Simulation of Food Effect on Cilostazol Exposure in Human

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Introduction:

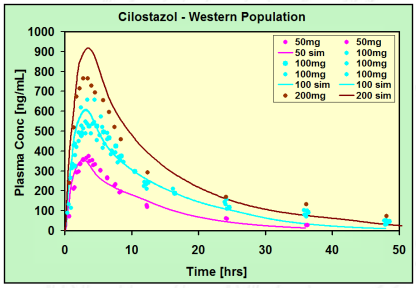
For certain drugs, the time of administration respective to meal times can have a significant impact on exposure. The effect of food is usually attributed to increased solubility/dissolution rate and/or modulation of the intestinal first pass. Administration of the drug with food can also lead to delayed T_{max} compared to administration in fasted state. The effect of food on differences in solubility/dissolution rate can be predicted [1, 2] using drug solubilities measured in biorelevant media mimicking the intestinal fluid in fasted and fed state [3].
The current work presents simulations explaining the dose-dependency of food effects on the dissolution and absorption of a Class II drug.

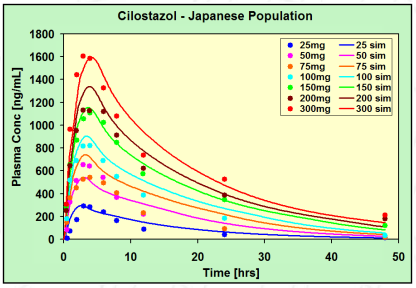
Methods:

The PBPKPlus™ module of GastroPlus™ 6.0 (Simulations Plus, Inc.) was used to construct a physiologically-based pharmacokinetic (PBPK) model for simulating cilostazol distribution and clearance. The model was based on the physiology (height, weight, tissue volumes and tissue blood flows) of typical 30-year-old ("30yo") adult male physiologies from Western and Japanese populations. Tissue/plasma partition coefficients (Kps) were calculated using a modified Rodgers [4, 5] 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 [6] combined with experimental values for the distribution of 3A4 in gut [7] and the average expressions of all four enzymes in liver [8]. Published fasted-state Cp-time profiles were used to calibrate the absorption model [9, 10] by fitting solubility and amount of fluid available for drug dissolution in colon . To model the fed state studies, the solubility was increased to account for the solubilizing effect of higher concentrations of bile acids (by increasing solubility) and the physiological gut parameters were modified to reflect the other physiological changes in fed state (mainly stomach pH, volume and stomach emptying rate represented by stomach transit time).

Results:

The calibrated absorption model combined with pharmacokinetics described by a PBPK model based on typical 30yo adult male (Western and Japanese physiologies) and *in silico* and *in vitro* data (calculated Kps and clearance) accurately reproduced the nonlinear dose-dependent exposure of cilostazol in Japanese and Western populations.
In the fasted state, the simulated fraction absorbed ranged from 100% for a 25 mg dose to 54% for a 300 mg dose. The bioavailability varied from 70% for a 25 mg dose to 43% for a 300 mg dose. The simulated fraction absorbed and bioavailability were the same for corresponding doses in Western and Japanese populations.

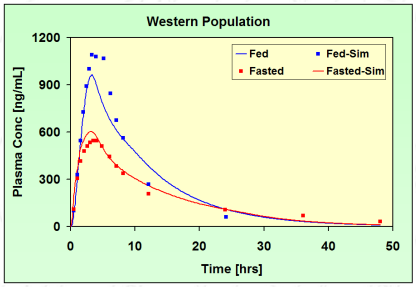


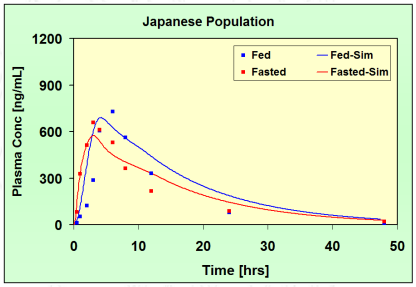


	Japanese	Western
Simulation results for 100 mg dose		
Fa [%]	87	88
FDp [%]	74	75
Fb [%]	66	63
CYP abundances [pmol/mg MP]		
3A4	77	111
3A5	3	72
2C8	14	24
2C19	1	14

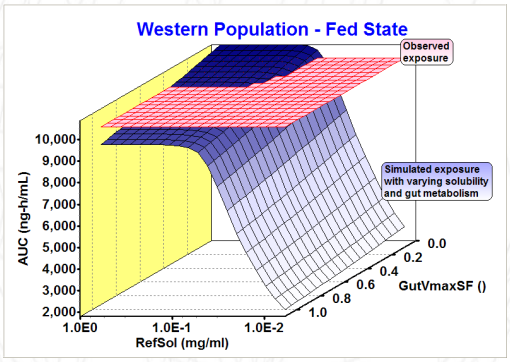
Experimental (points) and simulated (lines) Cp-time profiles for Western (top) and Japanese (bottom) subjects for oral doses ranging from 25 mg to 300 mg

For the 50 mg (Japanese) and 100 mg doses (Western), the simulated fractions absorbed in the fasted state were 100% and 88%, respectively, and the simulated bioavailabilities were 72% and 63%, respectively. For the 100 mg dose, increasing stomach fluid volume and solubility in the fed state resulted in increase in simulated fraction absorbed but this effect on dissolution alone was not able to completely account for the increased exposure [10]. The experimental C_{max} and AUC values were 1.09 ug/mL and 10.26 ug/mL/h, respectively, while the simulated C_{max} and AUC values were 0.853 ug/mL and 9.218 ug/mL/h, respectively. Assuming that food could also interfere with intestinal metabolism and removing the contribution of gut to first pass extraction further improved the match of simulated and experimental Cp-time profiles in fed state. The simulated C_{max} and AUC values increased to 0.962 ug/mL and 10.79 ug/mL/h, respectively. For the 50 mg dose, the simulated fraction absorbed in fasted state was already 100%, so no further increase in exposure due to increased solubility or dissolution rate in fed state could be obtained. The small increase in C_{max} and AUC, apparent from experimental data [9], was reproduced by removing the contribution of intestinal first pass metabolism similar to the result of the fed study at 100 mg dose.





Experimental (points) and simulated (lines) Cp-time profiles for Western (left) and Japanese (right) subjects for oral doses of 100 mg and 50 mg, respectively, in fasted and fed state.



Parameter sensitivity analysis exploring the effect of solubility and gut metabolism on exposure after 100 mg dose in Western subjects in fed state (shown in blue). The effect of food on solubility alone is not able to account for observed (shown in pink) exposure in fed state .

Conclusions:

This study demonstrates that in the absence of intravenous data, mechanistic simulations of oral doses can help to estimate fraction absorbed, first pass extraction in gut and liver, and therefore, bioavailability. A single model successfully simulated food effect at two different dose levels and explained the nearly double exposure for the 100 mg dose while there was only minimal increase in exposure for the 50 mg dose. It also provides another example of a successful application of the PBPK approach, which was able to describe the compound's nonlinear pharmacokinetics based on only the information about the physiology for a target population and the drug properties (*in silico* or measured *in vitro*).

References:

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