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

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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.

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

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