Simulation of Cilostazol Absorption and Pharmacokinetics

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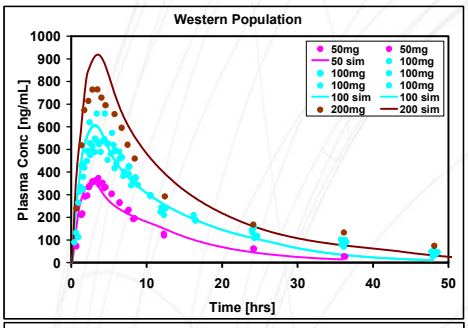
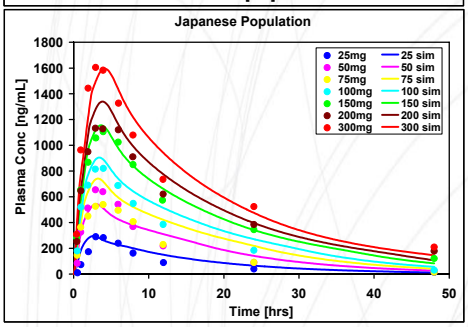
Abstract

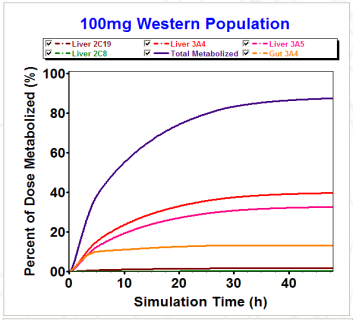
Cilostazol absorption and pharmacokinetics were simulated using GastroPlus™ 6.0 (Simulations Plus, Inc., Lancaster, CA). The program's Advanced Compartmental and Transit (ACAT) model described the absorption of the drug, while pharmacokinetics was simulated with physiologically-based pharmacokinetics (PBPK) model. Human organ weights, volumes, and blood perfusion rates were generated by the program's internal Population Estimates for Age-Related (PEAR) Physiology™ module. Tissue/plasma partition coefficients were calculated using a modified Rodgers (2007) & Lukacova (2008) algorithm from *in vitro* and *in silico* physicochemical properties (ADMET Predictor™, Simulations Plus, Lancaster, CA) . The metabolic clearance of cilostazol in gut and liver was estimated from *in vitro* enzyme kinetic constants for CYP3A4, 3A5, 2C8 and 2C19 (Hiratsuka 2007) combined with built-in *in vitro* values for the distribution of 3A4 in gut (Paine 1997) and the average expressions of all four enzymes in liver (Inoue 2006). The resultant model accurately reproduced human *in vivo* plasma concentration-time profiles for solid oral doses ranging from 25 to 300 mg. Simulations with doses from 10 to 1000 mg showed a nonlinear dose dependency of bioavailability with maximum at ~50 mg dose. For lower doses, the predicted fraction absorbed (Fa) was nearly 100 %, with predicted bioavailability affected mainly by saturable first pass extraction (FPE). The predicted bioavailability increased by ~5 % from 10 to 50 mg. Limited solubility caused a decrease in Fa with increasing dose. This decrease in Fa was more significant than the further decrease in FPE, resulting in ~50 % decrease in the predicted bioavailability from 50 to 1000 mg. This study demonstrates that even in the absence of intravenous data, mechanistic simulations of oral doses can help to estimate fraction absorbed and first pass extraction in gut and liver, and to provide information about processes affecting bioavailability which can be used in estimates of drug-drug interactions and/or formulation design.

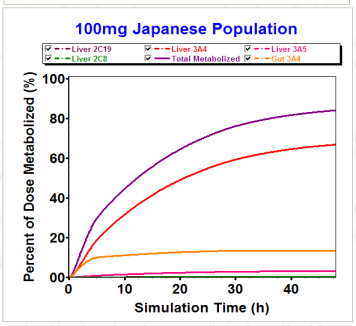
Results



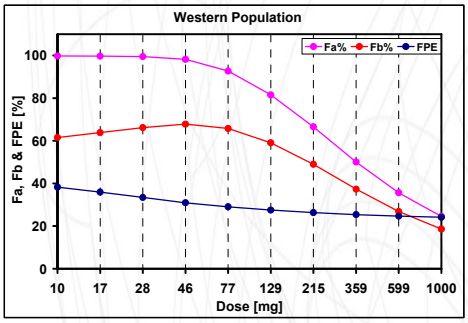


Experimental (points) and simulated (lines) Cp-time profiles for Western (top) and Japanese (bottom) subjects for oral doses ranging from 25 mg to 300 mg





Simulated metabolic profiles of cilostazol in Western (top) and Japanese (bottom) subjects



Simulated dose dependency of fraction absorbed and bioavailability in Western subjects. Similar profiles were obtained for Japanese subjects (not shown).

	Japanese	Western
Simulation results for 100 mg dose		
Fa [%]	87	88
FDp [%]	74	75
Fb [%]	66	63
CYP abundances [pmol/mg MP]		
3A4	77	111
3A5	3	72
2C8	14	24
2C19	1	14

- Absorption and pharmacokinetics of cilostazol were simulated in Western and Japanese populations using
  - typical adult male physiologies for each population
  - average expression levels of relevant enzymes in each population
  - *in vitro* K_m and V_{max} values. The same parameter values were used in both populations.
- Simulated Cp-time profiles were in good agreement with experimental data for all dose levels in Japanese subjects
- The 200 mg dose was slightly overestimated in Western subjects, however, considering that (1) only one profile was available for this dose level and (2) high variability was observed *in vivo* for the 100 mg dose, the fit was accepted as satisfactory, assuming that the mismatch was a result of high variability in the *in vivo* data
- Different simulated liver metabolic profiles in the two populations are a result of different expression levels of individual enzymes involved in cilostazol metabolism
- Simulations show similar dose dependency of fraction absorbed and bioavailability in both populations:
  - at low doses the bioavailability is affected by saturable first pass metabolism
  - at higher doses the bioavailability is affected by solubility-limited absorption

Conclusions

This study demonstrates that even in the absence of intravenous data, mechanistic simulations of oral doses:

- help to estimate fraction absorbed and first pass extraction in gut and liver
- provide information about processes affecting bioavailability which can be used in formulation design
- estimate *in vivo* metabolic profile of compound, an important factor in estimating drug-drug interactions

References

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