PBPK Model Simulation of CYP3A4 and Transporter Mediated Drug-drug Interactions Involving Erythromycin

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ABSTRACT

Purpose: Erythromycin, a macrolide antibiotic, is cleared primarily by cytochrome P450-3A4 metabolism to the N-demethylated metabolite and C-formaldehyde. Its uptake into hepatocytes is mediated by organic anion transporting polypeptides (OATPs), and it is effluxed by P-glycoprotein (P-gp). A total of 478 interactions with other drugs have been reported. For example, increased exposure of 100 – 400 % for simvastatin, midazolam, sildenafil, everolimus, and cyclosporine has been reported. This study employed dynamic drug-drug interaction (DDI) simulations to study both metabolic and transporter-related DDIs. Midazolam, talinolol, and digoxin were chosen as model compounds to study these interactions.

Methods: Physiologically Based Pharmacokinetic (PBPK) models were developed with GastroPlus™ (Simulations Plus, Inc.) for the perpetrator, erythromycin, and for the victim drugs, midazolam, talinolol, and digoxin using literature data. *In vitro* enzyme and transporter inhibition constants for midazolam, talinolol, and digoxin were obtained from literature data. Drug-drug interactions were predicted using dynamic simulations within the DDI Module in GastroPlus.

Results: The ~4-fold observed increase in exposure of midazolam after intravenous and oral administration with concomitant oral administration of erythromycin was well-predicted. Increased oral exposure (~1.5-fold) of talinolol caused by erythromycin inhibition of P-gp was captured with DDI simulations. Also, mechanisms behind transporter-mediated interactions between erythromycin and digoxin were simulated.

Conclusion: Enzyme- and transporter-mediated drug-drug interactions involving erythromycin were well-described by the models. These models can be employed to predict prospective enzyme- and transporter-mediated drug interactions using *in vitro* data.

METHODS

In the present study, metabolic (CYP3A4) and transporter-related (P-gp) DDIs were evaluated. Midazolam (CYP3A4), talinolol (P-gp) and digoxin (P-gp) were chosen as model compounds to study these interactions.

Table 1. Study design for clinical drug-drug interaction studies

	Dose of Victim Drug	Dose of Erythromycin
Midazolam	15 mg oral or 0.05 mg/kg intravenous bolus	500 mg 3 times a day for 1 week. Midazolam was given on the sixth day of erythromycin treatment
Talinolol	50 mg oral	2 g erythromycin was administered in two equal doses 15 min before and after talinolol administration
Digoxin	0.5 mg intravenous infusion	Erythromycin (200 mg 4 times a day) was given on the day before digoxin dosing and during the following 4 days

RESULTS AND DISCUSSION

The approximately 2- to 4-fold observed increase in exposure of midazolam due to inhibition of its metabolism after intravenous and oral administration with concomitant oral administration of erythromycin was well-predicted.

The increased oral exposure (~1.5-fold) of talinolol caused by erythromycin inhibition of P-gp secretory transport in the intestine was properly simulated with DDI simulations.

DDI simulations with erythromycin and digoxin do not indicate that inhibition of P-gp results in significant differences in the pharmacokinetic profile of intravenously administered digoxin.

Table 2. *In vitro* enzyme and transporter inhibition constants for the interacting compounds

	Interacting Enzyme/ Transporter	Maximal inactivation rate constant – k_{inact} (min^{-1})	Apparent inactivation constant (μM)	Concentration for 50% inhibition – IC_{50} (μM)
Midazolam[a] (2)	CYP3A4	0.012	81.8	-
Talinolol (3)	P-gp	-	-	75[b]
Digoxin (4)	P-gp	-	-	22.6[c]

[a] *In vitro* values were obtained from Yamano et. al (5).

[b] Erythromycin concentration that is required to produce 50 % inhibition (IC_{50}) of P-gp-mediated transport was estimated using clinical drug-drug interaction data (3).

[c] *In vitro* value was obtained from Eberl et. al (6).

Figure 1. PBPK Model Structure for Erythromycin (1) and Interacting Drugs

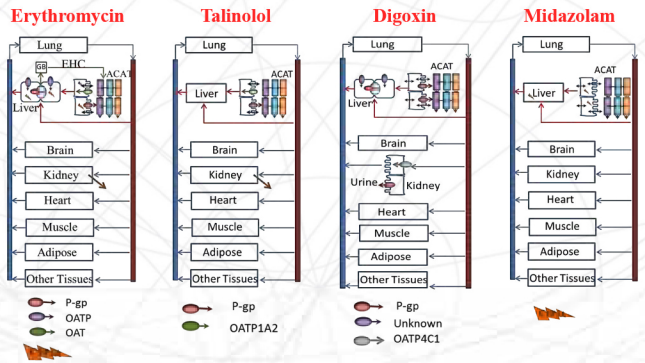

Table 3. Summary of predicted and observed DDI of erythromycin with midazolam (CYP3A4), talinolol (P-gp), and digoxin (P-gp)

	AUC Ratio	
	Observed	Predicted
Midazolam (i.v.)	1.9	1.5
Midazolam (p.o.)	4.4	3.0
Talinolol (p.o.)	1.5	1.6
Digoxin (i.v.)	1.0	1.0

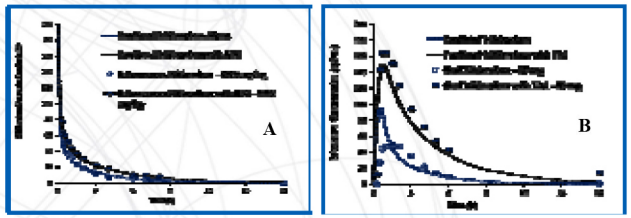

Figure 2. Plasma concentrations of midazolam after an oral dose of 15 mg (A) or an intravenous dose of 0.05 mg/kg (B) with oral erythromycin (500 mg three times a day) pretreatment or placebo

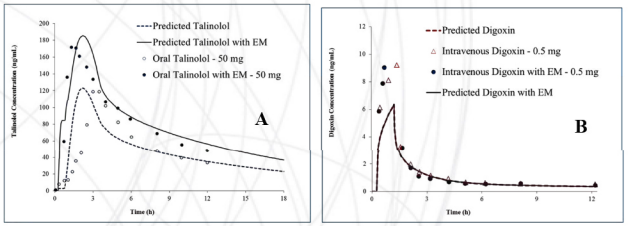

Figure 3. Plasma concentration-time profiles of talinolol - 50 mg, oral dose (A) and digoxin – 0.5 mg, intravenous infusion (B) after concomitant administration of erythromycin or placebo

CONCLUSIONS

Enzyme- and transporter-mediated drug-drug interactions involving erythromycin were well-described by the models. These models can be employed to predict prospective enzyme- and transporter-mediated drug interactions using *in vitro* data.

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