T2375

Physiologically-based pharmacokinetic (PBPK) models for prediction of time-dependent enzyme inhibition (TDI): effect of diltiazem on midazolam and quinidine

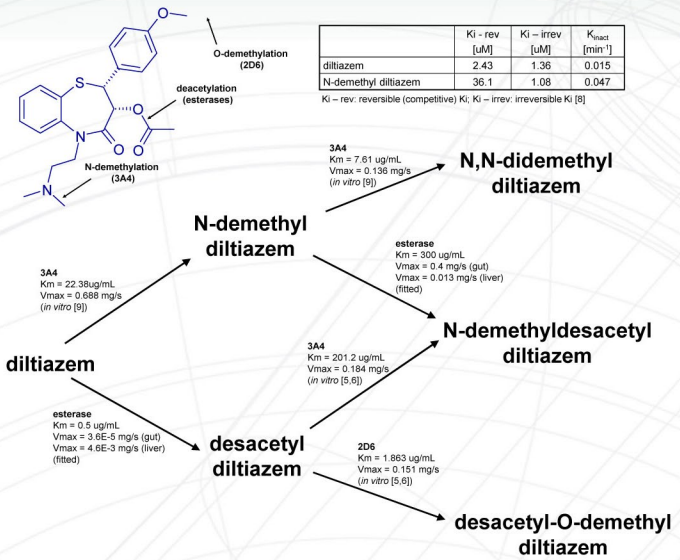
Lukacova, V., J.I. Chung, W.S. Woltosz, M.B. Bolger
Simulations Plus, Inc. Lancaster, California, USA,

Aim

Purpose of the study was to optimize a PBPK model to predict time-dependent and competitive inhibition of CYP 3A4 by diltiazem and to predict the effect on the pharmacokinetics (PK) of midazolam and quinidine.

Methods

Absorption and pharmacokinetics of all drugs were simulated using GastroPlus™ 7.0 (Simulations Plus, Inc., Lancaster, CA). The program's Advanced Compartmental Absorption and Transit (ACAT™) model described the intestinal absorption, coupled with its PBPKPlus™ module for pharmacokinetic distribution and clearance. Human physiologies were generated by the program's internal Population Estimates for Age-Related (PEAR) Physiology™ module. Tissue/plasma partition coefficients were calculated using a modified Rodgers equation based on tissue composition and *in vitro* and *in silico* physicochemical properties (ADMET Predictor™, Simulations Plus, Lancaster, CA). The diltiazem model accounted for the pharmacokinetics of the parent drug and two of its major metabolites, N-demethyldiltiazem and desacetyldiltiazem. Metabolic clearances of all drugs in gut and liver were based on built-in *in vivo* values for the expression levels of 3A4 in each gut compartment and the average expression of 3A4 in liver. Enzyme kinetic constants for 3A4 were either *in vitro* values from literature or fitted against *in vivo* plasma-concentration (Cp-time) profiles. Renal secretion of diltiazem and its metabolites were estimated as *fup*GFR* while their residual clearances due to other metabolic processes were fitted against *in vivo* Cp-time profiles. The PBPK models correctly described Cp-time profiles of midazolam, quinidine, diltiazem, N-demethyldiltiazem and desacetyldiltiazem for various doses after *i.v.* and *p.o.* administration. The validated PK models were then used in dynamic simulations in the GastroPlus 7.0 DDI Module to predict the effect of CYP 3A4 deactivation by diltiazem and N-demethyldiltiazem on quinidine and midazolam PK.



	Ki - rev [uM]	Ki – irrev [uM]	K_{inact} [min^{-1}]
diltiazem	2.43	1.36	0.015
N-demethyl diltiazem	36.1	1.08	0.047

Ki – rev: reversible (competitive) Ki; Ki – irrev: irreversible Ki [8]

Figure 1. *Metabolic and inhibition parameters for diltiazem and its metabolites used in the model. All enzymes were included in both gut and liver. Additional nonspecific clearance due to other metabolism and/or renal clearance was added (fitted) for diltiazem, N-demethyl diltiazem and desacetyl diltiazem. When in vitro values were available, the same Vmax was applied to both gut and liver (scaled by different expression levels). Otherwise, separate Vmax values were fitted for gut and liver. Any parameter optimization was done only during the process of building the PK model for diltiazem alone without the presence of any interacting compound. No additional fitting or parameter adjustment was done for the DDI predictions.*

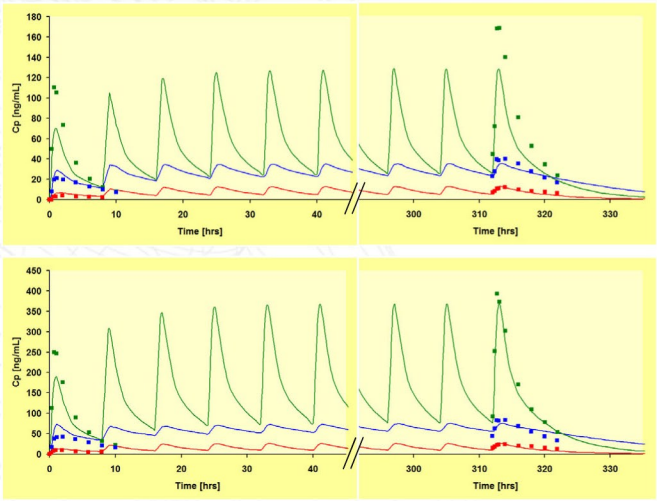


Figure 2. *Predicted (solid lines) and observed (squares) plasma concentration-time profiles of diltiazem (green) and its two primary metabolites, N-demethyl diltiazem (blue) and desacetyl diltiazem (red), after p.o. administration of 60 mg (top) and 120 mg (bottom) doses of immediate release diltiazem every 8hrs.*

Results

Dynamic simulations predicted higher effect of CYP 3A4 deactivation by diltiazem and N-demethyldiltiazem on midazolam than on quinidine PK, in agreement with reported clinical outcomes [7,10].

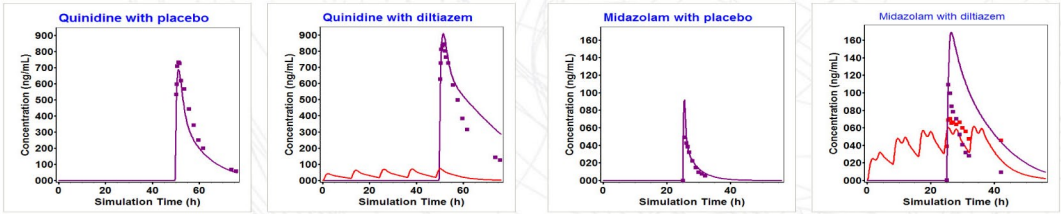


Figure 3. *Predicted (solid lines) and observed (squares) Cp-time profiles of quinidine (purple) administered (dose 200mg of quinidine sulfate) after placebo and after 5th dose of 90mg SR formulation of diltiazem given every 12hrs. Simulated diltiazem Cp-time profile is shown in red.*

Figure 4. *Predicted (solid lines) and observed (squares) Cp-time profiles of midazolam (purple) administered (15mg dose) after placebo and after 4th dose of 60mg of diltiazem given every 8hrs. Simulated and observed diltiazem Cp-time profiles are shown in red.*

Table 1. *Summary of predicted and observed effect of pretreatment with diltiazem on pharmacokinetics of quinidine and midazolam. Numbers in parentheses show contribution of gut to the DDI in terms of fold increase in fraction of dose getting into portal vein after pretreatment with diltiazem.*

Interacting Compound	Observed AUC ratio	Predicted AUC ratio
Quinidine	1.5	2.3 (gut 1.0)
Midazolam	3.8	8.5 (gut 1.7)

Conclusions

Dynamic simulations utilizing PBPK models with detailed descriptions of drugs' metabolism allowed exploring the contributions of the two irreversible inhibitors (diltiazem and N-demethyldiltiazem) on CYP 3A4 deactivation. The effect of diltiazem pretreatment on both compounds was overpredicted, but the model correctly predicted lower effect on the pharmacokinetics of quinidine than midazolam.

References

1. Rodgers T.; J Pharm Sci 2007, 96: 3151-3152
2. Rodgers T.; J Pharm Sci 2007, 96: 3153-3154
3. Hoglund P.; Ther Drug Monitor 1989, 11: 543-550
4. Hoglund P.; Ther Drug Monitor 1989, 11: 551-557
5. Molden E.; Clin Pharmacol Ther 2002, 72: 333-342
6. Molden E.; Drug Metab Dispos 2002, 30: 1-3
7. Backman J.T.; Br J Clin Pharmac 1994, 37: 221-225
8. Rowland-Yeo K.; Eur J Pharm Sci 2010, 39: 298-309
9. Zhao P.; Drug Metab Dispos 2007, 35: 704-712
10. Laganiere S.; Clin Pharmacol Ther 1996, 60: 255-264

simulationsplus, inc.