Modeling Disposition of Sotalol following Intravenous and Oral Administration in Healthy Adult Subjects

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OBJECTIVE

To simulate and predict the absorption and pharmacokinetics (PK) of sotalol following intravenous (IV) and oral (PO) administrations.

METHODOLOGY

Sotalol is a nonspecific adrenergic beta-antagonist that is used in the treatment of life-threatening arrhythmia [1]. Its absorption, distribution and systemic PK or, collectively, 'disposition' was modeled and simulated using GastroPlus™ v7.0 [2]. Biopharmaceutical properties were obtained from *in silico* predictions [3] and *in vitro* measurements [4-8] and are listed in Table 1 below.

Systemic PK was simulated using a physiologically based pharmacokinetic (PBPK) model with all perfusion-limited tissues. Human organ weights, volumes, and blood perfusion rates were generated by the built-in age-, gender- and body-weight-dependent Population Estimates for Age-Related (PEAR) Physiology™. Tissue/plasma partition coefficients (Kp's) were calculated using our default modified Rodgers method. Sotalol is cleared predominantly in the kidney. Renal clearance was estimated as the product of fraction of sotalol unbound to blood plasma proteins (fup) and glomerular filtration rate (GFR). The blood-to-plasma concentration ratio (Rbp) of sotalol was fitted to correct for the steady-state volume of distribution (Vss) against observed plasma concentration (Cp-time) data following IV administration of 20 mg sotalol [9]. This systemic PBPK model was further validated by predicting Cp-time profiles after IV administration of four other sotalol doses ranging from 17.375 mg to 139 mg in a different healthy population [10].

The validated PBPK model, combined with the GI absorption (ACAT™) model within GastroPlus, was used to simulate the Cp-time profiles for oral administration of an 80 mg solution [9] and a 100 mg immediate-release tablet [10] of sotalol. The stomach transit time (STT) was fitted to match the relatively late Tmax (~3hrs) in the Cp-time data for the solution dose and then used unchanged to predict the behavior of the tablet administration.

Table 1. Biopharmaceutical properties of sotalol

Physicochemical Properties for Sotalol	Value	Source
Reference Solubility (mg/mL)[1]	16.25 @ pH = 8.935	[3]
Log P	0.24	[4]
pKa	8.38, 9.47	[5]
% plasma protein binding	31.0	[6]
Intestinal Permeability (P_{eff}, cm/s)[2]	0.9687 x 10^{-4}	[7-8]

1. Profiles for variation of solubility and logD against varying pH was calculated using both *in silico* and *in vitro* inputs [3]
2. Mean of reported *in vitro* values converted to *in vivo* values using in-house correlation

RESULTS & DISCUSSION

Figure 1 shows the simulated Cp-time profile and observed values [9] for 20 mg sotalol administered as a 10-minute IV infusion to healthy male population "D" (n = 7, median age = 22 y, median weight = 79 Kg) by fitting the Rbp to 0.89. Figure 2 shows the predicted Cp-time profile and observed values [10] for a 5-minute infusion of 0.25 and 2 mg/Kg of sotalol to healthy male population "P" (n = 6, mean age = 23.8 y, mean weight = 69.5 Kg) using the same model built for population "D"

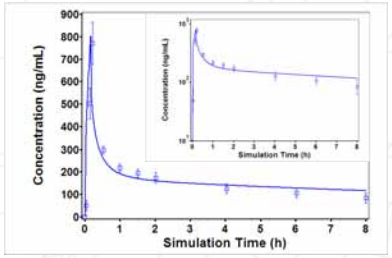

Fig 1. **Simulated** (line) and observed (points) Cp-time profile for 10-minute IV infusion of 20 mg sotalol. Inset shows the same image on a logarithmic scale.

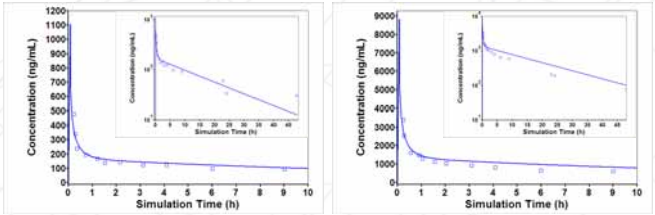

Fig 2. **Predicted** (line) and observed (points) Cp-time profile for 5-minute IV infusion of 17.375 mg (left) and 139 mg (right) of sotalol (shown up to 10 hours). Inset shows the same image on a logarithmic scale extended to 48 hours.

Figure 3 shows the simulated Cp-time profile and observed values for 80 and 100 mg of sotalol administered as an oral solution and as an immediate-release tablet, respectively. The stomach transit time was fitted to 0.6 h to population "D" and was used to predict the behavior in population "P". The figure shows that the Cp-time for the 100 mg oral tablet administration is overpredicted. This might be attributed to binding of sotalol with calcium [11] from milk or other ingredients in the diet; however, this has not yet been thoroughly investigated.

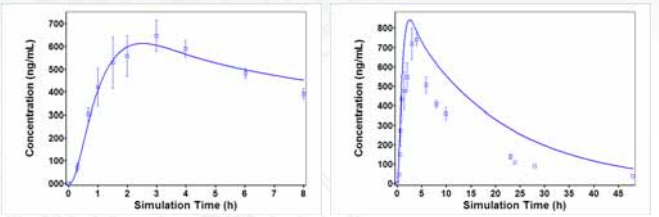

Fig 3. Simulated (line) and observed (points) Cp-time profile for an oral administration of an 80 mg oral solution (left) and 100 mg immediate-release tablet (right, with 100 mL water followed by a meal at 2 h) of sotalol.

CONCLUSIONS

- **A PBPK-ACAT model in GastroPlus was able to simulate the disposition of sotalol (both IV and oral solution doses) in healthy subjects using mainly *in silico* and *in vitro* inputs.**
- **The model successfully predicted the disposition of sotalol (for both IV and oral doses) across multiple dose levels in a different healthy population.**

REFERENCES

[1] Drug Bank
http://www.drugbank.ca/drugs/DB00489 (Accessed 2011-10-10)
[2] GastroPlus
http://www.simulations-plus.com/Products.aspx?grpID=3&cID=16&pID=11 (Accessed 2010-10-10)
[3] ADMET Predictor v5.5
http://www.simulations-plus.com/Products.aspx?grpID=1&cID=11&pID=13 (Accessed 2010-10-10)
[4] Burgot, G. et al. (1990), "Thermodynamics of partitioning in the n-octanol/ water system of some β-blockers", *Int. J. Pharm.*, 63, pp. 73-76
[5] Dahan, A. et al. (2010), "High-Permeability Criterion for BCS Classification: Segmental/pH Dependent Permeability Considerations", *Mol. Pharm.*, 7, pp. 1827-1834.
[6] Fiset, C. et al. (1993), "Stereoselective disposition of (±)-sotalol at steady-state conditions", *Br. J. Clin Pharmac.*, 36, pp. 75-77.
[7] Alt, A. et al. (2004), "Biopharmaceutical characterization of sotalol-containing oral immediate release drug products", *Eur. J. Pharm. Biopharm.*, 58, pp. 145-150.
[8] Yang, Y. et al. (2007), "Biopharmaceutics Classification of Selected β-Blockers: Solubility and Permeability Class Membership", *Mol. Pharm.*, 4, pp. 608-614.
[9] Deneer, V.H.M. et al. (1998), "Absorption Kinetics of oral sotalol combined with cisapride and sublingual sotalol in healhty subjects", *Br. J. Clin. Pharmacol.*, 45, pp. 485–490.
[10] Poirier, J.M. et al. (1990), "The pharmacokinetics of d-sotalol and d,l-sotalol in healthy volunteers", *Eur. J. Clin. Pharmacol.*, 38, pp. 579–582.
[11] Kahela, P. (1979), "Effect of Food, Food Constituents and Fluid Volume on the Bioavailability of Sotalol", *Acta pharmacol. et toxicol.*, 44, pp. 7-12

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