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Gender Related Differences and Pregnancy Induced Changes in Labetalol Glucuronidation Assessed via PBPK Modeling and Simulation

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PURPOSE

Glucuronidation is considered a major metabolic pathway for drugs containing carboxylic acid, hydroxyl, and amine moieties [1]. In the human body, UDP-glucuronosyltransferases (UGTs) are located hepatically and extrahepatically, with intestine as the main extrahepatic site [2]. Beta-blocker antihypertensive drugs, such as labetalol, with a hydroxyl group in their structures, are likely to be metabolized via glucuronidation [3]. The literature reports gender-related differences in labetalol PK [4, 5], as well as pregnancy-induced changes in labetalol clearance [6, 7].

OBJECTIVE(S)

The objective for this work was to develop and apply a mechanistic absorption/PBPK model for labetalol to: (i) explore the extent of UGT1A1 and/or UGT2B7-mediated intestinal versus hepatic metabolism; (ii) evaluate gender-related differences in labetalol PK; and (iii) assess changes to labetalol clearance during pregnancy.

METHOD(S)

A mechanistic absorption/PBPK model for labetalol was developed using GastroPlus® v. 9.8 software (Simulations Plus, Inc.). Physicochemical and biopharmaceutical properties reported in the literature and/or derived *in silico* from the structure using ADMET Predictor® v. 9.5 software (Simulations Plus, Inc.) are summarized in the table below.

Parameter	Log P	pKa	pH solubility	Rbp	Fup	Peff	Mean Prec. Time	Diffusion Coeff	Particle Density
Value	3.09	7.35 (OH); 9.42 (NH)	2.61 mg/mL	1.36	0.5	1.7748 cm/s x 10^{-4}	900 s	0.68 cm/s x 10^{-5}	1.2 g/mL

Labetalol metabolism information (CYP2C19, UGT1A1, and UGT2B7) was obtained from literature [8, 9] . The contribution of intestinal and liver metabolism was modeled using default GP 9.8 gut and liver expressions of UGT1A1, UGT2B7 and CYP2C19, while *in vitro* Km and Vmax values were fitted to match the reported contributions. Systemic distribution and clearance were calibrated against observed PK profiles obtained after IV administration [10-13]. Intestinal absorption and metabolism was modeled using the Advanced Compartmental Absorption and Transit model (ACAT™) and validated with *in vivo* data obtained after PO administration to male volunteers [11-15]. Subsequently, the model was evaluated against the PK profiles reported by Johnson et al. for male and female subjects at steady state [4] and against observed PK profiles in pregnant women (3rd trimester of pregnancy) and postpartum as reported by Fisher et al. [6]. Default physiologies were used for non-pregnant and pregnant subjects, with modifications to UGT expressions as described in the Results.

RESULT(S)

(i) UGT-mediated Metabolism: Intestinal vs. Hepatic

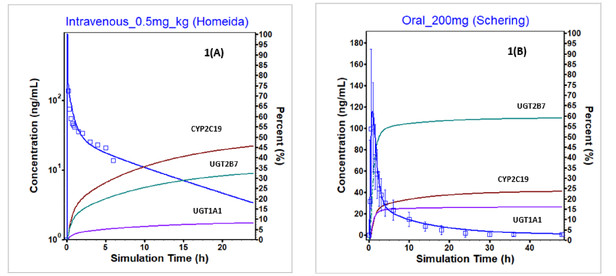
Simulated systemic distribution and CL of labetalol were assessed by goodness of fit of the simulated to observed PK profiles after IV administration depicted in Fig.1 (A). The extent of metabolism via CYP2C19, UGT1A1, and UGT2B7 after IV administration matched the reported literature contributions and is also shown in Fig. 1 (A). Intestinal absorption and metabolism of labetalol was validated using *in vivo* data obtained after PO administration to male volunteers [14] as shown in Fig. 1 (B). The simulation results indicate that CYP2C19 metabolism is dominant for the IV route of administration, while UGT pathways are dominant after PO administration, mainly due to significant UGT2B7 expression in the gut.

(ii) Gender-related Differences in Labetalol PK

To evaluate gender-related differences, simulations were conducted and compared with the PK profiles reported for male and female subjects [4]. The default model developed in part (i) performed well for male subjects (Fig. 2(A)). For female subjects, reduction of UGT activities to 60% of those used for male subjects resulted in an improved fit to the observed profile (Fig. 2(B)). As such, higher labetalol concentrations in female relative to male subjects [4,5] may be attributed to reduced UGT activities.

(iii) Changes to Labetalol Clearance in Pregnancy

The model with UGT activities adjusted for female subjects was further assessed against the PK data for pregnant and postpartum subjects [6]. The non-pregnant female physiology matched the observed plasma profiles of the postpartum subjects well. During pregnancy, the reported UGT1A1 activity is ~3x higher than in non-pregnant subjects [7]. Incorporating this change in UGT1A1 activity into the model resulted in improved predictions of labetalol exposure in pregnant women in the 3rd trimester of pregnancy (Fig. 3).



Enzyme	Modeled [%] of IV Dose	Modeled [%] of PO Dose	Literature Reported [%]
CYP2C19	46	25	~50
UGT1A1	8	15	~15
UGT2B7	32	60	~35
Total metabolism	86	95	~95

1(C)

Figure 1: Simulated (line) and observed (squares, Ref [13 & 14]) PK profiles after IV (A) and PO (B) administration of labetalol to male volunteers, and summary of enzyme contributions to labetalol elimination after IV and PO administration (C)

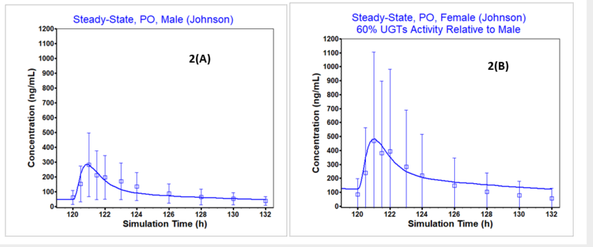


Figure 2: Simulated (line) and observed (squares, Ref [4]) PK profiles after PO administration of labetalol to male (A), and to female (B) volunteers. Note that for simulation in female subjects, both UGT1A1 and UGT2B7 activities were 60% relative to those in male subjects

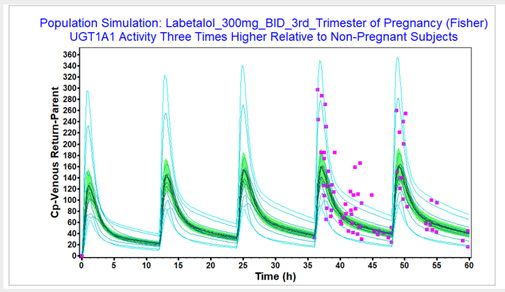


Figure 3: Population simulation of labetalol PK profile in third trimester of pregnancy, gestational age 30 weeks, compared with the observed data (pink squares) [6]

CONCLUSION(S)

The mechanistic absorption and PBPK model of labetalol was able to capture the metabolism differences between healthy male and female subjects, as well as pregnant women. Involvement of UGT1A1, UGT2B7 and CYP2C19 in labetalol metabolism results in the switch from CYP2C19 to UGT2B7 as the dominant metabolizing enzyme when going from IV to PO administration. Employing the metabolism information available in literature, our model was able to reproduce the PK data of male subjects, while reduction of UGT activities was needed to match the PK data for females. Pregnancy-related hormones were reported to increase UGT1A1-mediated labetalol metabolism *in vitro* in human hepatocytes [8]. The simulation results suggest about three-fold higher UGT1A1 activity in pregnant subjects relative to non-pregnant subjects.

In summary, these findings were consistent with: (1) higher overall UGT activity in males versus females reported in literature [9, 16]; and (2) increased labetalol clearance during pregnancy [7, 8] due to the induction of UGT1A1-mediated metabolism [16].

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