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Influence of Gestational Age and Body Weight on the Pharmacokinetics of Labetalol in Pregnancy

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Abstract

Background and Objectives—Labetalol is frequently prescribed for treatment of hypertension during pregnancy. However, the influence of pregnancy on labetalol pharmacokinetics is uncertain, with inconsistent findings reported by previous studies. This study examined the population pharmacokinetics of oral labetalol during and after pregnancy in women receiving labetalol for hypertension.

Methods—Data were collected from 57 women receiving the drug for hypertension from the 12th week of pregnancy through 12 weeks postpartum using a prospective, longitudinal design. A sparse sampling strategy guided collection of plasma samples. Samples were assayed for labetalol by high performance liquid chromatography. Estimation of population pharmacokinetic parameters and covariate effects was performed by nonlinear mixed effects modeling using NONMEM. Final population model was validated by bootstrap analysis and visual predictive check. Simulations were performed with the final model to evaluate the appropriate body weight to guide labetalol dosing.

Results—Lean body weight (LBW) and gestational age, i.e., weeks of pregnancy, were identified as significantly influencing oral clearance (CL/F) of labetalol, with CL/F ranging from 1.4-fold greater than postpartum values at 12 weeks gestational age to 1.6-fold greater at 40 weeks. Doses adjusted for LBW provide more consistent drug exposure than doses adjusted for total body weight. The apparent volumes of distribution for the central compartment and at steady-state were 1.9-fold higher during pregnancy.

Conclusions—Gestational age and LBW impact the pharmacokinetics of labetalol during pregnancy and have clinical implications for adjusting labetalol doses in these women.

1 INTRODUCTION

Pregnancy is accompanied by marked biochemical and physiological adaptations. These changes may alter drug absorption [1], distribution [2-4], metabolism [5, 6], or renal excretion [1, 7]. As changes in drug disposition tend to be dynamic, devising dosage strategies that maintain therapeutic concentrations without exposing the mother or fetus to excess drug requires an understanding not only of the type but also the profile of any alterations. These considerations are particularly important for conditions requiring continual therapy, such as diabetes mellitus, epilepsy, and hypertension [8-10].

Hypertension complicates 6% to 10% of pregnancies, and carries an increased risk of adverse outcomes for mother and infant [9, 11-13]. Approximately 3% of women are prescribed an antihypertensive during pregnancy [14]. In the absence of evidence showing that antihypertensive agents reduce the risks of pre-eclampsia or adverse perinatal effects

[15], antihypertensive treatment in pregnancy aims to balance the benefits of controlling blood pressure and preventing the consequences of severe hypertension in the mother versus risks of fetal drug exposure [9, 11, 12]. Labetalol, an antagonist of α -1 and β adrenergic receptors [16], is considered a first-line drug for treating mild to moderate hypertension in pregnancy [9, 12].

However, as with many drugs, the impact of pregnancy on labetalol disposition and dosing is uncertain. One study reported an increase in apparent labetalol clearance in pregnant women [17], while three others found no change [18-20]. Shortcomings in study designs explain these discrepancies.

We describe a longitudinal study examining the pharmacokinetics of oral labetalol during the second and third trimesters of pregnancy and first three months postpartum in women being treated for hypertension. Demographic and clinical factors influencing pregnancy related changes in labetalol disposition were assessed. A population analysis approach was selected to provide informative data, while minimizing the impact of the research on the medical care of subjects and need for additional study-related procedures.

2 METHODS

2.1 Subjects

Women at least 18 years of age and receiving labetalol for treatment of chronic or gestational hypertension were recruited. Subjects entered the study at any time between the 12th week of pregnancy and 12 weeks postpartum. No other eligibility criteria were instituted to ensure a population representative of individuals receiving labetalol for treatment of hypertension during pregnancy. Informed consent was obtained from all subjects, and the study protocol was approved by the Institutional Review Boards at the University of Illinois at Chicago, University of Wisconsin-Madison and Meriter Hospital, Madison, WI.

2.2 Study Design

A prospective, open-label, longitudinal design was implemented. Management of hypertension, including modification of labetalol doses, occurred independent of the research. Subjects continued participation until 12 weeks postpartum, labetalol treatment was stopped or they chose to withdraw from the study. Study visits coincided with subject's regularly scheduled perinatal or postnatal clinic visits, and involved the collection of routine clinical and laboratory data, drug administration records and blood samples for determining labetalol concentrations.

A sparse sampling design guided the collection of labetalol plasma concentrations. Sampling windows were constructed from the D-optimal sampling times computed for one- and two-compartment pharmacokinetic models using the ADAPT II software [21, 22]. Sampling windows were: (i) immediately before the dose, (ii) 0.5 to 1 hour after the dose, (iii) 1.5 to 3 hours after the dose, (iv) 4 to 6 hours after the dose, and (v) 6 to 10 hours after the dose. A blood sample of approximately 8 ml was obtained within one of the sampling windows at each study visit. Further, at one morning and one afternoon clinic visit during each study

period (second trimester, third trimester, and postpartum) that the subject participated in the research, two additional samples were obtained within different sampling windows. Following collection, blood samples were centrifuged, and plasma separated and stored at -20°C .

Subjects were provided with medication event monitoring system (MEMS, AARDEX Ltd., Union City, CA USA) caps for electronically recording labetalol administration times. Dosing information was also obtained by diary and subject interviews.

2.3 Analytical Methods

Labetalol plasma concentrations were determined by a high-performance liquid chromatographic procedure modified from Alton *et al* [23]. Modifications included changing the extraction solvent from ethyl acetate to methyl-tert-butyl ether and the internal standard from monomethyl-hydroxylabetalol to prazosin. The assay was linear between 10.4 ng/ml to 1020 ng/ml. For sample concentrations above the upper limit, samples were diluted with blank plasma to fall within the range of the standard curve. Mean accuracy ranged from 95.8% to 105.7% of the theoretical concentration and precision (relative standard deviation) less than 7% for back-calculated calibration standards ($n=5$ assay runs). The between run accuracy and precision for quality control samples were 103.5% and 3.7% at 844 ng/ml, 104.8% and 1.7% at 405 ng/ml, 102.8% and 7.6% at 16.2 ng/ml and 106% and 6.8% at the lower limit of quantitation.

Labetalol binding to plasma proteins was measured by equilibrium dialysis [24]. Following incubation for 24 h at room temperature in a humidified chamber, labetalol concentrations in phosphate buffer and plasma were determined by a previously reported liquid chromatography-tandem mass spectrometer procedure [25]. The fraction of labetalol bound to plasma proteins was calculated by subtracting the post-dialysis ratio of labetalol concentration in the buffer to the plasma from 1. The binding study was conducted in duplicate and average reported. Mean (standard deviation, $n=9$) recovery of labetalol following dialysis was 99.3% (3.6%), indicating minimal non-specific binding. Labetalol protein binding was independent of labetalol concentration within the range of 50 ng/ml to 400 ng/ml. Reproducibility of the unbound fraction of labetalol was 3.4% for within run replicates ($n=3$) and 6.5% for between run replicates ($n=3$).

The concentration of α -1 acid glycoprotein in plasma was measured by radial immunodiffusion (Kent Laboratories, Bellingham, WA USA). Other laboratory values were gathered from the medical record.

2.4 Pharmacokinetic analysis

Population analysis of labetalol plasma concentrations was performed using NONMEM (version 7.2, ICON Development Solutions, Ellicott City, MD USA) with the first-order conditional estimation method. Subjects having at least one quantifiable labetalol plasma concentration with documented dosing and sampling times were included. Plasma concentrations below quantifiable limits were 8% of the total samples collected and were handled by method M6 as proposed by Beal [26]. One- and two-compartment models with

first-order or mixed first-zero order absorption and lag time to absorption were evaluated as structural (base) models. Clearance and volume parameters were expressed as apparent values, i.e., ratio between the actual parameter and undetermined oral bioavailability (F). Model selection criteria included diagnostic plots, standard errors of the parameter estimates and minimum value of the objective function (OFV). The difference in OFV (Δ OFV) between hierarchical models is approximately χ^2 distributed with degrees of freedom (df) equal to the number of additional model parameters. Inter-individual variability (IIV) was modeled as an exponential error. Covariance between parameters was explored by estimating the full variance-covariance matrix. Residual variability was described as a proportional error.

Next, covariates explaining the inter-individual variability in parameter estimates were identified. Relationships between body size measures and the clearance and volume terms were examined as linear and allometric functions. Body size measures included total body weight (TBW), lean body weight (LBW) [28], body surface area [29] and body mass index [30]. The body size measure producing the greatest reduction in OFV for each parameter, with at least a minimum drop of 7.9 (χ^2 , $p < 0.005$, $df = 1$), was included in the model. Subsequently, other variables were evaluated, including age, gestational age (i.e., weeks of pregnancy; confirmed by ultrasound), time postpartum, estimated creatinine clearance [31], serum albumin, plasma α -1 acid glycoprotein, aspartate serum transaminase, total bilirubin, and labetalol dose as continuous variables. Categorical variables included pregnancy status, ethnicity, study site, type of hypertension (chronic or gestational), significant hepatic or renal impairment, and concurrent medications.

Relationships between empirical Bayesian estimates of the pharmacokinetic parameters and covariates were screened by graphical and generalized additive modeling procedures (S-Plus version 6.1, Insightful Corporation, Seattle WA USA). Covariates identified in the screening analysis were first added alone to expressions for the pharmacokinetic parameters in the base model. Variables producing a decrease in OFV > 3.84 ($p < 0.05$, χ^2 , $df = 1$) were entered in a stepwise fashion into an intermediate model and retained if their addition decreased the OFV by > 3.84 . A backward elimination step followed with covariates retained if their removal increased the OFV by > 7.9 ($p < 0.005$, χ^2 , $df = 1$). Continuous covariates were normalized (e.g., 70 kg for TBW, 50 kg for LBW, normals for lab values) and modeled as linear or power functions of the parameter. Categorical covariates were input as indicator variables with a value of 1 if the trait was present and 0 otherwise.

2.5 Model Evaluation

The validity of the final population pharmacokinetic model was evaluated by bootstrap analysis using Wings for NONMEM (http://wfn_sourceforge.net/) [32] to construct 1000 datasets. Each dataset was fit to the final population model, and median and 2.5th and 97.5th percentiles determined for the fixed and random effect parameters. The performance of the population model was also evaluated by visual predictive check [33]. Briefly, 250 datasets were simulated for an oral labetalol dosage regimen of 300 mg every 12 hours for 6 doses. The simulations employed covariate values from the dataset and the final population estimates for the fixed and random effect parameters. The median and 80% prediction

intervals for the simulated labetalol plasma concentrations partitioned by pregnancy status were plotted against the observed values. To adjust for the varying labetalol dosage regimens, observed values were normalized to reflect the simulated dose. Reports support the assumption of a linear relationship between labetalol dose and plasma concentration [34].

2.6 Statistical analysis

The influence of modifying labetalol dose by either TBW or LBW on systemic exposure was evaluated by simulation. Employing the final population model, steady-state labetalol plasma concentrations over a 12 hour dosage interval were simulated for the following oral regimens: 300mg every 12 hours, 300mg per 50 kg LBW every 12 hours and 300 mg per 70 kg TBW every 12 hours. The simulation dataset included 65 subjects to match the distributions of TBW and BMI in the study population. Covariate values, including gestational age and pregnancy status, were reproduced in the simulation dataset. At each dose, 500 replicates of the dataset were simulated. The area under the labetalol plasma concentration-time curve over the 12 hour steady-state dosage interval (AUC) was calculated for each simulated profile. The findings were examined by constructing box plots of the AUC categorized by TBW (< 70 , $> 70 - 100$, $> 100 - 130$ and > 130 kg) for each group.

The fraction of labetalol bound to plasma proteins was compared among the second trimester, third trimester and postpartum periods with a one-way analysis of variance for repeated measures. A $p < 0.05$ was considered statistically significant.

3 RESULTS

3.1 Patients and Data Collection

Sixty-four pregnant or post-partum women receiving labetalol for treatment of hypertension were enrolled. Seven patients were excluded from the pharmacokinetic dataset as a result of incomplete drug administration records or lack of evaluable labetalol plasma concentrations. Accordingly, the population pharmacokinetic database consisted of 57 women contributing 649 plasma concentrations. Among the women included in the analysis, 53 began participation during the second or third trimesters and four postpartum. Over half the women ($n=30$) contributed pharmacokinetic data during the second or third trimester and postpartum, with 17 women providing plasma concentrations within all 3 periods.

The demographic and clinical characteristics of the individuals in the pharmacokinetic dataset are summarized in Table 1. Subject characteristics were similar across the three study periods except for expected pregnancy-related changes in body weight, plasma α -1 acid glycoprotein, serum albumin, and creatinine clearance. Despite lower concentrations of α -1 acid glycoprotein and albumin during pregnancy, no significant differences in the fraction of labetalol bound to plasma proteins were observed across the 3 periods in the 9 women included in the protein binding evaluation, with a mean (SD) percentage bound of 62% (16%) in the second trimester, 59% (17%) in the third trimester, and 61% (18%) postpartum.

3.2 Pharmacokinetic Analysis

A two-compartment model with first-order input and elimination most aptly described the disposition of labetalol. Compared to a one-compartment model, the two-compartment model significantly decreased the OFV by 406 ($p < 0.001$, χ^2 , $df=2$). The lack of bias and symmetrical distribution around the lines of identity in Figures 1a and 1b and zero intercept lines in Figures 1c and 1d further support selection of the two-compartment model. Parameters in the base model included absorption rate constant (k_a), oral clearance (CL/F), apparent intercompartmental clearance from the central to peripheral compartment (Q/F), apparent volume of distribution of the central compartment (V_c/F) and apparent steady-state volume of distribution (V_{ss}/F). Owing to an inability to estimate the absorption rate constant (k_a) at a reasonable level of precision (i.e., relative standard error $< 40\%$), k_a was fixed at 1 h^{-1} [27]. Sensitivity analysis for the fixed value of k_a showed only a small change, $< 10\%$, in the estimates of other parameters as k_a was varied between 0.4 h^{-1} and 6 h^{-1} .

The use of a full variance-covariance matrix improved the model fit compared to a diagonal matrix. A term for IIV of Q/F was not included as its addition caused the model to terminate abnormally during the covariance step, suggesting the model was overparameterized.

3.3 Covariate analysis

Among the body size descriptors evaluated as covariates of labetalol CL/F, TBW (OFV = -13 , $p < 0.001$, χ^2 , $df=1$), LBW (OFV = -15 , $p < 0.001$, χ^2 , $df=1$) and body surface area (OFV = -10 , $p < 0.005$, χ^2 , $df=1$) produced significant decreases in the OFV. However, LBW was the only descriptor retained in the final model as a result of the greatest reduction in OFV and failure of TBW or body surface area to further improve the fitting following their addition to the covariate model containing LBW. The form of the relationship was also different among the body size indicators. A linear expression best described the relationship between LBW and CL/F, while a power function best described the relationships of TBW, exponent of 0.4, and body surface area, exponent of 0.6, with CL/F. For V_c/F and V_{ss}/F , TBW as a linear function produced the greatest reduction in OFV (OFV > -7.8 , $p < 0.005$, χ^2 , $df=1$ for both). Expression of the relationships between LBW and CL/F and TBW and V_c/F and V_{ss}/F as a proportionality factor rather than linear function provided a comparable fit and more parsimonious model.

The screening and univariate analysis identified: (1). α -1 acid glycoprotein concentration, gestational age, pregnancy status, and ethnicity as potential covariates for LBW-adjusted CL/F and (2). α -1 acid glycoprotein concentration and pregnancy status as potential covariates for TBW-adjusted V_c/F and V_{ss}/F . Following the forward inclusion and backward elimination processes, the model retained gestational age (OFV = -145 , $p < 0.001$, χ^2 , $df=1$) as the only covariate of LBW-adjusted CL/F and pregnancy status as a covariate for TBW-adjusted V_c/F (OFV = -8.4 , $p < 0.005$, χ^2 , $df=1$) and V_{ss}/F (OFV = -7.9 , $p < 0.005$, χ^2 , $df=1$). The covariates modestly reduced the IIV from 45% to 38% for CL/F, 90% to 84% for V_c/F and 37% to 33% for V_{ss}/F . Other covariates did not produce a statistically significant change in OFV, and were not included in the final model. Unlike pregnancy, postpartum CL/F did not vary with time over the 12-week postpartum period.

Given that the coefficients describing the effect of pregnancy on V_c/F and V_{ss}/F were nearly identical, use of a single coefficient for expressing the influence of pregnancy on both parameters was evaluated. Substitution of a single coefficient produced no deterioration in fit, with the OFV declining by 12 even with the loss of a parameter. This more parsimonious approach was adopted in the final model.

Parameter estimates and covariate expressions for the final model are presented in Table 2. The typical value for labetalol CL/F in a 50 kg LBW non-pregnant woman was 188 L/h. Pregnancy increased CL/F of labetalol by approximately 70 L/h at 12 weeks gestation and 108 L/h at 40 weeks gestation. For the labetalol V_c/F or V_{ss}/F , values were 1.9-fold higher during pregnancy regardless of gestational age.

Figure 2A plots median individual Bayesian estimates for labetalol CL/F versus gestational age during the second trimester, third trimester and postpartum for 30 women who had evaluable labetalol plasma concentrations during and after pregnancy. While higher CL/F during pregnancy and trend for CL/F to increase with increasing gestational age is evident, equally notable is the nearly 6-fold IIV. This wide variability is similar during and after pregnancy. A marked reduction in variability occurred after each woman's CL/F during pregnancy was divided by their postpartum value (Figure 2B), corroborating a similar degree of IIV during and after pregnancy.

3.4 Model validation

The bootstrapped medians for fixed and random effect parameters (Table 2) were within 10% of the parameter estimates from the final model, supporting the stability of the population model and accuracy of the parameter estimates. The 2.5th – 97.5th percentiles from the bootstrap and relative standard errors from the model fitting indicate that the fixed and random effect parameters were estimated with reasonable precision. The covariances among CL/F, V_c/F and V_{ss}/F are an exception as their bootstrap confidence intervals overlapped zero. Visual predictive checks indicate acceptable predictive performance (Figures 3A-C).

3.5 Influence of adjusting dose for total or lean body weight on labetalol exposure

Across all weight groups, the simulations at 300 mg, 300 mg per 50 kg LBW (LBW-adjusted) and 300 mg per 70 kg TBW (TBW-adjusted) every 12 hours produced similar labetalol steady-state AUCs (Figure 4A). However, when the AUCs for each regimen are grouped by TBW, marked differences are observed among the three doses (Figures 4B-4D). For example, as TBW increases from 70 to > 130 kg, median AUC with administration of the 300 mg (unadjusted for body size) dose decreases by approximately 36% (Figure 4B) and with administration of the 300 mg TBW-adjusted dose increases by approximately 37% (Figure 4D). Conversely, for LBW-adjusted dose, median labetalol AUC remains identical across groups (Figure 4C). These observations were independent of pregnancy status.

4 DISCUSSION

Pregnancy significantly influenced the disposition of labetalol. The CL/F increased with increasing gestational age from 1.4-fold greater than postpartum values at 12 weeks

gestational age to 1.6-fold greater at 40 weeks, corresponding to a proportional decrease in dose-normalized AUC. The V_d/F and V_{ss}/F were also larger during pregnancy.

Our findings agree with the lower than expected labetalol plasma concentrations observed during the third trimester of pregnancy by Nylund and colleagues [17]. Conversely, three studies reported no changes in labetalol pharmacokinetics in pregnancy [18-20]. These studies, however, are hampered by design flaws, including: 1). administration by Rubin et al [19] of intravenous labetalol, which is insensitive to pregnancy-related alterations in protein binding or hepatic enzyme activity compared to the oral route, 2). low statistical power due to small subject numbers, 10 or fewer, and large IIV for CL/F [18-20], and 3). reliance on historical rather than prospective longitudinal data for comparison [18, 20, 35]. In contrast to their conclusion of no pregnancy-related changes, labetalol CL/F found by Saotome *et al* [20] in the third trimester approached values observed during pregnancy in our study and were substantially higher than those reported in non-pregnant women [36].

The postpartum labetalol CL/F of 188 l/h in our study is similar to the mean of 165 l/h reported in non-pregnant women [36]. Another finding consistent with reports of labetalol pharmacokinetics in men and non-pregnant women is the high degree of IIV for CL/F [16, 27, 36, 37]. The similar degree of IIV during and after pregnancy (Figures 2A and 2B) suggests that the IIV observed in this study is not a pregnancy-specific effect but reflects the inherent pharmacokinetic variability of labetalol.

Labetalol is a high extraction ratio, hepatically eliminated drug [16, 27, 37]. Its systemic availability following oral administration is low and highly variable. Glucuronidation by uridine diphosphate-glucuronosyltransferases (UGT) 1A1 and 2B7 represents the major pathways of hepatic metabolism [25, 38]. An increase in CL/F of labetalol may reflect a reduction in absorption from the gastrointestinal tract, decrease in plasma protein binding or increase in hepatic intrinsic clearance [39]. Reduced gastrointestinal bioavailability appears unlikely due to complete absorption of labetalol from the gastrointestinal tract in other populations and lack of effect of pregnancy on bioavailability of other drugs [1, 38]. Labetalol is approximately 50% - 60% bound to plasma proteins in men and non-pregnant women [38, 40]. Although the lower serum albumin and plasma α -1 acid glycoprotein concentrations during pregnancy suggest the potential for a decrease in plasma protein binding, the fraction of labetalol bound to plasma proteins was not significantly different between the second or third trimester and postpartum. The binding of labetalol to lipoproteins and globulins, representing approximately 40% of bound drug in adults, as well as albumin and α -1 acid glycoprotein explain the unexpected observations [40]. In contrast to albumin and α -1 acid glycoprotein, concentrations of lipoproteins and globulins rise during pregnancy [2, 3, 41].

Thus, the higher CL/F of labetalol in pregnant women most likely represents an increase in hepatic intrinsic clearance and enhanced first pass metabolism. This mechanism is supported by an *in vitro* study from our group [25]. Concentrations of progesterone comparable to those attainable during pregnancy induced UGT 1A1 activity in transfected HepG2 cells through a pregnane X receptor mediated process. Activity of UGT 2B7 was not affected by either estrogen or progesterone. This mechanism, and subsequent decrease in F, is also

probably responsible for the larger V_c/F and V_{ss}/F in pregnancy, although an alteration in tissue binding cannot be ruled out.

Among body size indices evaluated in the covariate analysis, a linear relationship involving LBW best explained the IIV in CL/F and TBW best explained the IIV for the volume terms. When expressed as a power function, TBW was also a significant covariate of CL/F , albeit producing a lower reduction in OFV. These findings mirror those reported with other drugs during pregnancy [42, 43] and in men and non-pregnant women [44-46].

These findings are relevant for individualizing doses. Labetalol is typically started at a dose of 50 mg/d to 200 mg/d, with doses subsequently titrated to the desired antihypertensive response. When individualizing initial and incremental doses, the clinician considers factors, such as age, concurrent drugs or illnesses, and body weight. If the clinician relies on TBW to guide this process, the nonlinear relationship between TBW and CL/F must be kept in mind and any TBW-related adjustment in dose should be less than proportional to the difference in TBW to ensure similar drug exposure. For example, the allometric model relating TBW to CL/F in the current study has an exponent of 0.4. Based on this relationship, a 140-kg woman requires only a 1.3-fold higher dose than a 70-kg woman of similar pregnancy status to achieve the same level of systemic labetalol exposure; not the two-fold higher dose that the proportional difference in TBW would predict. The potential for confusion and error in clinically applying this nonlinear relationship between TBW and CL/F supports either using LBW, where dose is adjusted proportional to the difference in LBW, or ignoring body weight, a less optimal option due to the potential for under dosing obese women.

A limitation of our study was the small number of subjects in whom protein binding was measured. Nevertheless, the plasma protein binding studies concurred with theoretical expectations. Also, as the stereoisomers of labetalol differ in their pharmacological properties [27, 36, 47], analysis of stereoisomers rather than racemate may have provided greater insight into the relevance of the pharmacokinetic changes. However, agreement in the relative proportions of the 4 stereoisomers between pregnant [35] and non-pregnant women [36] suggests a limited effect of pregnancy on the stereoselective metabolism of labetalol.

5 CONCLUSION

The influence of gestational age and LBW on the pharmacokinetics of labetalol has clinical implications for adjusting labetalol doses during pregnancy. First, selection and adjustment of labetalol doses should be guided by LBW, or without regard to body weight, rather than TBW to reduce the likelihood of excessive maternal and fetal drug exposure. Second, the increase in CL/F with increasing gestational age indicates the potential for dose requirements to change as pregnancy progresses independent of a worsening in the underlying pathophysiology. Future studies evaluating labetalol pharmacodynamics in pregnancy are needed to more completely understand the implications of pregnancy on labetalol use.

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Figure 1.

Goodness of fit plots for labetalol plasma concentrations fitted to a two-compartment model with first order absorption and elimination. (a) Observed versus model-predicted labetalol plasma concentrations. (b) Observed versus individual-predicted labetalol plasma concentrations. (c) Individual weighted residuals versus time after dose. (d) Conditional weighted residuals versus time after dose. The solid lines in (a) and (a) represent the line of identity and in (c) and (d) represent the zero-intercept line. The dotted lines are the linear regression line.

Figure 2.

Individual Bayesian estimates for labetalol oral clearance (CL/F) were obtained from 30 women with evaluable labetalol plasma concentrations during and after pregnancy. (a) The median CL/F estimate for each woman during the second and/or third trimester and postpartum are plotted versus gestational age (or postpartum). The lines connect the estimates for each woman. The heavy set line represents the values predicted by the final population model. (b) Labetalol CL/F from the second and third trimester in Figure 2A divided by the same individual's postpartum CL/F plotted versus gestational age.

Figure 3.

Visual predictive check plots showing the 10th (dashed line), 50th (solid line) and 90th (dashed line) percentile labetalol plasma concentrations (log scale) versus time simulated from the final covariate model for an oral dosage regimen of 300 mg every 12 hours for 6 doses for women in the (a) second trimester, (b) third trimester and (c) postpartum. Only the final 3 doses are portrayed on the graph. The close circles represent observed concentrations normalized to reflect the simulated dose.

Figure 4.

Influence of scaling labetalol doses by lean body weight, total body weight or no body weight on labetalol exposure, as represented by the steady-state area under the plasma concentration-time curve (AUC). AUCs were determined by simulating 500 replicates of the final population model for each of the following doses: 300 mg every 12 hours, 300 mg per 50 kg lean body weight every 12 hours (LBW-adjusted dose) and 300 mg per 70 kg total body weight every 12 hours (TBW-adjusted dose). (a) Box plot of simulated labetalol AUCs for each of the 3 doses. (b) Box plot of simulated labetalol AUCs following 300 mg every 12 hours grouped by the patients' TBW: ≤ 70 kg, >70-100 kg, > 100-130 kg or > 130 kg. (c) Box plot of simulated labetalol AUCs following 300 mg per 50 kg lean body weight every 12 hours (LBW-adjusted dose) grouped by the patients' TBW: ≤ 70 kg, >70-100 kg, > 100-130 kg or > 130 kg. (d) Box plot of simulated labetalol AUCs following 300 mg per 70 kg total body weight every 12 hours (TBW-adjusted dose) grouped by TBW: ≤ 70 kg, >70-100 kg, > 100-130 kg or > 130 kg. The limits of the box represent the 25th to 75th percentile of the distribution, the solid line in the box is the median value, the whiskers represent the 10th and 90th percentiles of the distribution and the symbols the 5th and 95th percentiles of the distribution.

Table 1

Characteristics of Subjects in Pharmacokinetic Dataset

Parameter	Overall	2 nd Trimester	3 rd Trimester	Postpartum
No. of subjects	57	29	47	34
Age (y)	30(18-41)	31 (18-41)	30 (18-38)	30 (18-40)
Total Body Weight (kg)	90 (49-161) ^a	99 (51-160)	101 (54-162)	102 (59-155)
Lean Body Weight (kg)	50 (32-68) ^a	52 (33-71)	53 (37-72)	52 (37-67)
BMI (kg/m ²)	32 (21-62) ^a	36 (22-62)	36 (22-61)	36 (23-60)
Gestational Age (wk)	20 (11-39) ^b	---	---	---
Plasma Concentration Samples per Subject	11 (1-33)	---	---	---
Labetalol Plasma Concentrations (ng/ml)	10.0-1381	10.2-585	10.0-1231	10.1-1381
Labetalol Dose (mg/d)	50-2400	50-2000	50-2200	25-2400
Race (self-reported)				
Black	34	19	31	21
White	15	6	11	9
Hispanic	5	4	4	2
Asian	3	2	2	2
Type of Hypertension				
Chronic	37	21	30	22
Gestational	20	10	18	12
Concomitant medications ^c				
At least 1 other drug	55	---	---	---
Prenatal vitamins	48	---	---	---
Insulin	11	---	---	---
Methyldopa	9	---	---	---
Ferrous Sulfate	7	---	---	---
Acetaminophen	5	---	---	---
Albuterol	5	---	---	---
Other Illnesses ^c				
Asthma	7	---	---	---
Diabetes mellitus	13	---	---	---
Preeclampsia (current pregnancy)	11			
AAG (mg/dL)	72 (43-158) ^b	69 (44-98)	58 (30-102)	120 (54-224)
Albumin (g/dL)	3.0 (2.0-4.0) ^b	3.1 (2-4)	2.9 (2.0-4.0)	3.4 (2.9-4.0)
AST (mU/mL)	20 (11-133) ^b	20 (12-116)	20 (11-113)	20 (14-31)

Parameter	Overall	2 nd Trimester	3 rd Trimester	Postpartum
Total Bilirubin (mg/dL)	0.6 (0.1-2) ^a	0.6 (0.2-2.0)	0.6 (0.1-2)	0.6 (0.5-0.9)
CL _{CR} (mL/min)	115 (17-200) ^b	123 (17-200)	123 (17-184)	105 (20-154)

Values are expressed as median (range), range or n

Abbreviations: AAG – α -1 acid glycoprotein, AST - aspartate serum transaminase, BMI – body mass index, CL_{CR} – creatinine clearance.

^a pre-pregnancy,

^b at time of study entry,

^c present in at least 5 patients.

Table 2

Population Pharmacokinetic Parameters and Bootstrap Results from the Final Model

Parameter	Final Model		Bootstrap (n=1000)	
	Estimate (Shrinkage,)	RSE (%)	Median	2.5 th - 97.5 th Percentiles
k_a (h ⁻¹)	1	---	---	---
$CL/F = CL/F_{non-pregnant} + CL/F_{pregnancy}$				
$CL/F_{non-pregnant}$ (L/h/50 kg LBW)	188	6	190	161 - 235
$CL/F_{pregnancy} = \theta_{CL,GA} \times \left(1 + \frac{GA}{10}\right)$ or 0 if not pregnant				
$\theta_{CL,GA}$ (L/h/50 kg LBW)	54	9	52	35 - 72
Q/F (L/h)	422	8	420	323 - 519
V_c/F [or V_{ss}/F] = $V_c/F_{non-pregnant}$ [or $V_{ss}/F_{non-pregnant}$] $\times$ (1 + $\theta_{V, pregnancy}$ [or 0 if not pregnant])				
$V_c/F_{non-pregnant}$ (L/70 kg TBW)	197	17	189	110 - 316
$V_{ss}/F_{non-pregnant}$ (L/70 kg TBW)	691	12	687	617 - 1080
$\theta_{V, pregnancy}$ (L/70 kg TBW) [$\theta_{V, pregnancy} = 0$ if not pregnant]	0.9	23	0.89	0.3 - 1.6
Inter-Individual Variability (%) [Shrinkage, %]				
CL/F	38 [9]	22	38	30 - 45
V_c/F	84 [32]	33	89	62 - 124
V_{ss}/F	40 [27]	39	41	25 - 59
Covariance (%)				
CL/F, V_c/F	42	---	42	-3 - 72
CL/F, V_{ss}/F	55	---	51	-2 - 85
V_c/F , V_{ss}/F	16	---	12	-12 - 74
Residual error (%) [Shrinkage, %]	36 [8]	6	36	31 - 42

Abbreviations: RSE: relative standard error, k_a : absorption rate constant, CL/F: oral clearance, $CL/F_{non-pregnant}$: oral clearance in non-pregnant women, $CL/F_{pregnancy}$: oral clearance in pregnancy, $\theta_{CL,GA}$: coefficient describing effect of gestational age in weeks on CL/F pregnancy, GA: gestational age, LBW: lean body weight, Q/F: apparent intercompartmental clearance from the central to peripheral compartment, V_c/F : apparent volume of the central compartment, V_{ss}/F : apparent steady-state volume of distribution, $V_c/F_{non-pregnant}$ women: apparent volume of the

central compartment in non-pregnant women, $V_{ss}/F_{non-pregnant}$ women: apparent steady-state volume of distribution in non-pregnant women, TBW: total body weight, $\theta_{V,pregnancy}$: proportionality factor for effect of pregnancy on V_c/F and V_{ss}/F .