PBPK modeling of metoprolol and its metabolites

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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 metaolites. The *in vitro* metabolism of metoprolol to its two major metabolites (alpha-hydroxy-metoprolol and O-demethylmetoprolol) measured in human liver microsomes [1] was used to describe 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, alpha-hydroxy-metoprolol [3], a significant contribution from metabolic clearance had to be considered.

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

References:

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