Prediction of the impact of Pregnancy on Sotaolol Pharmacokinetics using the Simcyp Pregnancy PBPK Model

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Background

According to the FDA Pregnancy and Lactation Labelling rules, drug companies are required to provide information about using their drug during pregnancy [1]. Physiologically based pharmacokinetic (PBPK) models have a unique advantage in integrating both the drug characteristics with the underlying physiological changes during pregnancy [2], along with variability within this population to predict drugs kinetics at different gestational ages [3].

Objectives

The objective of this study is to use a PBPK approach to predict sotalol concentration time profiles after intravenous and oral administration to non-pregnant and pregnant women [4].

Methods

A compound file was developed in the Simcyp simulator V17R1. The compound pharmacokinetic specifications are as follows:

Absorption: ADAM: Permeability predicted based on the entered Peff,man of 2 x10-4 cm/s, while an immediate release formulation using the diffusion layer model was used (aqueous solubility of 0.782 mg/mL) to predict dissolution.

Distribution: Full PBPK distribution model (Rodgers & Rowland method with a Kp scaler of 0.63) adjusted to match the reported volume for non-pregnant group (1.2L/kg) after intravenous administration.

Elimination: this was represented by renal clearance which constitutes 100% of CLiv (CLR= 5.85 L/h), which was obtained from the original study for non-pregnant group after infusion. GFR is significantly changed during pregnancy. The Simcyp model used the following function to describe GFR and renal blood flow changes during pregnancy:

$$GFR\ (mL/min) = 114 + 3.2367 \cdot GA - 0.0572 \cdot GA^2$$

$$renal\ blood\ flow\ (L/h) = 53 + 2.6616 \cdot GA - 0.0661 \cdot GA^2$$

where GA is the gestational age in weeks. The model was used to simulate PK profiles using the Sim-Pregnancy population within the Simulator. The results were compared with the clinical observations, where sotalol was administered as single doses of 100mg intravenously and 400mg orally to non-pregnant and 32-36 GW pregnant women [4].

Results

Simulated profiles were in agreement with the reported concentration time profiles (Fig 1). The figure shows that the clearance is slightly under-predicted for the intravenous during pregnancy, however this trend is not the same after oral administration. The PRED/OBS ratio for clearance in pregnant women are within bioequivalence criteria 0.8 to 1.25 (Table 1). Whether this was due to the pregnancy PBPK (GFR, RBF) parameters or due to the fact that CLR does not represent 100% of total drug clearance is not apparent. However, the clinical observations only came from 6 subjects in each group who may not be representative.

Conclusion

The pregnancy PBPK model was able to replicate the clinical observations for sotalol. The fraction of drug bound to plasma protein is insignificant (fu=1) so the unbound drug concentration is reflecting the total concentration.

Results (Cont)

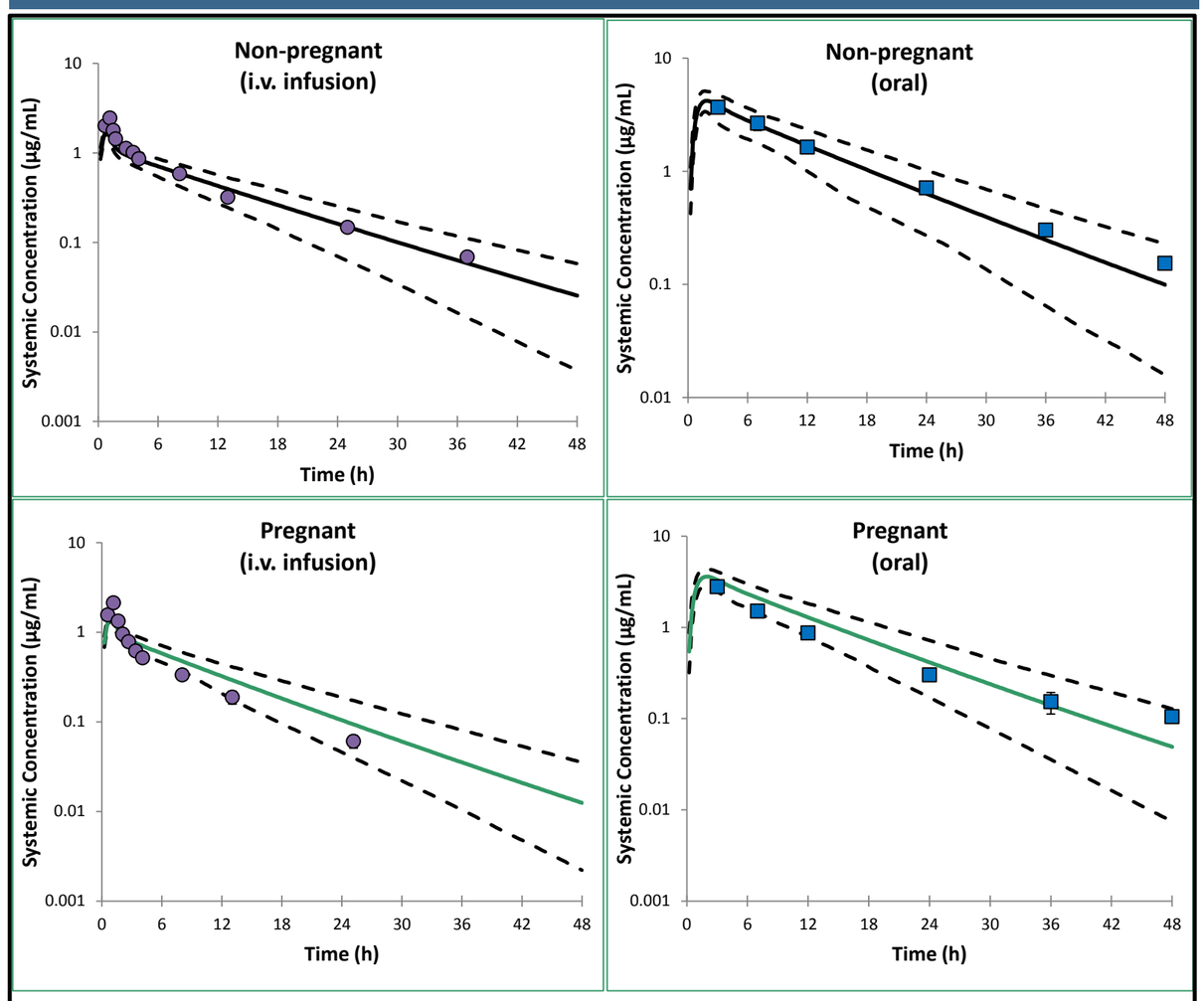

Figure 1. Plasma concentration-time profile for Sotalol in non-pregnant and pregnant population after intravenous infusion (left) and oral (right) administration. Predicted mean (solid lines), Predicted 90% interval (dashed line) and reported [4] (filled circles and squares).

Parameter	Non-Pregnant			Pregnant		
	Predicted	O'Hare 1983	PRED/ OBS	Predicted	O'Hare 1983	PRED/ OBS
	Mean±SD	Mean		Mean±SD	Mean	
100mg intravenous infusion						
LambdaZ	0.09±0.02	0.08	1.12	0.10±0.02	0.11	0.89
Half-life	8.42±1.76	9.30	0.91	7.21±1.49	6.60	1.09
AUCINF (µg/mL.h)	14.80±2.95	15.30	0.97	11.24±2.18	9.30	1.21
CL (L/h/kg)	0.11±0.02	0.09	1.22	0.125±0.024	0.14	0.87
V(L/kg)	1.18 ±0.15	1.20	0.98	1.15±0.14	1.30	0.88
TMax (h)	0.98±0.02			1.00±0.01		
CMax (µg/mL)	2.09±0.19			1.74±0.14		
CL (Dose/AUC) (L/h)	7.05±1.56			9.33±1.76		
400 mg oral						
LambdaZ	0.09±0.02	0.09	0.96	0.10±0.02	0.07	1.43
Half-life	8.42±1.76	10.30	0.82	7.21±1.49	10.90	0.66
AUCINF (µg/mL.h)	53.89±12.31	55.80	0.97	41.00±8.94	31.10	1.32
Bioavailability		91.10			86.20	
CL (L/h/kg)	0.12±0.03	0.10*	1.2	0.14	0.17*	0.84
TMax (h)	1.91±0.35			2.00±0.32		
CMax (µg/mL)	4.26±0.53			3.66±0.41		
CL (Dose/AUC) (L/h)	8.05±2.15			10.39±2.50		

Table 1. Predicted pharmacokinetic parameters in pregnant and nonpregnant women after oral and intravenous administration of sotalol.

*** CLpo was calculated using reported mean bioavailability.**

References

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