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Mechanistic Modeling of Metoprolol Absorption and Pharmacokinetics from Immediate and Modified Release Formulations

Viera Lukacova, John Chung, John Crison, Michael Bolger, Walter Woltosz
Simulations Plus, Inc., Lancaster, CA 93534

Introduction

As one of the most widely used β-blocking agents, metoprolol is also a popular drug in research studies. A number of published studies describe the pharmacokinetics as well as the pharmacodynamics of metoprolol after administration of immediate release or modified release formulations [1-3, 6-12]. Numerous IVIVC studies for extended release formulations have also appeared in the literature [1-3]. However, the studies published to date generally focus on a very specific formulation type (either immediate release, single unit modified release or multi-particulate modified release) without a translation into different types of formulations, e.g. comparing immediate release directly with modified release. This makes the general use of such models risky for prediction of other types of formulations.

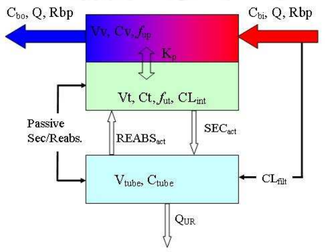
The focus of this study was to combine the information available in literature for *in vitro* metabolism, *in vivo* pharmacokinetics after intravenous, immediate release and modified release as well as formulation parameters into a single comprehensive model. In addition to the utility of the model across multiple formulation types, the model provides a greater insight into the mechanism of metoprolol's absorption and metabolism, as well as relationships between *in vitro* and *in vivo* release.

Methods

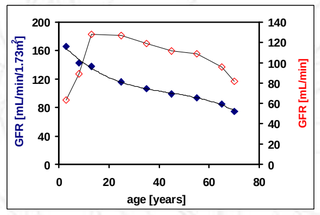
The PBPKPlus™ module of GastroPlus™ (Simulations Plus, Inc.) was used to construct the physiologically based pharmacokinetic model for simulating metoprolol's distribution and clearance. The model was based on physiology (height, weight, tissue volumes and tissue blood flows) of a typical 30-year-old male. The method of Rodgers and Rowland [4-5] was used to estimate tissue:plasma partition coefficients (Kp). Initial estimates for metabolic clearance parameters (Km, Vmax and enzyme expressions) in liver and gut were based on *in vitro* measurements in human liver and intestinal microsomes [6]. Due to high polymorphism in the expression of 2D6 in the intestine and liver, the average expressions were modified for certain groups of subjects (the same expression level was used for all formulations from the same study; the same ratio of enzyme expression in intestine and liver was assumed). The renal clearance of metoprolol was estimated by glomerular filtration assuming healthy subjects with normal GFR for ~30 year old adult. The filtration rate was calculated as:

$$CL_{filt} = F_{up} \times GFR$$

where Fup is fraction unbound in plasma and GFR is glomerular filtration rate.
The age dependency of GFR in range of ages 3 to 75 years was based on data from literature [13-14].

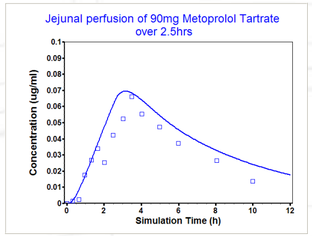


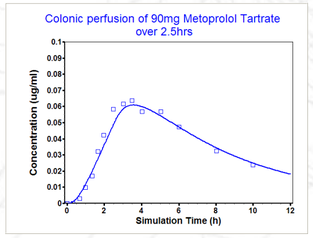
Physiological model of kidney tissue as implemented in the PBPK model in GastroPlus.



Glomerular filtration rate vs. age [6-7].

The absorption model was calibrated using the plasma concentration time profiles obtained for a solution dosed directly to the jejunum and colon [7].



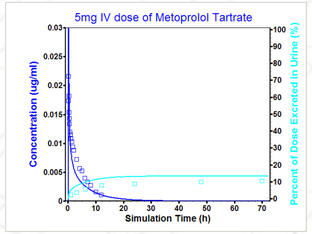


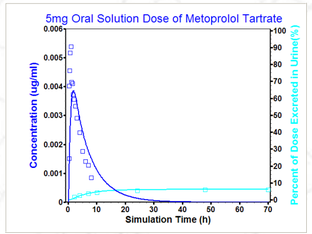
The colon transit time for pellets and integral tablet was used as reported in literature [8].
For modified release formulations, the *in vitro* dissolution profiles were used directly to model the drug release *in vivo*.

Results

The volume of distribution calculated using the tissue volumes and *in silico* Kp values was 275 L. The total volumes of distribution fitted to available sets of intravenous data ranged from 200 to 535 L. The variability in enzyme expression in the intestine and liver that needed to be used in order to model different sets of data from different studies was ~ 25%.

The kidney clearance based on glomerular filtration rate and binding of metoprolol to plasma proteins resulted in simulated urinary secretion close to observed values. The simulation showed 13% of unchanged drug excreted in urine 70 hrs after intravenous administration and 6% of drug excreted in urine 70 hrs after *p.o.* administration. The reported experimental values were 9% and 6%, respectively [12].



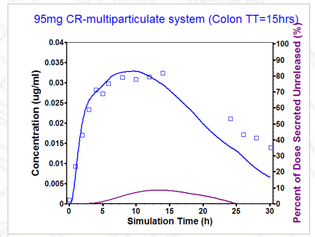


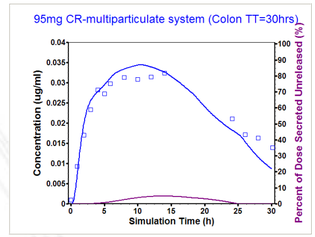
Conclusion

The fitted Absorption/PBPK model combines various pieces of information related to metoprolol's absorption and pharmacokinetics available in literature. Unlike IVIVC models for metoprolol published to date, its use is not limited to a single type of formulation. The comprehensive mechanistic model allows for prediction of Cp-time profiles of formulations for various *in vitro* release profiles (e.g. sustained vs pulsed or IR) as well as for the evaluation of effects of different types of formulations (e.g. multi-particulate system versus integral tablets). It also provides insight into possible behaviors of different types of formulation *in vivo*, e.g. longer transit time of small particles in colon compared to tablets (which was confirmed experimentally [8]) or the possibility of the single unit formulation not releasing drug effectively once it reaches the colon.

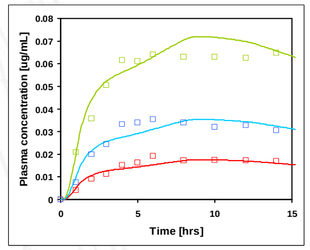
Multi-particulate modified release formulations

The colon transit times reported in the literature were significantly different for pellets (~30 hrs) and integral tablet (~15 hrs) [8]. Experimentally determined colon transit times resulted in correct predictions of plasma concentration time profiles for both types of formulations as well as correct time dependent profile of appearance of pellets in the colon.



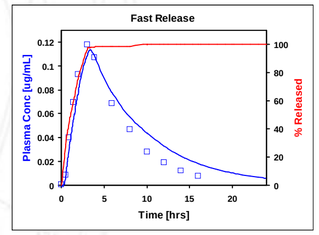


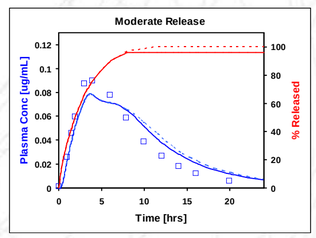
The dose dependent pharmacokinetics was correctly reproduced for 3 different doses of multi-particulate modified release formulations containing metoprolol succinate (red-50mg, blue-100mg, green 200mg) assuming that the drug release *in vivo* is the same as measured in *in vitro* experiment

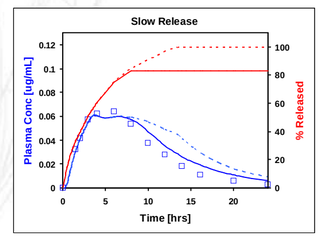


Single-unit modified release formulations

Among the single unit modified release formulations, only the one that released all drug before reaching the colon (right) was well modeled assuming that *in vivo* release is equal to the measured *in vitro* release. For the two slower formulations (below) a match could be obtained with the assumption that the *in vivo* release in small intestine is equal to the measured *in vitro* release, but no drug is released once the formulation reaches the colon.







red – percent released, blue – plasma concentration time profile, solid lines – no drug release in colon, dotted lines – drug release continues in colon

References

1. Mahayani H., J Pharm Sci 2000, 89: 1354-1361
2. Sirisuth N., Eur J Pharm Biopharm 2002, 53:301-309
3. Sirisuth N., Pharm Res 2000, 17:1019-1025
4. Rodgers T., J Pharm Sci 2007, 96:3153-3154
5. Rodgers T., J Pharm Sci 2007, 96: 3151-3152
6. Madani S., Pharm Res 1999, 16:1199-1205
7. Godbillon J., Br J Clin Pharmac 1985, 19:113S-118S
8. Abrahamsson B., Int J Pharmaceut 1996, 140:229-235
9. Regardh C., J Cardiovasc Pharmacol 1980, 2:715-723
10. Sandberg A., Int J Pharm 1991, 68:167-177
11. Sandberg A., Eur J Clin Pharmacol 1988, 33(Suppl):S3-S7
12. Regardh C., J Pharmacokinet Biopharm 1974, 2:347-364
13. Mego S. 36th Annual Scientific Meeting of the Australian and New Zealand Society of Nuclear Medicine (poster)
14. Stevens L. FAQ about GFR Estimates (National Kidney Foundation publication)

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