W5381

Physiologically-based pharmacokinetic (PBPK) models for prediction of saquinavir effect on midazolam pharmacodynamics

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Abstract:

Purpose: To predict the drug-drug interaction effect of saquinavir on midazolam pharmacodynamics (PD).

Methods: The absorption and pharmacokinetics (PK) of midazolam and saquinavir were simulated using a beta version of GastroPlus™ 8.0 (Simulations Plus, Inc., Lancaster, CA). Independent saquinavir and midazolam models were previously validated by comparing the simulated plasma concentration-time (Cp-time) profiles with experimental data for intravenous (*i.v.*) and oral (*p.o.*) administration for each drug, as well as by comparing the prediction of the observed drug-drug interaction (DDI) of saquinavir on midazolam PK. Models were fitted for several reported PD responses after midazolam administration based on the drug's unbound Cp-time profiles. The fitted PD models were then used with the earlier prediction of saquinavir's effect on midazolam PK to estimate the drug-drug interaction effect of saquinavir on midazolam PD.

Results: Baseline PD responses for midazolam (i.e., without saquinavir), such as the digit symbol substitution test (DSST) and the Maddox Wing Test (MWT), were equally well described by several different types of direct or indirect PD models, each resulting in a different prediction of the magnitude of saquinavir's effect on midazolam PD. Several models predicted the maximum response within 20% of the observed maximum response; however, the prediction error was as high as 40% with other models. In the absence of PD response data for different dose levels of midazolam, there was no obvious most relevant baseline PD model for each response.

Pharmacokinetic Models:

Validated absorption/PBPK models for saquinavir and midazolam were used to simulate pharmacokinetics of midazolam after *p.o.* administration of 7.5 mg with and without saquinavir pretreatment (for details see AAPS 2011 poster W5380).

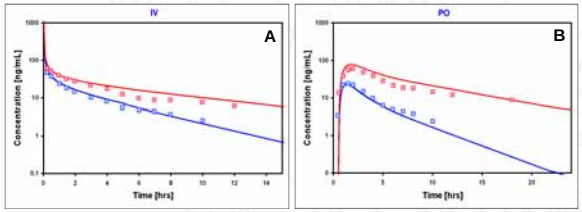

Figure 1. Simulated (lines) and observed (points) Cp-time profiles of midazolam after A) *i.v.* administration of 0.05 mg/kg bolus dose with (red) and without (blue) saquinavir pretreatment; B) *p.o.* administration of 7.5 mg dose with (red) and without (blue) saquinavir pretreatment. Saquinavir pretreatment consisted of 3-5 days of 1200 mg of *p.o.* saquinavir dosed TID. Simulation of midazolam PK after pretreatment with saquinavir used a fitted maximum inactivation rate constant (k_{inact} = 0.02 min^{-1}) for saquinavir inactivation of CYP3A4. Common model parameters are identical across all simulations.

Pharmacodynamic Models:

- Multiple direct and indirect PD models were fitted to Cp-time and PD effect-time profiles for 7.5 mg *p.o.* midazolam administered without saquinavir [4]
- Three direct PD models (Linear, Emax and Sigmoid) resulted in close matches between observed and simulated effect-time data for two types of midazolam PD effects (MWT and DSST) with Sigmoid model being the best model for description of both midazolam PD effects without saquinavir.
- All three models were used to predict effect-time profile for 7.5 mg *p.o.* midazolam after saquinavir pretreatment [4].
- The Sigmoid model gave the best prediction of maximum effect for both PD effects with prediction errors of 10% and 20% for DSST and MWT, respectively.
- The maximum effect prediction errors for the Linear and Emax models were 20% and 40% for DSST and MWT, respectively.
- The shape of the predicted effect-time profile was better-represented with Linear and Emax models than with Sigmoid model (Figure 2 and Figure 3).

$$E = E_0 + Slope \times Cp \qquad E = E_0 + \frac{E_{max} \times C_p}{EC_{50} + C_p} \qquad E = E_0 + \frac{E_{max} \times C_p^{\gamma}}{EC_{50}^{\gamma} + C_p^{\gamma}}$$

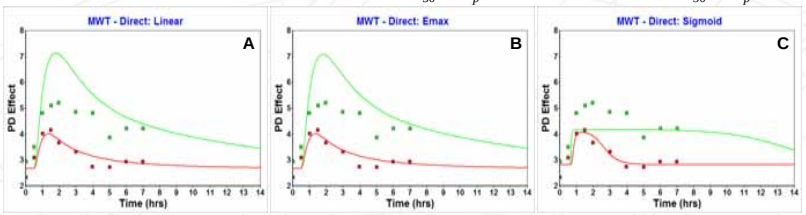

Figure 2. Simulated (lines) and observed (points) PD effect-time profiles for midazolam after *p.o.* administration of 7.5 mg with (green) and without (red) saquinavir pretreatment. PD effect (MWT) data was fitted with Direct:Linear (A), Direct:Emax (B), and Direct:Sigmoid (C) model to observed data from a study without saquinavir (red). The fitted models were then used to predict the effect of midazolam after saquinavir pretreatment (green). Saquinavir pretreatment consisted of 3-5 days of 1200 mg of *p.o.* saquinavir dosed TID.

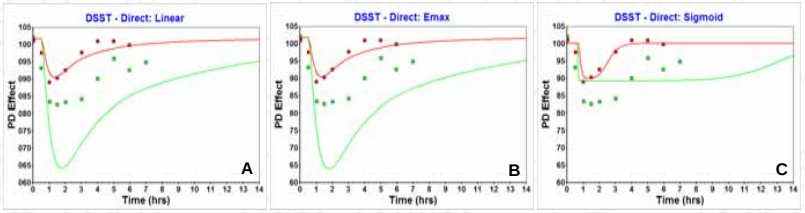

Figure 3. Simulated (lines) and observed (points) PD effect-time profiles of midazolam after *p.o.* administration of 7.5 mg with (green) and without (red) saquinavir pretreatment. PD effect (DSST) data were fitted with Direct:Linear (A), Direct:Emax (B), and Direct-·Sigmoid (C) model to observed data from a study without saquinavir (red). The fitted models were then used to predict PD effect of midazolam administered after saquinavir pretreatment (green). Saquinavir pretreatment consisted of 3-5 days of 1200 mg of *p.o.* saquinavir dosed TID.

- Additional observed data for DSST effect after 15 mg *p.o.* of midazolam were available in literature from a different study without saquinavir [2].
- The three direct models were refitted across two sets of data (7.5 mg and 15 mg) for *p.o.* administration of midazolam without saquinavir.
- Refitted models were used to predict the effect-time profile for 7.5 mg *p.o.* midazolam dose [4] after saquinavir pretreatment.
- The prediction errors for the maximum effect for Linear and Emax models were 17%.
- The maximum effect prediction error for the Sigmoid model was ~20%.
- The shape of the effect-time profile predicted by Sigmoid model was better-represented than with the earlier model fitted to a single set of observed data.

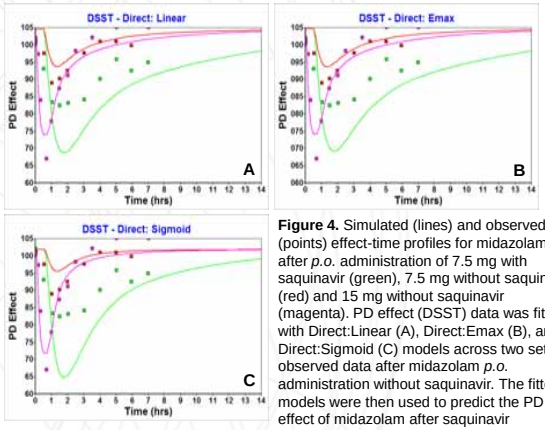

Figure 4. Simulated (lines) and observed (points) effect-time profiles for midazolam after *p.o.* administration of 7.5 mg with saquinavir (green), 7.5 mg without saquinavir (red) and 15 mg without saquinavir (magenta). PD effect (DSST) data was fitted with Direct:Linear (A), Direct:Emax (B), and Direct:Sigmoid (C) models across two sets of observed data after midazolam *p.o.* administration without saquinavir. The fitted models were then used to predict the PD effect of midazolam after saquinavir pretreatment. Saquinavir pretreatment consisted of 3-5 days of 1200 mg of *p.o.* saquinavir dosed TID.

Conclusions:

- The present study describes an approach for predicting the effect of DDI on pharmacodynamics of the victim drug.
- The selection of the most relevant model relating the PD response to the victim drug's unbound concentration affects the quality of prediction of DDI on the PD of the victim drug.
- Fitting PD models across multiple sets of observed data resulted in more robust and more predictive PD models.

References:

1. Lukacova V, Poster presentation, *AAPS* 2008,Altanta,GA
2. Kupferschmidt HHT, Clin Pharmacol Ther 1995, 58: 20-28
3. Mao J, Drug Metab Dispos 2011, 39: 591-602
4. Palkama VJ, Clin Pharmacol Ther 1999, 66: 33-39

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