PBPK modeling of metoprolol and its metabolites

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Abstract:

Purpose: Develop a model describing absorption and pharmacokinetics of metoprolol and the formation and pharmacokinetics of its metabolites.

Methods: GastroPlus™ (Simulations Plus, Inc.) was used to fit the model describing absorption and pharmacokinetics of metoprolol and its metabolites. A physiologically-based pharmacokinetic (PBPK) model was used to describe the distribution and pharmacokinetics (DPK) of metoprolol along with the simultaneous DPK of its metabolites. The *in vitro* metabolism of metoprolol to its two major metabolites (α-hydroxy-metoprolol and O-demethylmetoprolol) measured in human liver microsomes [1] was used to describe the metabolic clearance of metoprolol and formation of the metabolites. The renal clearance of metoprolol was estimated using glomerular filtration rate and fraction unbound in plasma. The renal clearance of the final metabolites was fitted to match the amount of radioactive metabolites secreted in urine [2].

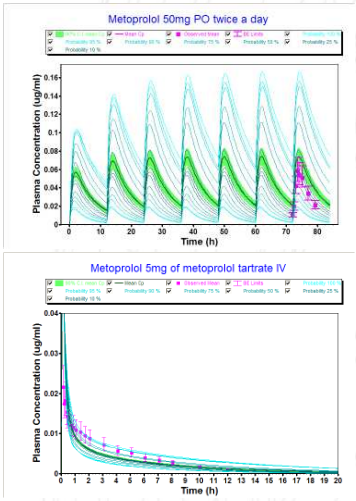
Results: Cp-time profiles of metoprolol and the metabolites as well as urinary secretion of metoprolol and total metabolites were successfully modeled for IV and oral administration of metoprolol. The major metabolizing enzyme for metoprolol (CYP 2D6) is present in intestinal microsomes. However, our simulation shows that the contribution of gut metabolism to first pass extraction was not significant for this compound. Urinary secretion was sufficient to describe the clearance of the final metoprolol metabolites (measured as total radioactive metabolites). To describe the pharmacokinetics of one of the direct metabolites of metoprolol, α-hydroxy-metoprolol [3], a significant contribution from metabolic clearance had to be considered.

Conclusions: A model was developed that describes the pharmacokinetics of metoprolol and its metabolites, including both total metabolite fraction as well as α-hydroxy-metoprolol alone. The model accurately describes plasma concentration and urinary secretion of total metabolites as well as plasma concentration of α-hydroxy-metoprolol alone under the assumption that α-hydroxy-metoprolol undergoes further biotransformation [4].

Methods:

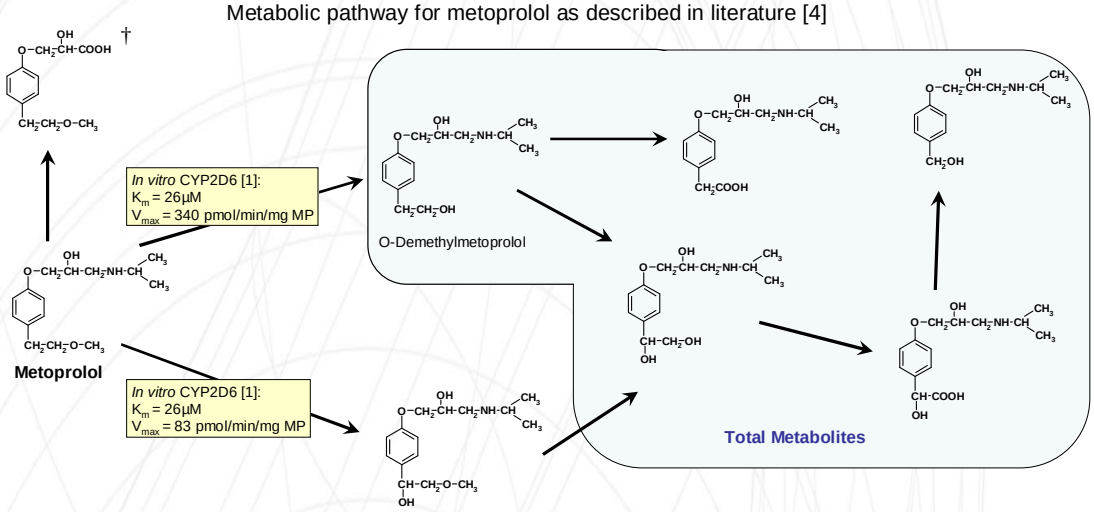
- *In vivo* data (Cp-time and urine secretion profiles for metoprolol, α-hydroxymetoprolol and total metabolites) after IV and repeated PO administration were obtained from literature [2,3]. The Cp-time profile for one of the metabolites, α-hydroxymetoprolol, was simulated separately. The plasma concentrations of all remaining metabolites [4] were "lumped" under Total Metabolites, because there was not sufficient information/data to model each of them individually.
- Distribution of metoprolol and metabolites was simulated using the default GastroPlus PBPK model for a 30YO American male.
- Metabolic clearance of metoprolol was simulated using kinetic constants for formation of two major metoprolol metabolites, α-hydroxymetoprolol and O-demethylmetoprolol, from *in vitro* experiments [1].
- Metabolic clearance of α-hydroxymetoprolol was fitted to match the Cp-time profile of α-hydroxymetoprolol after repeated PO dosing.
- Urinary secretion of parent metoprolol was estimated by "Fup x GFR"
- Urinary secretion of total metabolites was fitted to match the *in vivo* urine data for total metabolites after IV administration of metoprolol.
- Virtual trial simulations were used to predict the variability in plasma concentration of metoprolol and its metabolites in a population.

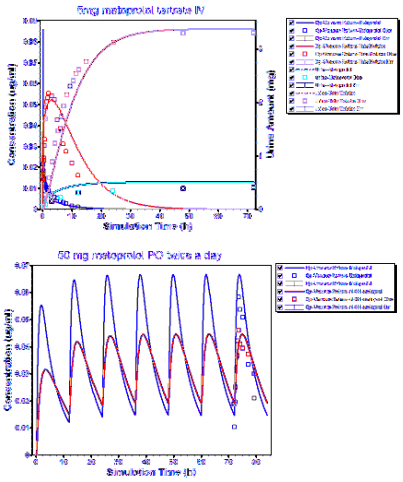
Results:



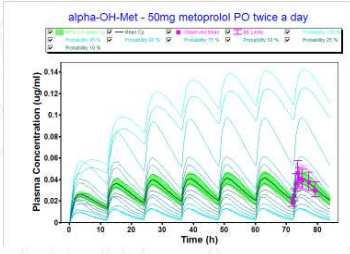
Population predictions of metoprolol plasma concentration after IV and repeated PO dosing

Metabolic pathway for metoprolol as described in literature [4]

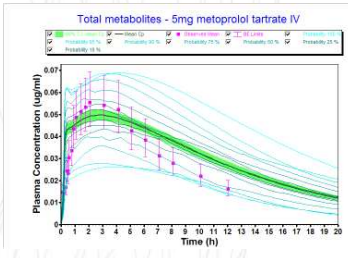




Mean simulations of metoprolol and its metabolites in plasma and urine after IV and repeated PO dosing



Population simulation results of one of the main metoprolol metabolites, α-hydroxymetoprolol, after repeated PO dosing of metoprolol



Population simulation results for total metoprolol metabolites (with exception of α-hydroxymetoprolol) after IV administration of metoprolol.

Conclusions:

1. The default GastroPlus PBPK model with *in vitro* metabolic clearance was able to accurately predict the plasma concentration for metoprolol after IV and PO dose.
2. The simulation showed that the contribution of gut metabolism to first pass extraction of metoprolol was not significant.
3. A single comprehensive absorption/PK model was able to accurately simulate the plasma concentration and urinary secretion of metoprolol and its metabolites after both IV and PO administration.
4. Urinary secretion of the parent drug metoprolol was accurately simulated as GFR x Fup, while metabolite urinary secretion was fitted from IV data.

References:

[1] Madani S., Pharm Res 1999, 16(8) : 1199-1205
[2] Regardh C.G., J Pharmacokinet Biopharm 1974, 2(4) : 347-364
[3] Regardh C.G., Eur J Clin Pharmacol 1983, 24: 221-226
[4] Hoffmann K.J., Biomed Environ Mass Spectrom 1987, 14(10) :543-8

† - minor metabolite – not included in current simulation
* - in vivo Cp-time profile of total metabolites was adjusted by subtracting the simulated amount of α-hydroxymetoprolol which is simulated separately and not included in simulated total metabolites

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