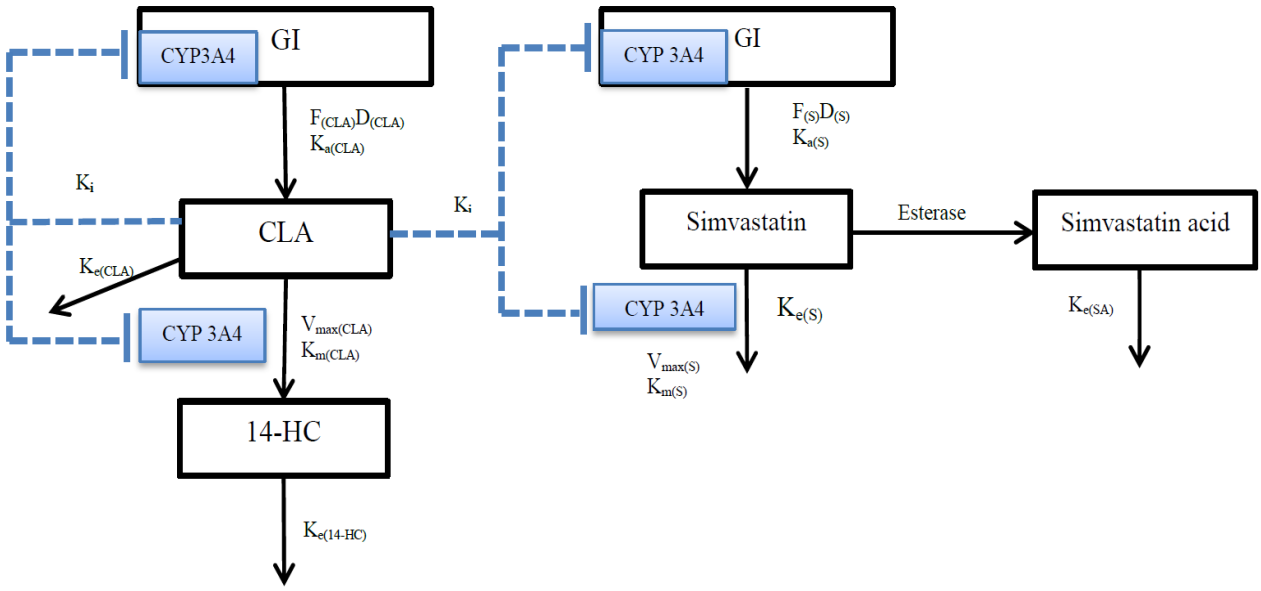

Figure 1. Schematic diagram of Simvastatin and Clarithromycin pharmacokinetic interaction

Rate of simvastatin metabolism:

$$\text{Rate} = \left(K_{a(S)} \times A_{(S)GI}\right) - \left(K_{e(S)} \times A_{(S)}\right) - \frac{V_{max(S)} \times C_{(S)}}{K_{m(S)}\left(1 + \frac{C_{(CLA)}}{K_i}\right) + C_{(S)}} \quad (1)$$

Where $K_{a(S)}$, $K_{e(S)}$, $K_{m(S)}$, and $V_{max(S)}$ are absorption rate constant, elimination rate constant, Michaelis-Menten constant, and maximum rate of metabolism of simvastatin, respectively. $A_{(S)}$ and $A_{(S)GI}$ are the amount of simvastatin in central and gastrointestinal compartment, respectively. $C_{(S)}$, and $C_{(CLA)}$ are the concentrations of simvastatin and clarithromycin, respectively. K_i is the inhibition constant of clarithromycin.

TABLE I. PHARMACOKINETIC PARAMETERS OF SIMVASTATIN AND CLARITHROMYCIN USED IN SIMULATION PROCESS

Drug	Pharmacokinetic	Result
Clarithromycin (CLA)	$F_{(CLA)}$	0.55
	$K_{a(CLA)}$ (h^{-1})	5
	$V_{D(CLA)}$ (L)	100
	$V_{D(14HC)}$ (L)	0.25
	$V_{max(CLA)}$ (μM/h)	22.0
	$K_{m(CLA)}$ (μM)	60.0
	$K_{e(CLA)}$ (h^{-1})	0.136
	$K_{e(14HC)}$ (h^{-1})	0.099
S + CLA	K_i (μM)	0.3
	F	0.375
Simvastatin (S)	$F_{(S)}$	0.04
	$K_{a(S)}$ (h^{-1})	0.60
	$V_{D(S)}$ (L)	150
	$V_{D(SA)}$ (L)	22.5
	$V_{max(S)}$ (μM/h)	6.0
	$K_{m(S)}$ (μM/h)	5.25
	$K_{e(S)}$ (h^{-1})	0.30
	$K_{e(SA)}$ (h^{-1})	0.90

CLA: clarithromycin, S: simvastatin, SA: simvastatin acid, 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

Computer simulations were used to evaluate the performance of the final model. Figure 2 shows the simulated simvastatin concentrations plotted against the actual observed data from the literature. Overall, this pharmacokinetic interaction model adequately described the observed simvastatin concentrations. The final model predicted higher concentrations during the absorption phase which could be explained by efflux transporters expressed in the gastrointestinal tracts [5].

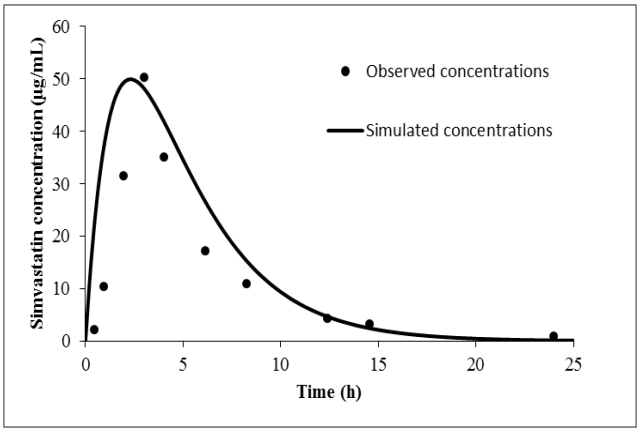

Figure 2. Simulated simvastatin concentrations co-administered with clarithromycin plotted against the actual extracted data from the literature.

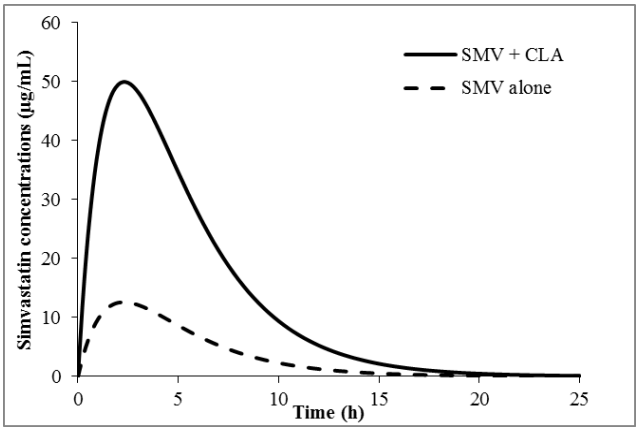

Figure 3. Simulated concentrations of simvastatin administered as monotherapy (40 mg once daily) versus combination therapy with clarithromycin (500 mg twice daily).

A physiologically based pharmacokinetic model of clarithromycin inhibition of CYP3A has reported time-dependent changes in gastrointestinal and hepatic metabolism of clarithromycin [16]. Our model, however, did not account for time-dependent changes in gut wall CYP3A activity. Figure 3 is the simulations for simvastatin given as monotherapy (40 mg once daily) versus in combination with clarithromycin (500 mg twice daily). As would be expected, simvastatin concentrations when co-administered with clarithromycin were higher as compared to those administered as monotherapy. With the estimated inhibition effect of clarithromycin of 0.3 μM, we found 5-fold and 4-fold higher in maximum concentration and area under concentration time curve of simvastatin, respectively.

Rhabdomyolysis occurrence in patients co-prescribed simvastatin and clarithromycin has been reported [1-2], [18].

Although, the mechanism of simvastatin's myotoxic effects is unclear, several studies have reported that these adverse effects are higher when the plasma levels of simvastatin are increased especially when the drug is prescribed with CYP3A4 inhibitors [19-21]. In this case, our developed model would be useful in predicting simvastatin concentrations in patients co-prescribed clarithromycin and in identifying patients who are at higher risks of developing rhabdomyolysis. However, given that this model was developed based on the data obtained from only 15 healthy subjects of whom simvastatin pharmacokinetics might be different from those in patients, extrapolation to other populations will be limited. To refine our current model, development of a physiologically based pharmacokinetic model [22-24] with a description of a competitive inhibition at the level of CYP3A4 may improve our predictions. The validity of this model should be confirmed by another data set obtained from patients with larger sample size.

IV. CONCLUSIONS

The final pharmacokinetic drug interaction model adequately described the observed concentrations of simvastatin co-administered with clarithromycin. The extent of CYP3A4 inhibition by clarithromycin was explained by Michaelis-Menten equation. The presented pharmacokinetic drug interaction model may allow for future model development that can be used to predict the risk of rhabdomyolysis in clinical practice.

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