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

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Abstract— **Background: Verapamil is a calcium channel blocker commonly used in treatments of hypertension. Verapamil and its active metabolite, norverapamil, are known to be CYP3A4 inhibitors. Co-administration of verapamil with CYP3A4 substrates can alter the pharmacokinetics of the substrates. Simvastatin, a commonly used HMG-CoA reductase inhibitor for the treatment of hypercholesterolemia is extensively metabolized by CYP3A4. Therefore, concomitant use of simvastatin and verapamil can increase simvastatin plasma concentration levels, resulting in a higher risk of rhabdomyolysis, a serious adverse drug reaction. Even though, pharmacokinetic data regarding the interaction between both drugs have been published, their use is limited to semi-quantitative applications. Therefore, we aimed to develop a mathematical model describing drug-drug interaction between simvastatin and verapamil in humans. Methods: Eligible pharmacokinetic interaction study between simvastatin and verapamil in humans was selected from PubMed database. The concentration-time courses from this study were digitally extracted and used for model development. Results: The drug-drug interaction between simvastatin and verapamil was modeled simultaneously with a two compartment model for verapamil with its active metabolite, norverapamil and a one compartment model for simvastatin with its active form, simvastatin hydroxy acid. The effects of verapamil and norverapamil on pharmacokinetics of simvastatin and its active form, simvastatin hydroxy acid were described by Michaelis-Menten equation. Simulated simvastatin and simvastatin hydroxy acid concentrations obtained from the final model produced a good fit to the dataset from a literature. Conclusion: The final model adequately describes pharmacokinetic interaction between simvastatin and verapamil which can be helpful in prediction of rhabdomyolysis in patients with concurrent use of these drugs.**

I. Introduction

Simvastatin, a HMG-CoA reductase inhibitor (statin), is widely used to lower LDL cholesterol and reduce cardiovascular risk. It has been recognized that statins can occasionally cause myopathy or even rhabdomyolysis (a severe form of myopathy, typically with creatine kinase level > 10 times the upper limit of normal) [1-3]. Moreover, statin therapy is also known to increase hepatic transaminase levels even though clinical hepatitis is uncommon [2]. Simvastatin is extensively metabolized via cytochrome P450 (CYP) 3A4. Its active form (simvastatin hydroxy acid) is also metabolized by CYP 3A4 and CYP2C8 [1], [4]. The risk of simvastatin adverse effects can increase when the drug is co-adminstered with CYP3A4 inhibitors such as itraconazole, ritonavir, verapamil and diltiazem [5-8].

Verapamil, a calcium channel blocking drug, is widely used in the treatment of arrhythmias. Because of its vasodilator and negative inotropic properties, verapamil is also used in the treatment of ischemic heart disease and hypertension [9-10]. The drug is extensively metabolized by the liver via N-dealkylation, N-demythylation and O-demethylation with less than 5% being excreted unchanged in the urine. The enzymes responsible for verapamil biotransformation include CYP3A4 and CYP1A2. Verapamil is metabolized to three initial metabolites, norverapamil, D-617, and D-702. Both verapamil and its major metabolite, norverapamil, have been reported to inhibit CYP3A4 [11-13].

In clinical setting, simvastatin and verapamil are often prescribed together in patients with hypercholesterolemia and hypertension. Given the substantial overlap between the pharmacokinetic pathways involved in metabolism of both simvastatin and verapamil, the objective of this study was to develop a mathematical model describing drug-drug interaction between simvastatin and verapamil in humans.

II. Materials and Methods

Prior to our experiments, our protocol was approved by Naresuan University Institutional Review Board and was performed using data obtained from selected papers as follows:

A. Study design and sample collection of the selected study used for drug-drug interaction model development [6]

This study was a double-blind, three-phase crossover study with a 3 week washout interval. Twelve healthy volunteers aged 20-29 years were included in the study. All subjects were administered three pre-treatments (erythromycin 500 mg, verapamil 80 mg or matching placebo) three times a day for 2 days. Simvastatin 40 mg was then administered on day 2. Blood samples were collected at pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after administration. HPLC was used for quantification of both simvastatin and simvastatin hydroxy acid concentrations.

Simvastatin and simvastatin hydroxy acid concentration time courses were extracted from this study using Plot Digitizer 2.1 (Free Software Foundation, Inc., Boston, MA).

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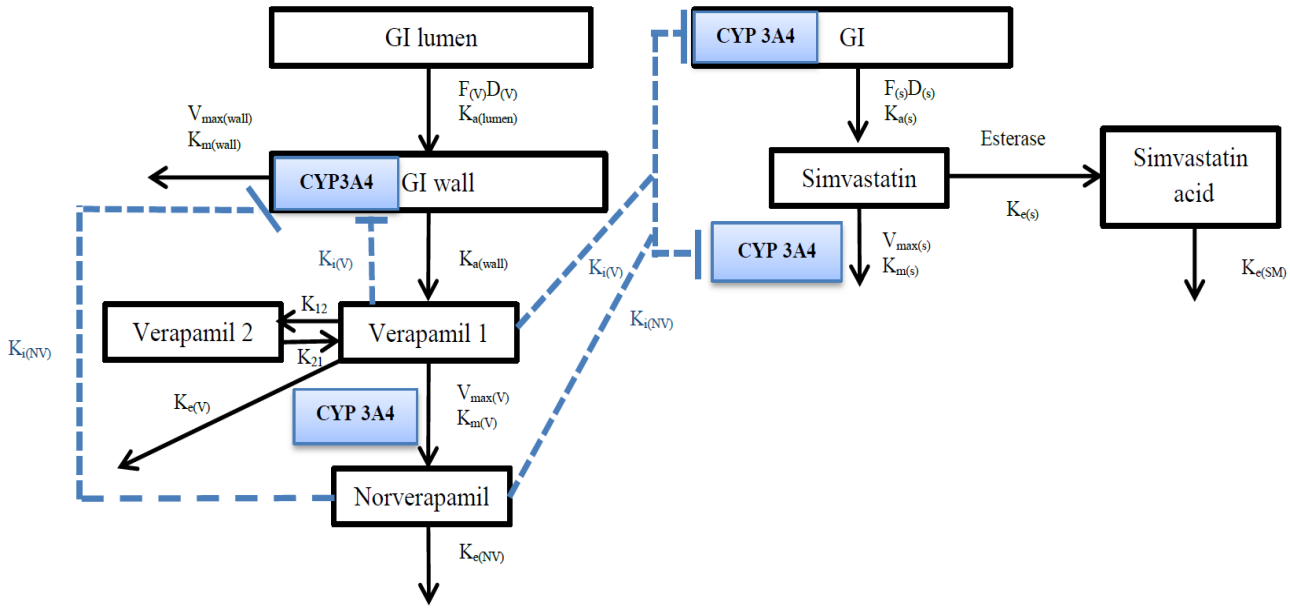


Figure 1. Schematic diagram of simvastatin and verapamil pharmacokinetic interaction

B. Drug-drug interaction model of simvastatin and verapamil

Model development was performed using ACSLX 3.0.2.2 Tox Sim (Aegis Technologies, Huntsville, AL, USA), a FORTRAN language-based computer program. We first developed a model for simvastatin and verapamil separately using concentration data from selected studies [9], [13-14]. Then, pharmacokinetic drug-drug interaction of simvastatin and verapamil was modeled simultaneously. A competitive inhibition process at the level of CYP3A4 was incorporated into the interaction model. A mathematical description of the competitive inhibition was described in equation 2 and 3. The effects of verapamil inhibition of CYP3A4 were explored.

C. Model evaluation

The final drug-drug interaction model between simvastatin and verapamil 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

We first developed separate models for both simvastatin and verapamil administered alone. The pharmacokinetics of verapamil was best described by a two-compartment model linked with its major active metabolite, norverapamil. A one-compartment model linked with its active form, simvastatin hydroxy acid, adequately explains pharmacokinetics of simvastatin. Both developed models for verapamil and simvastatin yielded good predictability as evidenced by the goodness of fit plots of the simulated concentration levels obtained from the model to the actual data (results not shown). The fitted model parameters of both drugs are shown in Table 1.

According to the non-compartmental analyses of drug-drug interaction between simvastatin and verapamil, verapamil has shown to increase mean maximum concentration (C_{max}) and area under serum simvastatin concentration time curve from time zero to 24 hours (AUC_{0-24}) by 3.6 and 4.6 fold, respectively [6]. Additionally, verapamil increased C_{max} and AUC_{0-24} of simvastatin hydroxy acid by 3.4 and 2.8 fold, respectively [6]. Based on these results, pharmacokinetic interaction between simvastatin and verapamil were judged to merit investigation.

For the drug-drug interaction model, we hypothesized that verapamil and norverapamil can inhibit CYP3A4 expressed in both gastrointestinal walls and hepatocytes. The schematic diagram of simvastatin and verapamil pharmacokinetic interaction is shown in Fig. 1 (Note: all parameters' descriptions and their values are shown in table 1). For the inhibition of CYP3A4 on gastrointestinal walls by verapamil, the following relationship was proposed:

$$F_S = FR \times F_{S\text{-}V} \quad (1)$$

Where F_S and $F_{S\text{-}V}$ denote simvastatin bioavailability administered as monotherapy and combination therapy with verapamil, respectively. FR is the bioavailability ratio of simvastatin monotherapy to combination therapy. Due to the inhibition of CYP3A4 on gastrointestinal walls, the bioavailability of simvastatin co-administered with verapamil is expected to be increased. Based on the reported increased in AUC_{0-24} of simvastatin by 4.6 fold, we proposed a 5 fold

increase in bioavailability of simvastatin when co-administered with verapamil. The proposed mathematical equations for the elimination of simvastatin were as follows:

Simvastatin:

$$\text{Rate} = \left(K_{a(S)} \times A_{(S)GI}\right) - \frac{V_{max(S)} \times C_{(S)}}{K_{m(S)}\left(1 + \frac{C_{(V)}}{K_{i(V)}} + \frac{C_{(NV)}}{K_{i(NV)}}\right) + C_{(S)}} - \left(K_{e(S)} \times A_{(S)}\right) \quad (2)$$

Simvastatin acid:

$$\text{Rate} = (K_{e(S)} \times A_{(S)}) - (K_{e(SM)} \times A_{(SM)}) \quad (3)$$

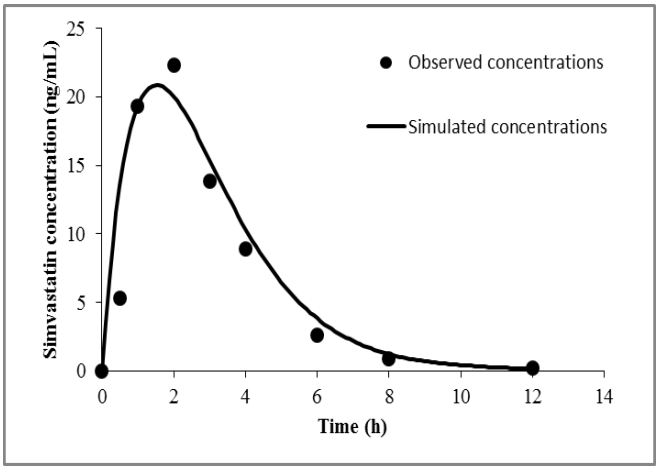
Where $K_{a(S)}$, $K_{e(S)}$, $K_{m(S)}$, and $V_{max(S)}$ are absorption rate constant, elimination rate constant, Michaelis constant, and maximum rate of metabolism of simvastatin, respectively. $K_{e(SM)}$ is the elimination rate constant of simvastatin acid. $A_{(S)}$ and $A_{(S)GI}$ are the amount of simvastatin in central and gastrointestinal compartment, respectively. $A_{(SM)}$ is the amount of simvastatin hydroxy acid. $C_{(S)}$, $C_{(V)}$, and $C_{(NV)}$ are the concentrations of simvastatin, verapamil, and norverapamil, respectively. $K_{i(V)}$ and $K_{i(NV)}$ are inhibition constants of verapamil and norverapamil, respectively. The verapamil model parameters were fixed at their estimates obtained from the previous step. The pharmacokinetic parameters of the final drug-drug interaction model are summarized in Table 1.

To our knowledge, this is the first study quantitatively investigating the effect of verapamil and its metabolite on simvastatin pharmacokinetics. The effects of verapamil and norverapamil inhibition (K_i) on simvastatin metabolism were estimated to be 0.5 and 5.9 μM, respectively.

Simvastatin is an inactive lactone form which is converted to an active form, simvastatin hydroxy acid, by esterases and even without enzymes. This conversion is not subject to inhibition of CYP3A4 as evidenced by the concomitant increase in both simvastatin and simvastatin hydroxy acid concentrations when co-administration with verapamil [6]. In addition to the effect of CYP3A4 inhibitors, simvastatin pharmacokinetics is affected by transporters including P-glycoprotein (P-gp) and organic anion transporting polypeptide (OATP) [1]. Even though, our model did not take into account the effects of these transporters, the simulation results indicated a reasonable fit of the model to the data for both simvastatin and simvastain hydroxy acid (Fig. 2).

Despites its usefulness in the treatment of hypercholesterolemia, simvastatin has been known to induce rhabdomyolysis. Even though the mechanism by which simvastatin induce necrosis of skeletal muscle is not yet fully understood, the risk of this adverse effect partially depends on dose and plasma levels [15]. Therefore, co-administration of simvastatin with other drugs that elevate simvastatin levels can increase the adverse event rate. Our drug-drug interaction model between simvastatin and verapamil might be helpful in predicting simvastatin concentrations in patients receiving both drugs concurrently and might be an aid to identify patients who are at higher risk of rhabdomyolysis occurrence. However, our model has some limitations in that it was developed using data obtained from healthy volunteers with narrow range of demographic characteristics. Therefore, the simulation results might not be applicable to other populations with different characteristics and further study with larger and diverse population should be conducted.

Physiologically based pharmacokinetic (PBPK) modeling is a useful computational method in incorporating any biological process into the models [16-18]. Therefore, to further improve the model, a PBPK model development of simvastatin and verapamil with a description of a competitive inhibition at CYP3A4 level may be justified.



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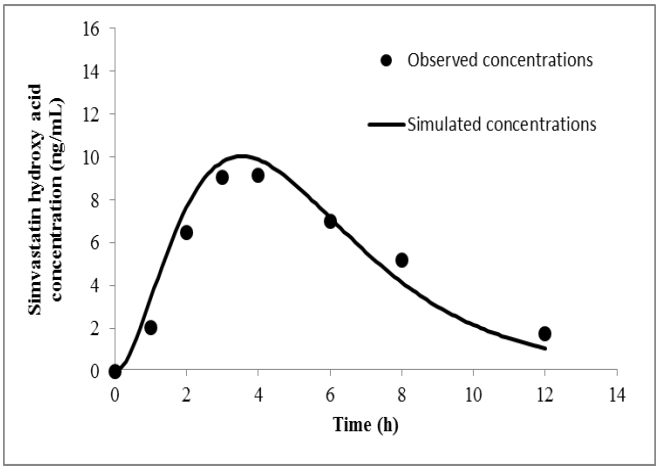

B

Figure 2. Simulated simvastatin (A) and simvastatin hydroxy acid (B) concentrations administered after four pre-treatment doses of 80 mg verapamil plotted against the actual extracted data from the literature.

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

Drug	Parameter	Value
SIMVASTATIN (S)	F	0.05
	K_a (h^{-1})	0.6
	$V_{D(S)}$ (L)	150
	$V_{D(SM)}$ (L)	22.5
	V_{max} (μM/h)	700
	K_m (μM)	5.25
	$K_{e(S)}$ (h^{-1})	0.02
	$K_{e(SM)}$ (h^{-1})	0.4
S + V	$F_{(S)}$	0.25
	$K_{i(V)}$ (μM)	0.5
	$K_{i(NV)}$ (μM)	5.9
VERAPAMIL (V)	F	0.17
	$K_{a(lumen)}$ (h^{-1})	2.6
	$K_{a(wall)}$ (h^{-1})	1.4
	$V_{D(1)}$ (L)	37.65
	$V_{D(NV)}$ (L)	172.67
	$V_{D(2)}$ (L)	7.7
	K_{12} (h^{-1})	19.4
	K_{21} (h^{-1})	4.24
	V_{max} (μM/h)	4
	K_m (μM)	0.726
	$V_{max(wall)}$ (μM/h)	0.00125
	$K_{m(wall)}$ (μM)	0.726
	$K_{e(V)}$ (h^{-1})	1.16
	$K_{e(NV)}$ (h^{-1})	0.6

V: verapamil, NV: norverapamil, S: simvastatin, SM: 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

IV. CONCLUSIONS

We successfully developed a mathematical model describing drug-drug interaction between simvastatin and verapamil. Our model can be used as the base to further develop a model predicting the risk of rhabdomyolysis and as prior information in guiding optimal simvastatin dose in patients receiving both drugs in combination.

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