PBPK Modeling of Erythromycin Absorption and Disposition Mediated by Transporters in Humans

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ABSTRACT

Purpose: Erythromycin, a macrolide antibiotic, is cleared primarily by cytochrome P450-3A4 metabolism. Its uptake into enterocytes and hepatocytes is mediated by organic anion transporter (OAT) and organic anion transporting polypeptides (OATPs), respectively. Erythromycin is actively secreted into the gastrointestinal lumen, where it is partially degraded, and into the bile by P-glycoprotein (P-gp), and it undergoes enterohepatic recirculation. The purpose of this study was to build a comprehensive and mechanistic Physiologically Based Pharmacokinetic (PBPK) model of erythromycin incorporating all of the above-mentioned processes.

Methods: A mechanistic PBPK model that describes the pharmacokinetics of erythromycin in healthy humans was developed with GastroPlus™ (Simulations Plus, Inc.) using literature plasma concentration-time (Cp-time) profiles after intravenous and oral administration of doses ranging from 125 to 1000 mg [1, 2]. Human organ weights, volumes, and blood perfusion rates were generated by the program's internal Population Estimates for Age-Related (PEAR) Physiology™. Different physicochemical and biochemical parameters that predict absorption and distribution were obtained from literature or using ADMET Predictor™ (Simulations Plus, Inc.). Tissue:plasma partition coefficients (Kps) were calculated using Lukacova method [3]. Metabolic clearance of erythromycin was parameterized from *in vitro* measurements of erythromycin N-demethylation in human liver microsomes. Renal clearance rate reported in the literature was used in the model [1]. Gastrointestinal distribution of P-gp and OAT was derived from experimental data [5, 6]. A single set of V_{max} and K_m values each for OAT, P-gp and OATP were fitted to describe the intravenous and oral profiles at different dose levels.

Results: A single PBPK model provided a close fit to the experimental data for intravenous (125, 250, 500 and 900 mg) and oral (250, 500 and 1000 mg) doses. Predictions for C_{max} and AUC were within 2-fold of that of the observed values. The model also closely reproduced the clinically observed nonlinear dose dependence.

Conclusions: A physiological and mechanism-based model was developed for erythromycin. The model provided insights into mechanisms involved in the absorption and disposition of erythromycin and aided in translating *in vitro* data to the *in vivo* situation.

METHODS

The erythromycin PBPK model was implemented in GastroPlus™ version 8.0.
Intestinal absorption was described by the Advanced Compartmental Absorption and Transit (ACAT™) Model; distribution and clearance were modeled with the PBPKPlus™ Module within GastroPlus.

Processes incorporated in the erythromycin ACAT/PBPK model were:

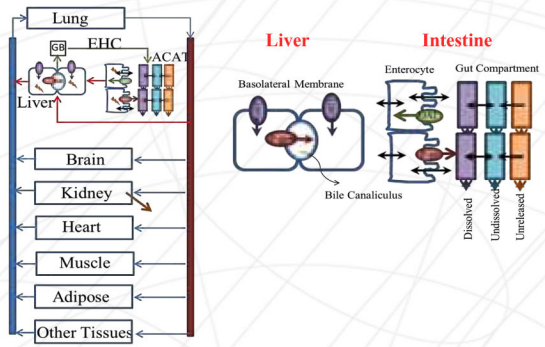
- Influx (OAT) and efflux (P-gp) transporters in enterocytes
- CYP3A4 metabolism in the gut and liver
- Active hepatic uptake (OATP) and active biliary secretion (P-gp)
- Renal clearance
- Chemical degradation in intestinal lumen
- Enterohepatic recirculation

CYP3A4-related metabolic clearances in gut and liver were based on enzyme kinetic constants from *in vitro* studies and built-in expression levels of 3A4 in gut and liver.
CYP3A4 distribution in gut and average expression in liver were from Paine *et al* [6]. Distribution of P-gp and OAT in the intestine was obtained from Mouly *et al.* and, Meier *et al.*, respectively [4, 5].
In vitro transporter K_m values were obtained from literature when available or both V_{max} and K_m were optimized across different p.o. and i.v. doses [7].

Table 1. Key physicochemical and biopharmaceutical properties of erythromycin

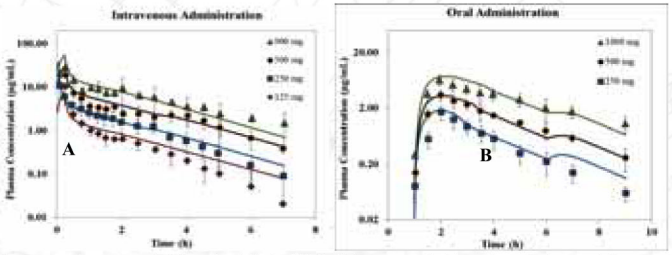
Property	Value	Reference
Log P	3.1	McFarland J. W. et al., 1997 [8]
Solubility, pH 10.2 (mg/mL)	2.1	McFarland J. W. et al., 1997 [8]
Passive Jejunal Permeability (cm/s)	1.1 X 10^{-4}	Estimated from CaCo-2 data
pKa (base)	8.9	McFarland J. W. et al., 1997 [8]
Plasma Unbound (%)	20	Lam J.L. et.al., 2006 [9]
Blood to Plasma Concentration Ratio	0.65	From ADMET Predictor
Renal Clearance (L/h)	2.7	Austin K.L. et al., 1980 [1]
P-gp K_m (µM)	74	Fitted Across I.V. and P.O. doses
OAT K_m (µM)	18	Kobayashi Y. et al., 2005 [7]
OATP K_m (µM)	7.8	Fitted Across I.V. and P.O. doses
CYP3A4 Vmax (pmol/min/mg) (*in vitro*)	345	Riley, R. J. et al., 1997 [10]
CYP3A4 Km (µM) (*in vitro*)	88	Riley, R. J. et al., 1997 [10]

Figure 1. Erythromycin PBPK model development



RESULTS AND DISCUSSION

Figure 2. Plasma concentrations of erythromycin after administration of intravenous (A) and oral (B) doses



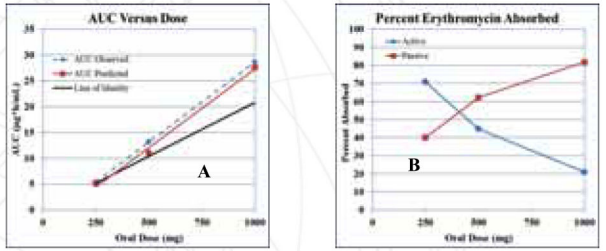
Intravenous doses were administered as infusion [1]. Oral doses were administered as capsules containing enteric-coated pellets [2]. Physiology was changed to fed state at 6 h to reflect meals given to the subjects.

Simulated C_{max} and AUC values were within 2-fold of the observed values.
The PBPK model well described both intravenous and oral experimental data at different dose levels. The model reproduced well the clinically observed nonlinear dose dependence after oral administration.

Super-proportional increase in exposure with increasing dose appears to be due to saturation of both P-gp mediated efflux and metabolism at higher doses.

A higher percentage of erythromycin appears to be absorbed by passive diffusion at higher doses due to saturation of the influx transporter and lower P-gp efflux.

Figure 3. Exposure versus dose (A) and percent of erythromycin absorbed through active and passive mechanism (B)



CONCLUSIONS

A comprehensive and mechanistic oral absorption ACAT and PBPK model of erythromycin incorporating all of the relevant pharmacokinetic processes was developed.
This model was further employed to study drug-drug interactions involving erythromycin [11].

REFERENCES

1. Austin K.L. *et.al., Br J Clin Pharmacol.* 1980;**10**(3):273-9.
2. Josefsson K. *et.al., Br J Clin Pharmacol* (1982) **13**:685-691.
3. Lukacova V, Poster - AAPS Annual Meeting 2008, Atlanta, GA, *General approach to calculation of tissue:plasma partition coefficients for PBPK modeling*
4. Mouly S. *et al., Pharm Res.* 2003;**20**(10):1595-9.
5. Meier Y. *et al., Drug Metab Dispos.* 2007;**35**(4):590-4.
6. Paine M.F. *et al., J Pharmacol Exp Ther.* 1997;**283**(3):1552-62.
7. Kobayashi Y. et.al., *Drug Metab Dispos.* 2005;**33**(5):619-22.
8. McFarland J.W. *et.al., J Med Chem.*1997;**40**(9):1340-6.
9. Lam J.L. *et al., Drug Metab Dispos.* 2006;**34**(8):1336-44.
10. Riley, R. J. & D. Howbrook., *J. Pharmacol. Toxicol. Meth.* 1997;**38**:189–193.
11. Atluri H. et. al., *PBPK Model Simulation of CYP3A4 and Transporter Mediated Drug-drug Interactions Involving Erythromycin* – poster T2283- AAPS 2012 Annual Meeting

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