35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Compartmental Pharmacokinetic Modeling of Lopinavir in Humans

Khanita Duangchaemkarn[1,2], *Student Member, IEEE,* and Manupat Lohitnavy [2,*]

Abstract— **Background: Lopinavir is a highly potent protease inhibitors commonly used in treatment of HIV infection. The drug has a very low bioavailability due to a rapid metabolism by cytochrome P450 3A (CYP3A) isoenzyme. We aimed to develop a biologically relevant pharmacokinetic model of lopinavir with a description of a CYP3A4-mediated first pass metabolism and enterohepatic circulation (EHC).**

Methods: A theoretical model of lopinavir was developed using the classical pharmacokinetic modeling concept. The model consisted of one compartment with first-order absorption from gastrointestinal (GI) depot and first-order clearance into recycling depot which incorporated into the model structure using ACSLX. Results: Lopinavir plasma concentration-time course was successfully simulated against a dataset from the literature. The model had an absorption rate constant (K_a) of 0.991 h^{-1}, a reabsorption rate constant ($K_{reabsorb}$) of 0.171 h^{-1}, and a volume of distribution (V/*F*) of 54.7 L. The 12 hours area under the concentration-time curve ($AUC_{0\text{-}12h}$) values from our model simulation compares to the experimental data were 0.8141 μg/ml.h and 0.7058 μg/ml.h, respectively. Maximum plasma concentration of the drug (C_{max}) predicted from our model compare to the experimental data were 0.273 μg/ml and 0.442 μg/ml, respectively. While, minimum plasma concentration of the drug (C_{trough}) predicted from our model compare to the experimental data were similar at 0.0015 μg/ml. Conclusions: Modified one compartment with first-order absorption from gastrointestinal (GI) depot and first-order clearance into recycling depot describes a pharmacokinetic of oral single dose of lopinavir 400 mg. The model can also simulate a concentration-time course with a difference dosing and variable which can be used for further describing the pharmacology of the drug interaction when combine with the other drugs.

I. Introduction

Compartmental pharmacokinetic (PK) modeling is an *in silico* approach in which pharmacokinetic and pharmacodynamic processes can be incorporated and quantitatively described [1]. PK/PD or pharmacokinetic/ pharmacodynamic modeling and simulation are now widely used in all phases of drug development, from preclinical phase studies to post-marketing surveillance (PMS) studies. In late clinical phase, PK/PD modeling is useful for determining a safe dose, verifying a dose exposure-response relationship, and assessing the impact of applicable covariates [2].

[1]Graduate School, Naresuan University. Phitsanulok 65000 Thailand.
[2]Pharmacokinetic Research Unit, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok 65000 Thailand and Center of Excellence for Environmental Health and Toxicology. Naresuan University, Phitsanulok 65000 Thailand.
*Corresponding Author (phone: + 66-5596-1888; e-mail: manupatl@gmail.com).

The antiretroviral therapy guidelines recommend the use of combination therapy, including a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor (NRTI). Protease inhibitors (PI) is one of a class of antiretroviral agents for treatment HIV-1 infection in human including of saquinavir, indinavir, amprenavir, atazanavir, nelfinavir, tipranavir and lopinavir, which is used in combination with low dose ritonavir as a recommended choice in PI class to treat the HIV-1 infected children and pregnancy patients [3–5].

Lopinavir (ABT-378), with a chemical structure shown in Fig.1, is the most potent inhibitor of the human immunodeficiency virus (HIV) protease enzyme by forming an inhibitor-enzyme complex result in preventing cleavage of the gag-pol polyproteins. Immature or noninfectious viral particles are subsequently produced. Despite of a very low bioavailability due to a rapid metabolism by gastrointestinal and hepatic cytochrome P450 3A4 (CYP3A4) isoenzyme [6–9]. Ritonavir is used to increase lopinavir bioavailability primarily by inhibiting CYP3A4 isoenzyme. A boosted regimen between lopinavir and ritonavir, a known potent CYP3A4 inhibitor, has been shown to achieve desirable plasma therapeutic concentration of lopinavir in many clinical studies. To determine the efficacy of the regimen, safety assessment has been studied but revealed little insight of such mechanism of the interaction [10–13].

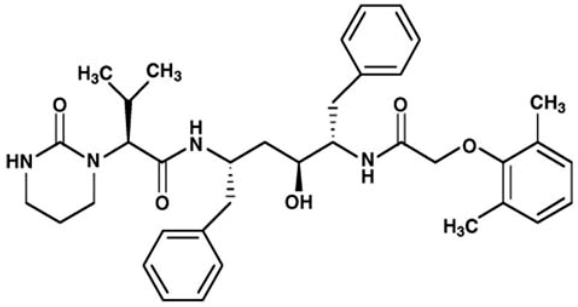

Figure 1. A chemical structure of Lopinavir (ABT-378)

To understand a pharmacokinetic behavior of lopinavir, the aim of this study was to develop the theoretical model of oral plasma lopinavir concentration-time course following a 400-mg single oral dosing in humans.

II. Materials and Methods

A. Lopinavir pharmacokinetics

Lopinavir has been introduced to market in a form of soft gelatin capsule combined with ritonavir (Kaletra; Abbott Laboratories, Chicago, IL) [14]. Single oral dosing pharmacokinetic studies in rats and human without ritonavir

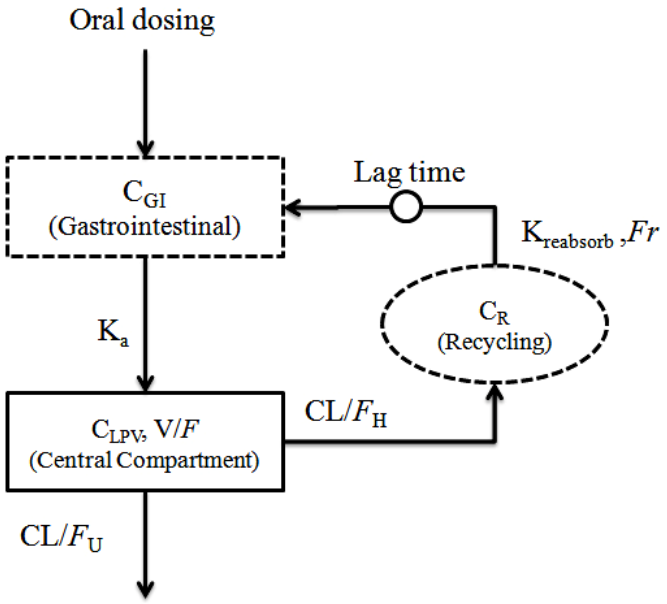

Figure 2. A Pharmacokinetic Model of Lopinavir

were available and revealed low levels of the drug plasma concentration below 0.01 μg/ml, while a recommendation require through plasma concentration level of lopinavir in both children and adult naïve patients to be above 1 μg/ml [3–5]. These results may be due to its poor oral bioavailability and extensively metabolized before entering the systemic circulation [8]. Using an *in vitro* liver microsomal experimental model, the metabolic pathway of lopinavir has been described elsewhere [6] and CYP3A4 have found to be responsible for the metabolism of the drug [6]. Plasma protein binding of lopinavir is relatively high (97.4 - 99.7%) in humans. The drug is predominantly eliminated by fecal excretion and a small amount (2%) of the drug is excreted in urine [8].

B. Compartmental Modeling of Lopinavir

Based on available pharmacokinetic information including metabolism of the drug mediated by hepatic and gastrointestinal cytochrome P450 3A4, a theoretical model of lopinavir was developed. Pharmacokinetic parameters used in this model were obtained from C. Zhang et al. (2012) [15] and Heine et al. (2011) [16]. Those included total clearance (CL/*F,* where *F* represent the relative bioavailability), volume of distribution (V/*F*), rate of absorption (K_a), and absorption lag time at 0.7 h. Those PK parameters are summarized in Table 1. The pharmacokinetic model structure of lopinavir with first-order absorption and first-order elimination processes is presented in Fig. 2. After an oral administration, lopinavir is absorbed into the central compartment. Subsequently, the drug can be metabolized by hepatic CYP3A4 and enters a hepatic recycling process, potentially through a transporter-mediated biliary excretion process within the liver [8], [9]. All of the parameters in these processes are also summarized in Table 1.

Our model with an expression of a differential equation (1) was used and plasma concentration-time courses were simulated;

$$\frac{dC_{LPV}}{dt} = (K_a \cdot C_{GI}) - \left(\frac{CL/F_H}{V/F} \cdot C_{LPV}\right) - \left(\frac{CL/F_U}{V/F} \cdot C_{LPV}\right) \quad (1)$$

Where K_a represents an absorption rate constant. C_{GI} and C_{LPV} are concentration of lopinavir in gastrointestinal depot and central compartment, respectively. CL_H and CL_U are clearance of the drug from central compartment to recycling depot and a clearance of the drug in urine. The parameter C_{GI} can be calculated by following (2) and (3);

$$\frac{dC_{GI}}{dt} = (Fr \cdot C_R \cdot K_{reabsorb}) - (K_a \cdot C_{GI}) \quad (2)$$

$$\frac{dC_R}{dt} = \left(\frac{CL/F_H}{V/F} \cdot C_{LPV}\right) - (K_{reabsorb} \cdot C_R) \quad (3)$$

Where *Fr* represents a percent reabsorbed fraction, $K_{reabsorb}$ is a first-order rate constant of drug absorption from the recycling depot into the gastrointestinal depot. C_R is represented concentration of lopinavir in the recycling depot.

TABLE I. PHARMACOKINETIC PARAMETERS OF LOPINAVIR USED IN SIMULATION PROCESSES [A]

Parameter	Value (95% CI or %RSE)	References
K_a (h^{-1})	0.991 (0.63-1.43)	[15]
CL/*F* (L/h)	37.9 (28.5-52.1)	[15]
V/*F* (L)	54.7 (50.5,64.7)	[15]
$K_{reabsorb}$ (h^{-1})	0.171 (12.3)	[16]
Fr (%)	17 (70.6)	[16]

C. Model validation

The plasma concentration-time curve was simulated using ACSLx 3.0.2.1 Tox Sim (AEgis Technologies, Huntsville, AL, USA). Lopinavir concentration-time course in healthy human volunteers (n=14) was used to validate the model.

Plasma lopinavir concentration levels were extracted from the literature [6] using Plot Digitizer 2.1 (Free Software Foundation, Inc., Boston, MA). Concentration levels at 0.5, 0.95, 1, 1.5, 2, 3, 4, 6, 8 and 10 h following a single 400-mg oral dose of lopinavir capsule were captured. The area under the plasma concentration-time curve ($AUC_{0\text{-}12h}$) and a goodness-of-fit were performed using GraphPad Prism version 6.01 for Windows, (GraphPad Software, San Diego, CA, USA, www.graphpad.com).

III. Results and Discussions

A one-compartment model with a first-order absorption and a recycling pathway with a first-order clearance to the gastrointestinal tract was developed (Fig. 2). Lopinavir plasma concentration-time course was simulated using the pharmacokinetic model. Our model performances were compared against the observed data from the study by Sham *et al* (1998). Our model can describe not only the concentration-time course profile of lopinavir, but it can also predict the area under the curve of the drug. The predicted value of AUC_{12h} was 0.8141 μg/ml.h, whereas the observed value from the study was 0.7058 μg/ml.h.

TABLE II. Lopinavir pharmacokinetic parameter obtained from the simulations compare to the real data from literature[A]

Parameter	Simulation results	Experimental results
$AUC_{0\text{-}12}$[a] (μg/ml.h)	0.8141	0.705
C_{max}[b] (μg/ml)	0.273	0.442
C_{trough}[c] (μg/ml)	0.001561	0.001596

a. area under the plasma concentration-time curve b. maximum observed concentration of lopinavir in plasma. c. minimum observed concentration of lopinavir in plasma.

Pharmacokinetic parameters simulated by our model are shown in Table II. The plasma concentration-time curves from our model simulation are shown in semi-log scale (Fig.3A) and in linear scale (Fig.3B). Our simulation results predicted higher plasma concentration levels in the first 3 hours after lopinavir administration compared to the experimental data might be the result of another route of clearance from central compartment such as protein transporters in the liver [7]. The goodness-of-fit from our simulation model to the data was satisfactorily acceptable with an R-squared (R^2) value of 0.7939. The fitted SD_{slope} and $SD_{intercept}$ at 95% confident interval were 0.0379 (-0.2254 to -0.05025) and 0.09438 (-0.7403 to -0.3051), respectively.

The simulated C_{max} level was slightly lowered at 0.273 μg/ml (0.442 μg/ml in the experimental data) whereas the simulated C_{trough} level (0.001561 μg/ml) was almost identical to the experimental data (0.001596 μg/ml) were However, the plasma lopinavir concentration was lower than 0.01 μg/ml after 8 hours of single dose administration in both studies and given not difference of $AUC_{0\text{-}12h}$ value.

Despite of many studies have been reported that enterohepatic recirculation responsible for a metabolism pathway of lopinavir, our simulation demonstrates similar results.

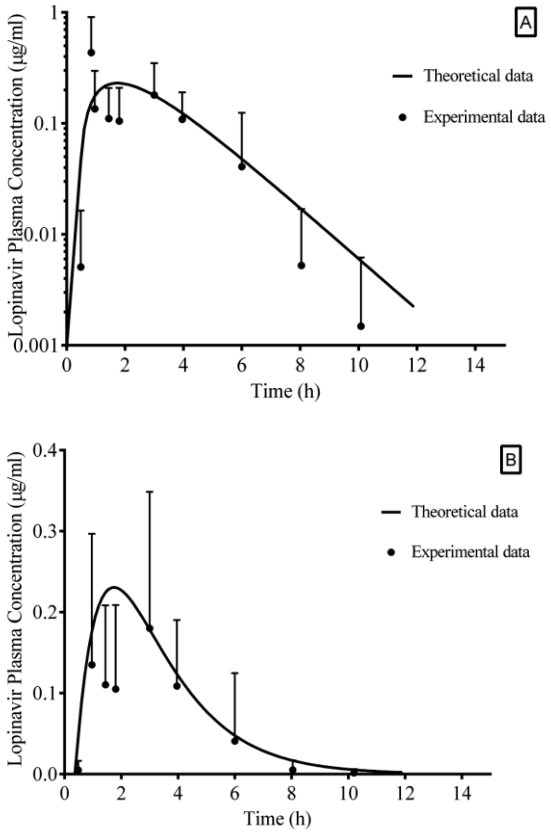

Figure 3. Lopinavir plasma concentration-time course in 12 hours of oral lopinavir 400 mg single dose. Semilog scale has shown as A. Solid dotted, data extracted from healthy human volunteer. Solid line, data obtained from model simulation.

From our model simulation exercises, relative bioavailablity (*F*) and the rate of elimination (K_e) were the most sensitive parameters in the changes of plasma concentration of lopinavir.

The data obtain from clinical study exhibited the second peak in the experimental data. This might be an effect of the enterohepatic recirculation process. Nonetheless, despite an addition of such process into our model, we could not mimic such second-peak phenomena in any of our simulations.

However, our model with biologically relevant processes provided an adequate understanding of oral single-dose lopinavir pharmacokinetic and its metabolism pathway associated with CYP3A4. Thus, this approach can simulate a concentration-time curve with difference dosing and variable which can be used for further application (i.e. other drugs in the same class, drug-drug interaction between lopinavir and a CYP3A4 inhibitor) in patients with HIV/AIDS.

IV. Conclusions

A pharmacokinetic model of lopinavir was successfully developed. Our model was featured by these following biologically relevant processes. Those included; 1) the CYP3A4-mediated relative bioavailability and 2) enterohepatic recirculation. The pharmacokinetic model could explain the selected experimental data.

ACKNOWLEDGMENT

Associate Professor Kohji Masuda, Graduate School of Bio-Applications and Systems Engineering (BASE), Tokyo University of Agriculture and Technology.

Financial support from the Center of Excellence for Innovation in Chemistry (PERCH-CIC), Office of the Higher Education Commission, Ministry of Education and Center of Excellence for Environmental Health and Toxicology, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University. There is no information on conflicts of interest directly relevant to this study.

REFERENCES

[1] J. Pérez-Urizar, V. Granados-Soto, F. J. Flores-Murrieta, and G. Castañeda-Hernández, "Pharmacokinetic-Pharmacodynamic Modeling," *Archives of Medical Research*, vol. 31, no. 6, pp. 539–545, Nov. 2000.

[2] I. Rajman, "PK/PD modelling and simulations: utility in drug development.," *Drug discovery today*, vol. 13, no. 7–8, pp. 341–6, Apr. 2008.

[3] S. Sungkanuparpha, W. Techasathit, C. Utaipiboon, S. Chasombat, S. Bhakeecheep, M. Leechawengwongs, K. Ruxrungtham, and P. Phanuphak, "Thai national guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents 2010," *Asian Biomedicine*, vol. 4, no. 4, pp. 515–528, 2010.

[4] Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection The Health Resources and Services Administration," *National Institute of Health*, 2011. [Online]. Available: http://aidsinfo.nih.gov/ContentFiles/lvguidelines/PediatricGuidelines.pdf. [Accessed: 02-Jan-2013].

[5] Panel on Antiretroviral Guidelines for Adults and Adolescents, "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents," *Department of Health and Human Services*, 2012. [Online]. Available: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. [Accessed: 02-Feb-2013].

[6] H. L. Sham, D. J. Kempf, a Molla, K. C. Marsh, G. N. Kumar, C. M. Chen, W. Kati, K. Stewart, R. Lal, a Hsu, D. Betebenner, M. Korneyeva, S. Vasavanonda, E. McDonald, a Saldivar, N. Wideburg, X. Chen, P. Niu, C. Park, V. Jayanti, B. Grabowski, G. R. Granneman, E. Sun, a J. Japour, J. M. Leonard, J. J. Plattner, and D. W. Norbeck, "ABT-378, a highly potent inhibitor of the human immunodeficiency virus protease.," *Antimicrobial agents and chemotherapy*, vol. 42, no. 12, pp. 3218–24, Dec. 1998.

[7] R. a B. van Waterschoot, R. ter Heine, E. Wagenaar, C. M. M. van der Kruijssen, R. W. Rooswinkel, a D. R. Huitema, J. H. Beijnen, and a H. Schinkel, "Effects of cytochrome P450 3A (CYP3A) and the drug transporters P-glycoprotein (MDR1/ABCB1) and MRP2 (ABCC2) on the pharmacokinetics of lopinavir.," *British journal of pharmacology*, vol. 160, no. 5, pp. 1224–33, Jul. 2010.

[8] G. N. Kumar, V. K. Jayanti, M. K. Johnson, J. Uchic, S. Thomas, R. D. Lee, B. a Grabowski, H. L. Sham, D. J. Kempf, J. F. Denissen, K. C. Marsh, E. Sun, and S. a Roberts, "Metabolism and disposition of the HIV-1 protease inhibitor lopinavir (ABT-378) given in combination with ritonavir in rats, dogs, and humans.," *Pharmaceutical research*, vol. 21, no. 9, pp. 1622–30, Sep. 2004.

[9] C. S. E. Ii, S. D. Hall, and D. R. Jones, "Mechanism-Based Inactivation of CYP3A by HIV Protease Inhibitors," vol. 312, no. 2, pp. 583–591, 2005.

[10] X. Sáez-Llorens, A. Violari, C. O. Deetz, R. a Rode, P. Gomez, E. Handelsman, S. Pelton, O. Ramilo, P. Cahn, E. Chadwick, U. Allen, S. Arpadi, M. M. Castrejón, R. S. Heuser, D. J. Kempf, R. J. Bertz, A. F. Hsu, B. Bernstein, C. L. Renz, and E. Sun, "Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children.," *The Pediatric infectious disease journal*, vol. 22, no. 3, pp. 216–24, Mar. 2003.

[11] S. S. Kaplan and C. B. Hicks, "Safety and antiviral activity of lopinavir/ritonavir-based therapy in human immunodeficiency virus type 1 (HIV-1) infection.," *The Journal of antimicrobial chemotherapy*, vol. 56, no. 2, pp. 273–6, Aug. 2005.

[12] K. M. L. Crommentuyn, B. S. Kappelhoff, J. W. Mulder, a T. a Mairuhu, E. C. M. van Gorp, P. L. Meenhorst, a D. R. Huitema, and J. H. Beijnen, "Population pharmacokinetics of lopinavir in combination with ritonavir in HIV-1-infected patients.," *British journal of clinical pharmacology*, vol. 60, no. 4, pp. 378–89, Oct. 2005.

[13] L. Dickinson, M. Boffito, D. J. Back, S. H. Khoo, A. L. Pozniak, P. Mugyenyi, C. Merry, R. S. Autar, D. M. Burger, and L. J. Aarons, "Population pharmacokinetics of ritonavir-boosted saquinavir regimens in HIV-infected individuals.," *The Journal of antimicrobial chemotherapy*, vol. 62, no. 6, pp. 1344–55, Dec. 2008.

[14] "Kaletra Dosage & Drug Information | MIMS.com Thailand." [Online]. Available: http://www.mims.com/Thailand/drug/info/Kaletra/?q=lopinavir&type=brief. [Accessed: 02-Feb-2013].

[15] C. Zhang, P. Denti, E. Decloedt, G. Maartens, M. O. Karlsson, U. S. H. Simonsson, and H. McIlleron, "Model-based approach to dose optimization of lopinavir/ritonavir when co-administered with rifampicin.," *British journal of clinical pharmacology*, vol. 73, no. 5, pp. 758–67, May 2012.

[16] R. Ter Heine, R. Van Waterschoot, R. J. Keizer, J. H. Beijnen, A. H. Schinkel, and H. D. Alwin, "An Integrated Pharmacokinetic Model for the Influence of CYP3A4 Expression on the In Vivo Disposition of Lopinavir and Its Modulation by Ritonavir," *Journal of Pharmaceutical Sciences*, vol. 100, no. 6, pp. 2508–2515, 2011.