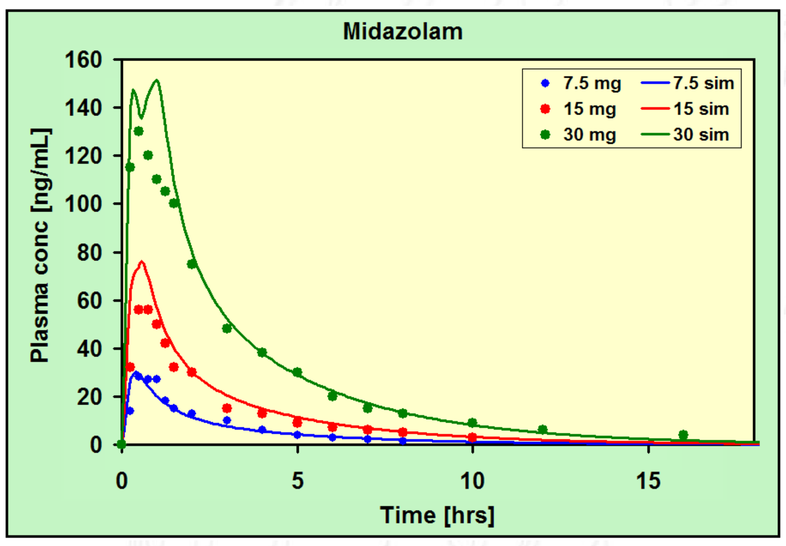
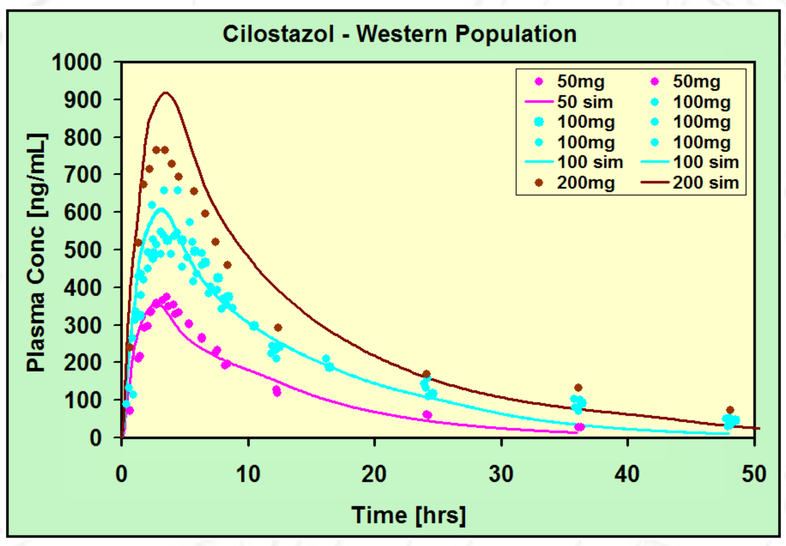
Prediction of dose-dependent intestinal and liver first pass extraction for CYP3A4 substrates

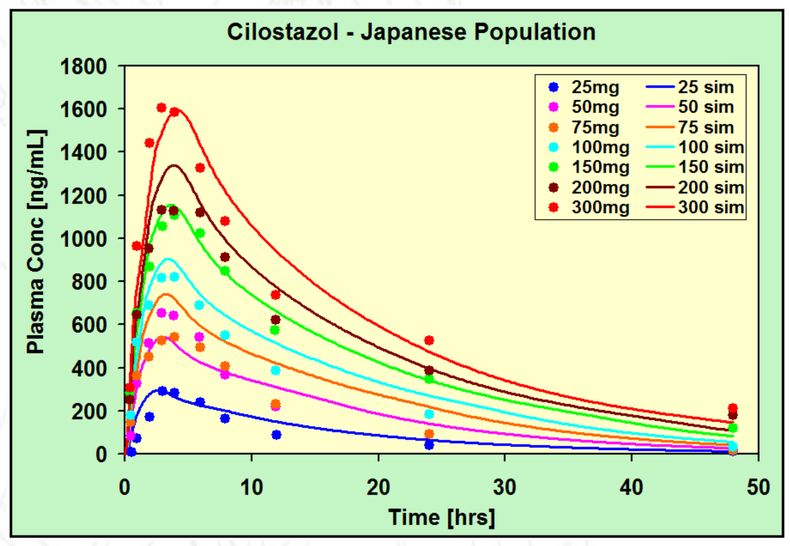
V. Lukacova, M.B. Bolger, and W.S. Woltosz
Simulations Plus, Inc., Lancaster, CA 93534, USA

Abstract

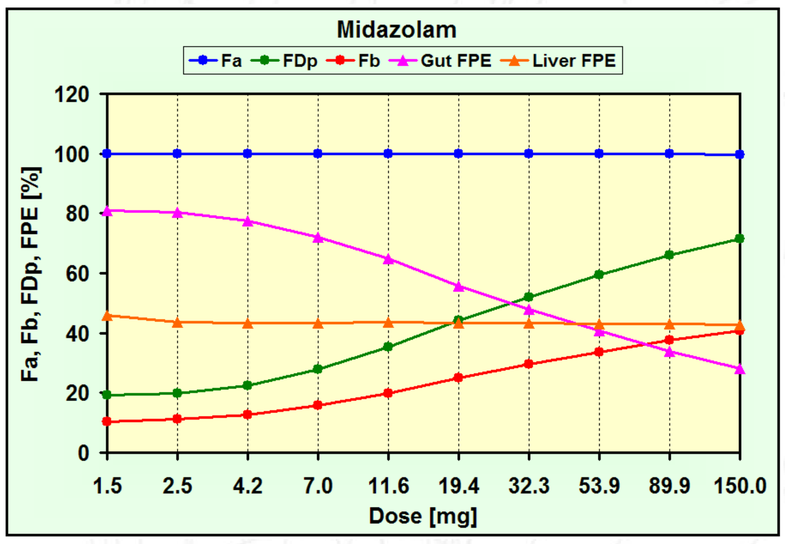
Cilostazol and midazolam absorption and pharmacokinetics were simulated using GastroPlus™ 6.0 (Simulations Plus, Inc.). The program's Advanced Compartmental and Transit model described the absorption and intestinal metabolism of both drugs; pharmacokinetics was simulated with a physiologically-based pharmacokinetics (PBPK) model. Human organ weights, volumes, and blood perfusion rates were generated by the program's internal Population Estimates for Age-Related (PEAR) Physiology™. Tissue/plasma partition coefficients were calculated using a modified Rodgers approach. The metabolism of both drugs in gut and liver was estimated from published *in vitro* enzyme kinetic constants combined with built-in *in vitro* values for 3A4 distribution in the gut and the average enzyme expressions in liver. The resultant models accurately reproduced *in vivo* plasma concentration-time profiles in human for solid oral doses in ranges 7.5-30mg and 25-300mg for midazolam and cilostazol, respectively. Both compounds show nonlinear dose-dependent bioavailability. Mechanistic simulations allowed estimating the contributions of limited dissolution (cilostazol) and first pass extraction (FPE) in gut and liver to low bioavailability. While gut FPE was dose-dependent, the liver FPE was nearly constant for both compounds. The main contributor to limited cilostazol bioavailability at higher doses was insufficient solubility.

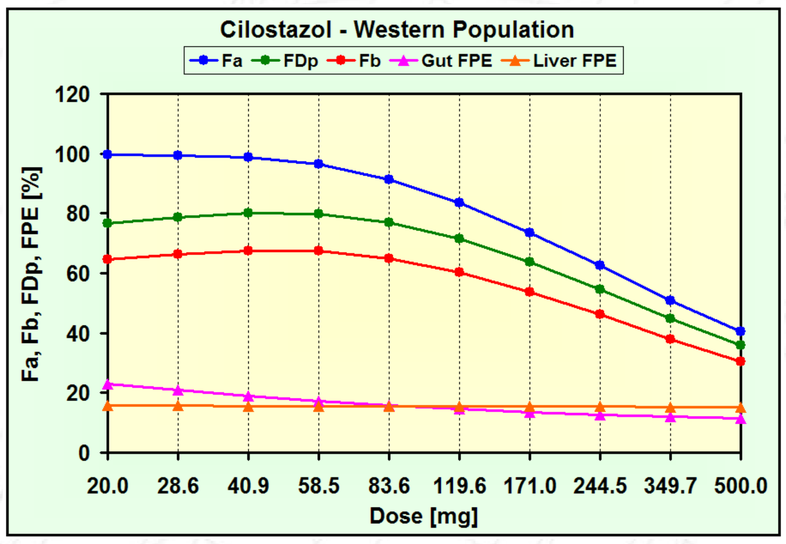


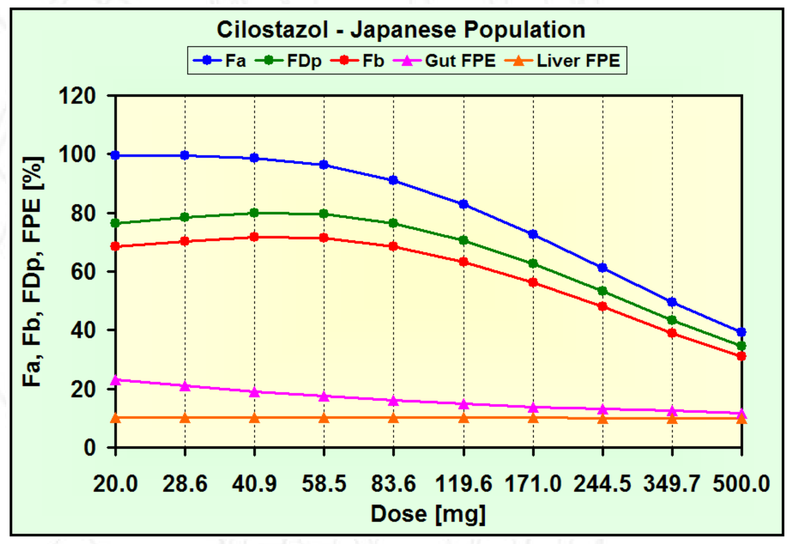




Experimental (points) and simulated (lines) Cp-time profiles of midazolam and cilostazol (in Western and Japanese population) after oral administration







Simulated dose-dependent fraction absorbed (Fa), fraction Dose to portal vein (FDp), bioavailability (F) and first pass extraction in gut (Gut FPE) and liver (Liver FPE) for midazolam and cilostazol (in Western and Japanese populations)

Results

- Pharmacokinetics of both compounds was successfully simulated with a PBPK model
- Clearance of both compounds was estimated from *in vitro* K_m and V_{max} values and average expression levels of relevant enzymes (3A4 for midazolam and 3A4, 3A5, 2C8, 2C19 for cilostazol) in gut and liver for two populations
- Simulations allowed exploring the effect of increasing dose on absorption and bioavailability of both drugs with respect to solubility, intestinal metabolism and liver FPE
- The main factor in dose-dependent bioavailability of midazolam is the saturation of intestinal metabolism
- For cilostazol, the dose-dependent bioavailability is affected mainly by limited solubility; the saturation of intestinal metabolism has only marginal effect at low doses
- Liver FPE is not significantly affected by the dose for either compound

Conclusions

This study demonstrates that mechanistic simulations of oral doses:

- help to estimate fraction absorbed and the separate contributions of gut and liver to first pass extraction
- provide information about processes affecting bioavailability which can be used in formulation design
- can provide an accurate description of a drug's pharmacokinetics even in the absence of intravenous Cp-time profiles (Cilostazol)

References

Rodgers T. J Pharm Sci. 2007, 96:3151-3154
Paine M. Pharmacol Exp Therap 1997, 283:1552-1562
Hiratsuka M. Drug Metab Dispos 2007, 37: 1730-1732
Niki T. Arzneim-Forsch 1985, 35:1173-1185
Bramer S. Clin Pharmacokinet 1999, 37:13-23
Lukacova V. Poster-AAPS National Meeting, Atlanta, Georgia 2008
Inoue S. Xenobiotica 2006, 36: 499-513
Suri A. Clin Pharmacokinet 1999, 37: 53-59
Woo S. Clin Pharmacol Ther 2002, 71:246-52
Bornemann L.D. Eur J Clin Pharmacol 1985, 29: 91-95

simulationsplus, inc.