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ORIGINAL ARTICLE

Gestational changes in buprenorphine exposure: A physiologically-based pharmacokinetic analysis

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Keywords buprenorphine, opioid dependence, PBPK, pharmacokinetics, pregnancy

AIMS

Buprenorphine (BUP) is approved by the US Food and Drug Administration for the treatment of opioid addiction. The current dosing regimen of BUP in pregnant women is based on recommendations designed for nonpregnant adults. However, physiological changes during pregnancy may alter BUP exposure and efficacy. The objectives of this study were to develop a physiologically-based pharmacokinetic (PBPK) model for BUP in pregnant women, to predict changes in BUP exposure at different stages of pregnancy, and to demonstrate the utility of PBPK modelling in optimizing BUP pharmacotherapy during pregnancy.

METHODS

A full PBPK model for BUP was initially built and validated in healthy subjects. A fetoplacental compartment was included as a combined compartment in this model to simulate pregnancy induced anatomical and physiological changes. Further, gestational changes in physiological parameters were incorporated in this model. The PBPK model predictions of BUP exposure in pregnancy and during the *postpartum* period were compared to published data from a prospective clinical study.

RESULTS

The predicted BUP plasma concentration–time profiles in the virtual pregnant populations are consistent with the observed data in the 2nd and 3rd trimesters, and the *postpartum* period. The differences in the predicted means of dose normalized area under the plasma drug concentration–time curve up to 12 h, average concentration and maximum concentration were within ±25% of the corresponding observed means with the exception of average concentration in the 3rd trimester (–26.3%).

CONCLUSION

PBPK model-based simulation may be a useful tool to optimize BUP pharmacotherapy during pregnancy, obviating the need to perform pharmacokinetic studies in each trimester and the *postpartum* period that normally require intensive blood sampling.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Maternal opioid use is associated with increased obstetrical complications. Buprenorphine (BUP) is approved by the US Food and Drug Administration for the treatment of opioid dependence.
- The current dosing regimen of BUP in pregnancy is based on recommendations designed for nonpregnant individuals.
- Pregnancy induces many physiological changes, which may alter BUP exposure and dosing requirement in pregnant women.

WHAT THIS STUDY ADDS

- A physiologically-based pharmacokinetic model for sublingual BUP in pregnancy was developed, and validated using data obtained from a clinical study during pregnancy and during the *postpartum* period.
- The model predicted decreased BUP exposure in all three trimesters, compared to the *postpartum* period, and the predictions were consistent with the published observations in 2nd and 3rd trimester in a small number of subjects.
- Model based simulation can be useful to optimize pharmacotherapy of BUP during pregnancy, since limited data exists and pharmacokinetic studies are difficult to perform in this population.

Introduction

Drug addiction has become a nationwide health crisis in the USA [1–3]. From 2013 to 2014, the death rate from an overdose of opioids increased by 14% [4]. Currently, death due to drug overdose has surpassed that of motor vehicle accidents as the leading cause of unintentional deaths in the USA [4]. Concurrently, the rate of opiate use in pregnant women has increased nearly 5-fold between 2000 and 2009 [5]. Maternal opioid use is associated with an increase in obstetrical complications, such as maternal death, cardiac arrest, intrauterine growth restriction and placental abruption [6]. *Antepartum* use of opioids commonly results in neonatal abstinence syndrome and is associated with an increased risk of birth defects, stillbirth, and preterm labour [7, 8]. **Buprenorphine** (BUP) is approved by US Food and Drug Administration for treatment of opioid addiction, but it is not approved for use in pregnancy. The efficacy of BUP in suppressing symptoms of withdrawal appears to be comparable to **methadone** [9–11]; but treatment with BUP is more convenient to patients and BUP exposed neonates appear to have less severe and less frequent neonatal abstinence syndrome [12–14].

The current dosing of BUP in pregnant women is based on recommendations designed for nonpregnant subjects since limited information is available to optimize BUP dosing in pregnant women. Pregnancy induces many physiological changes including the development of the fetal–placental compartment, an increase in renal filtration, body fluid volume and hepatic portal blood flow, as well as changes in the expression and activity of drug metabolizing enzymes and drug transporters [15–17]. These pregnancy-induced changes can impact absorption, distribution, metabolism and elimination of drugs which may ultimately alter efficacy and safety of medications used in pregnant women.

Response to BUP appears to be related to plasma concentration of BUP. Greenwald *et al*. reported that a plasma BUP concentration of 1 ng ml^{-1}, is required for prevention of withdrawal symptoms in opioid exposed subjects. This concentration is associated with 50–60% occupancy of the **μ-opioid receptors** in the brain [18]. We have demonstrated in a small cohort of pregnant women that plasma concentrations of BUP and the corresponding BUP exposure is significantly reduced during pregnancy compared to the *postpartum* state [19]. We have suggested that more frequent dosing of buprenorphine will reduce the time that treated women are likely to be subtherapeutic during pregnancy [19, 20]. Our observations may at least in part explain the report of Jones *et al*. [21], who in a large clinical trial reported higher study withdrawal rates in subjects assigned to BUP compared with methadone. This maybe due to 71% dropout rate attributed to dissatisfaction of the subjects with the dosage of BUP used in that study [21].

A better understanding of BUP exposure in pregnancy is required to optimize treatment outcomes in pregnant women with opiate addiction**.** In our published pilot study, we did not enrol subjects prior to 20 weeks and therefore we were not able to evaluate the changes in BUP pharmacokinetics during the first half of pregnancy [19].

A variety of physiologically-based pharmacokinetic (PBPK) modelling approaches have been used in drug development. PBPK modelling is a useful tool for predicting pharmacokinetic changes of a drug during pregnancy. Beside the differences in anatomy and physiology, the PBPK model can incorporate known pregnancy-related alterations in the activities of CYPs, UGTs and drug transporters, that can contribute to altered drug metabolism and clearance [22–27]. The objectives of this study were to develop a PBPK model for BUP in pregnant women, in order to predict changes in BUP exposure at different stages of pregnancy, and to demonstrate the utility of PBPK modelling in optimizing BUP pharmacotherapy in this understudied population.

Methods

PBPK modelling and simulations for BUP were conducted using SimCyp population-based simulator v15.1 (SimCyp limited, Sheffield, UK). WinNonlin software (Phoenix WinNonlin: version 6.4, Pharsight Corp, Mountainview, CA, USA) was used to simulate steady-state exposure of BUP after administration of the sublingual (SL) formulation. A systematic literature search to identify physiological changes throughout pregnancy, and to identify published clinical trials of BUP was conducted using the Medline database from the National Library Medicine through the PubMed interface.

We used the search terms "buprenorphine", or "subutex", plus "opioid", "pharmacokinetic", "concentration" and "ng/mL". The inclusion criteria used were clinical studies that reported PK data on intravenous (IV), and/or SL BUP. We excluded studies that evaluated the PK of BUP in solution or in film formulations or after continuous iv infusion; were performed in patients with severe disease (compromised liver or renal function); were published prior to BUP availability for sublingual administration (1990 or earlier); utilized a non-specific radioimmunoassay method to quantify BUP concentrations; or used a washout period between the IV and SL study of <5 half-lives of BUP. The bibliographies of the selected articles were also reviewed to identify additional relevant information. For PBPK model building and model validation, we used published data reporting the mean plasma concentrations of BUP following IV or SL administration. These mean plasma concentrations of BUP were digitized using GetData Graph Digitizer V.2.26 from BUP concentration–time profiles of reported in clinical studies.

A PBPK model for BUP in nonpregnant subjects

The details of building and validating the IV and SL BUP PBPK models in healthy nonpregnant opioid nondependent or dependent subjects have been previously published by our group [28]. In that study, we outlined how a mechanistic BUP PBPK model was established by employing the physiochemical properties of BUP including tissue to plasma partition coefficient (K_p), the first-order absorption (for SL administration), and the kinetic parameters for metabolism and elimination (CYPs and UGTs). The tissue specific K_p values of BUP for the full-PBPK model were estimated using the corrected Poulin and Theil method [29–31]. The intersystem extrapolation factors based *in vitro–in vivo* extrapolation methods were used to extrapolate *in vitro* enzyme kinetic data. Published data on BUP plasma concentration *vs*. time profile after IV and SL administration in opioid nondependent and dependent patients were employed to build the models. Sensitivity analysis was performed for parameters (plasma unbound drug fraction (f_u), and all tissue specific K_p values) with no or poor initial estimates. The parameters that were not sensitive were defaulted to the initial prediction estimates; when the parameters were sensitive to the analysis, a systematic optimization on a one-by-one basis using the built-in parameter estimation module was performed. After individual optimization, all the sensitive parameters were re-optimized together to get the best fit with the observed data. The SL BUP model was built by adapting the IV PBPK model and adding a BUP absorption component. Similar parameter optimization methods were used to optimize absorption characteristics of BUP after SL administration. Fourteen model naïve BUP-PK datasets were used for inter- and intrastudy validations [28]. Introducing a T_{lag} parameter (lag time between dose administration and the appearance of BUP in the systemic circulation) better explained the SL BUP PBPK model in nonpregnant subjects. The parameter estimation module was used to fit the T_{lag} value and this fit was verified by visual predictive check. It reduced the prediction error, when comparing the observed and predicted T_{max}, C_{max} and area under the plasma drug concentration–time curve (AUC). The physicochemical properties and PK parameters that were used to develop a BUP profile; the key PK parameters of BUP in the nonpregnant subjects are provided in the appendix (Appendix Tables A1 and A2).

A PBPK model for BUP in pregnant subjects

The perfusion limited BUP SL full PBPK model developed in healthy nonpregnant subjects was modified to create the BUP PBPK model in pregnant women [28]. The fetal–placental compartment characteristics in the custom virtual pregnancy population were adapted from the default SimCyp pregnancy population file. As with other compartments, the fetal–placental compartment is also a perfusion-limited compartment and its K_p value was estimated using the corrected Poulin and Theil method [29–31] (Table 1). The fetal–placental compartment combines the

Table 1

Distribution parameters for buprenorphine physiologically-based pharmacokinetic (PBPK) model in pregnant women

Parameter	Value
Model	Full PBPK
V_{ss} (l kg^{-1}): predicted[a]	2.48
V_{ss} (l kg^{-1}): observed[b]	2.77
Tissue partition coefficients (K_p)	
Adipose	0.0044
Bone/additional[c]	35
Brain	3.41
Gut	2.69
Fetoplacenta	1.31
Heart	0.83
Kidney	1.29
Liver	2.13
Lung	0.29
Pancreas	2.20
Muscle	1.31
Skin	1.60
Spleen	1.31
K_p scalar[d]	0.225

V_{ss}, volume of distribution at steady state
[a]Bullingham *et al.* [35];
[b]V_{ss} predicted and K_p values for all tissue were predicted by corrected Poulin and Theil method [37–39];
[c]Bone/Additional compartment K_p value was optimized using the Simcyp parameter estimation module, Nelder–Mead method was used for the minimization. The predicted K_p value, 3.73, by Poulin and Theil method was used as the initial value, and (0.001, 100) used as the boundaries;
[d]K_p scalar was optimized using the Simcyp parameter estimation module, Nelder–Mead method was used for the minimization. The default K_p scalar, 1, was used as the initial value, and (0.01, 100) used as the boundaries.

Table 2

Summary of gestational age associated physiological parameters incorporated into SimCyp healthy population

	Nonpregnant Female	1st trimester (≤12 gestation weeks)	2nd trimester (13–28 gestation weeks)	3rd trimester (≥ 29 gestation weeks)
Physiological and metabolic change				
Cardiac output [31]	100%	Increased 35%	Increased 40%	Increased 50%
Plasma volume [31]	100%	Increased 12.5%	Increased 32.5%	Increased 50%
Red cell volume [31]	100%	Remain same	Remain same	Increased 30%
Haematocrit [32]	100%	Decreased 3%	Decreased 4%	Decreased 5%
Albumin [32]	100%	Decrease 27%	Decrease 27%	Decrease 27%
Activity of CYP3A4 [33]	100%	Increased 35%	Increased 35%	Increased 38%
Parameter used in model				
Cardiac output scalar	1	1.35	1.4	1.5
Plasma volume scalar	1	1.125	1.325	1.50
Red blood cell volume scalar	1	1	1	1.3
Haematocrit (%)	38	35	34	33
Albumin (g l^{-1})	49	36	36	36
CYP3A4 (pmol mg $protein^{-1}$)	137	185	185	189

fetus, placenta, amniotic fluid, uterus and umbilical cord. The fetal–placental compartment is assumed to have the same characteristics as muscle tissue (SimCyp assumption). Given the lack of reports on BUP concentrations in the fetus or placenta it was not possible to validate model predictions in the fetal–placental compartment at this point. In this BUP PBPK model in pregnant women, all of the drug components including physiochemical properties of BUP, K_p values and initial enzyme kinetics that were used were the same as in the BUP PBPK model developed in healthy nonpregnant subjects. The changes applied to the pregnancy BUP PBPK model were selected based on the changes that were expected to impact BUP PK. These include changes in hepatic blood flow, plasma protein level, drug metabolizing enzyme activities, and the partition between plasma and red blood cells (Table 2) [32–34].

BUP is primarily metabolized by N-dealkylation [35]. This N-dealkylation of BUP is primarily mediated by **CYP3A4** in the liver [36, 37]. Although **CYP2C8**, **UGT1A1**, UGT1A3 and UG2B7 are also involved in the metabolism of BUP, their contributions are relatively minor. A quantitative mass–balance diagram describing the absorption, distribution, metabolism and excretion of BUP after SL and IV administration as implemented in the PBPK model is shown in Figure 1. The mass balance study following IV dosing of BUP showed that a total of 69% and 30% of the radioactivity is recovered in the faeces and urine, respectively [38]. The unconjugated BUP and norbuprenorphine in faeces probably comes from the hydrolysis of the conjugates of BUP and norbuprenorphine via biliary secretion [38]. As BUP is primarily eliminated by the liver, the changes in renal function during pregnancy should have minor impact on BUP elimination. This assumption was affirmed by performing a sensitivity analysis (Figure 2). Identical BUP concentration–time profiles were observed in all trimesters in the virtual pregnant women with and without an increase (50%) in GFR [32].

Comparison during pregnancy and the postpartum (nonpregnant) period

BUP exposure during the *postpartum* period was simulated in virtual female healthy subjects using SimCyp population simulator. The simulated BUP exposure during 2nd and 3rd trimesters and the *postpartum* period were validated using the observed plasma concentrations of BUP from a prospective clinical BUP PK study in pregnant women during pregnancy (2nd and 3rd trimesters) and the *postpartum* state conducted by our group [19]. In this clinical study, pregnant women with a singleton gestation who were on a stable twice-daily dose of SL BUP for opioid maintenance therapy for at least 7 days in the 2nd and 3rd trimesters and the *postpartum* period were evaluated. Participants were recruited through Magee-Womens Hospital of University of Pittsburgh Medical Center (UPMC) and written informed consents were obtained from all participants. Each woman participated at least in two PK studies; once during the *postpartum* period and once during the second or third trimesters of pregnancy or in both trimesters. At each study visit, a total of 10 blood samples were collected from 0 h (prior to the morning dose) up to 12 h after the dose and BUP plasma concentrations in these blood samples were measured using high-performance liquid chromatography with tandem mass spectrometric detection [19]. Our goal was to use the SL BUP pregnancy PBPK model to predict the AUC during pregnancy, and to compare it to the observed data. A ±50% difference between mean observed AUC in the prospective PK study and mean predicted AUC in 100 virtual

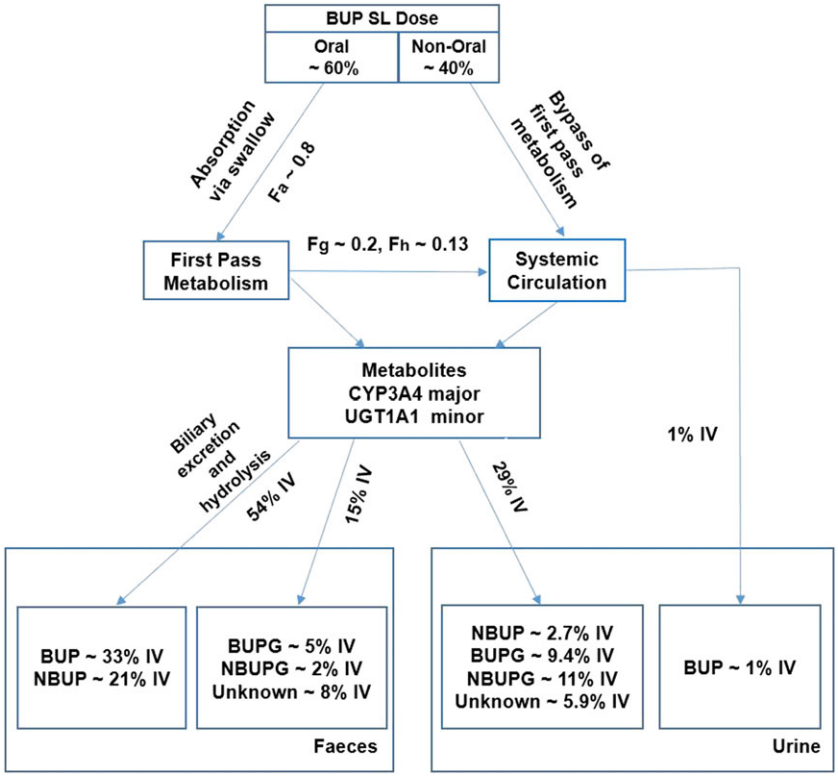

Figure 1

Quantitative mass balance diagram describing buprenorphine (BUP) absorption, distribution, metabolism and excretion after sublingual and intravenous (IV) administration. BUPG, Buprenorphine glucuronide; NBUP, Nor-buprenorphine; NBUPG, Nor-buprenorphine glucuronide

pregnant subjects using BUP PBPK model were used as the model validation criteria.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [39], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [40, 41].

Results

Steady-state BUP systemic exposure prediction

The disposition profiles of SL BUP following an 8 mg SL twice daily (BID) dose was predicted in 100 virtual pregnant female subjects spread over 10 trials during each trimester, and during the *postpartum* period. The predicted mean concentration–time profiles are shown in Figure 3. After SL BUP administration, plasma concentrations of BUP reached peak levels in approximately 1 h followed by a rapid decline and a subsequent slow disposition. Lower trough BUP concentrations, peak concentrations, average concentrations and systemic exposure (AUCs) were observed throughout pregnancy compared to the *postpartum* period, and the difference was pronounced in the 3rd trimester ($AUC_{0–12,ss}$ was approximately 50% lower in the 3rd trimester *vs*. the *postpartum* period and 40% lower in 1st and 2nd trimester *vs*. *postpartum*). Systemic exposure of BUP was similar in the 1st and 2nd trimesters.

Evaluation of the predictive performance of the BUP PBPK model in pregnant women

Figure 4 shows the predicted mean concentration–time profiles (with 5 and 95% confidence intervals) from 100 virtual pregnant women overlaid with the observed clinical data during a 12-h PK study. As shown in Figure 4, the predicted and observed dose normalized mean concentration–time profiles were visually similar. The predicted mean dose normalized concentration–time profiles fell within the 5th to 95th percentiles of the observed data. The difference in the predicted means of dose normalized $AUC_{0–12}$, C_{av} and C_{max} were within ±25% of the observed means during different trimesters of pregnancy and the *postpartum* period, with the exception of the dose normalized C_{av} in the 3rd trimester (–26.3%) (Table 3). The model did not adequately capture the T_{max}. The prediction of T_{max} is not clinically important since withdrawal symptoms are dictated not by the T_{max} of BUP, but rather by the maintenance of BUP plasma concentration above a threshold of 1 ng ml^{-1}.

Figure 5 compares the model predictions against individual observed BUP concentrations in women on a dose of 8 mg BID, the most common dosage used. The observed individual plasma concentrations of BUP were within the 5th -95th percentile of model predicted concentrations. PK parameters for of BUP during pregnancy and *postpartum* following 8 mg BID SL administration are provided in Table 4. The

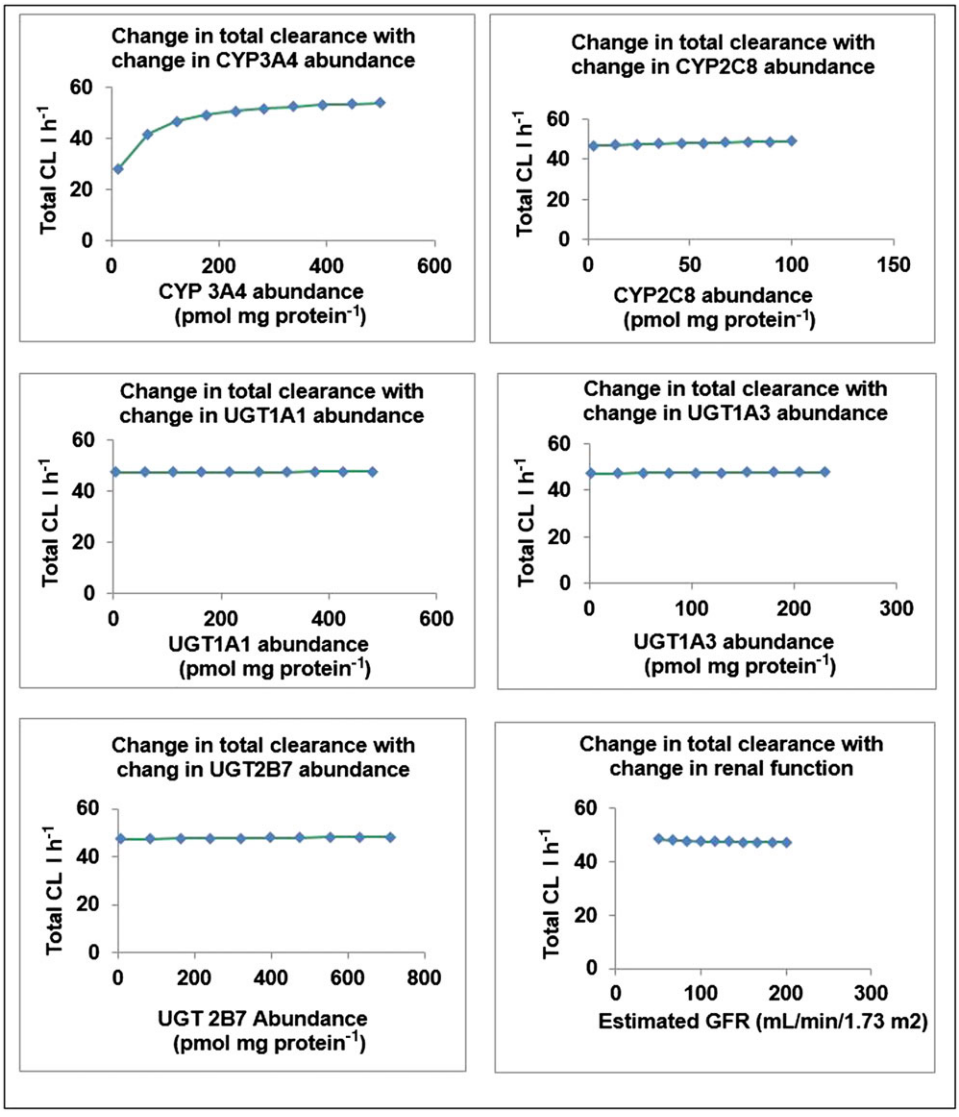

Figure 2

Sensitivity analysis to simulate the impact of the abundance of CYPs, UGTs and renal function on buprenorphine total clearance

simulations demonstrated that, at steady state with 8 mg BID SL BUP dose, trough plasma concentrations of BUP (at 12 h) remained above 1 ng ml^{-1} in 88%, 58%, 39% and 12% of the subjects in the *postpartum* period, 1st, 2nd and 3rd trimester. Figure 6 depicts the percentage of subjects who are below the BUP concentration required to prevent the appearance of withdrawal symptoms in pregnant subjects, on an 8 mg BID dose of SL BUP based on our PBPK model in pregnant and *postpartum* women. The table demonstrates that in all three trimesters, predicted concentrations are subtherapeutic in a substantial number of subjects long before the next scheduled dose. Seventy percent of women in the 3rd trimester are subtherapeutic by the 6th h after a dose.

Discussion

In the current study, we developed and validated a SL BUP PBPK model in pregnant women utilizing published data in nonpregnant women and adjusting for recognized anatomical and physiological changes associated with pregnancy that may impact BUP pharmacokinetics during gestation. The performance of our pregnancy model was evaluated by comparing it to the observed plasma concentrations of BUP in pregnant women during the 2nd and 3rd trimesters, and after delivery. The predicted concentration–time profiles in the virtual pregnant populations were consistent with the observed data. The model demonstrates that pregnancy is associated with a decrease in BUP systemic exposure, which is more pronounced in the 3rd trimester.

One of the limitations of PBPK modelling in special patient populations is the inability to assess the model predictive performance due to limited availability of drug concentration *vs.* time data. In the current study, the SL BUP PBPK model in pregnant women was systematically developed using a stepwise strategy, where the base model was extensively validated using many studies in nonpregnant populations over a wide

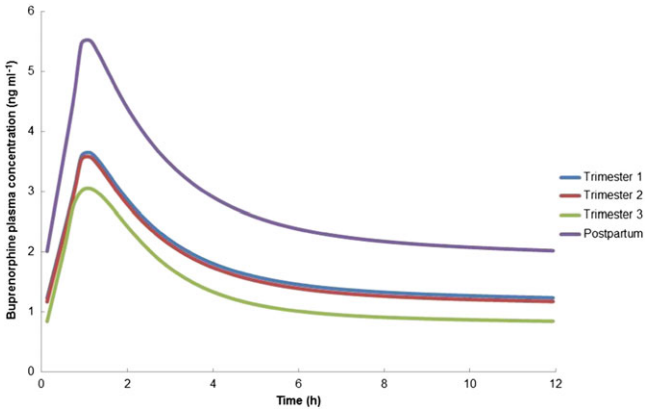

Figure 3

Predicted mean concentration–time profiles at steady-state following administration of 8 mg sublingual twice daily buprenorphine during 1st trimester, 2nd trimester, 3rd trimester, and *postpartum* in 100 virtual female subjects spread across10 trials

range of doses [28]. First, a BUP IV PBPK model was developed for nonpregnant healthy volunteers and then the absorption component was added to the BUP IV PBPK model to describe SL administration of BUP. After validation of the predicted plasma concentrations of BUP for both a single and multiple dose at steady state in a nonpregnant population, we developed the full BUP SL PBPK pregnancy model to predict BUP disposition in pregnant women.

In this study, we built a customized pregnancy PBPK model rather than using the SimCyp default parameters used for pregnancy, given the differences in certain parameters in the SimCyp default option and our clinical observations. For example, in SimCyp the pregnant default parameter describes changes of CYP3A4 activity during the entirety of pregnancy as a bell-shaped variable, increasing gradually at the beginning of pregnancy to a maximum level around 20 weeks of gestation, and then falling to normal level just prior to delivery. However, our in-house data showed that CYP3A4 activity is consistently, and significantly increased throughout pregnancy [34]. The increased CYP3A4 activity

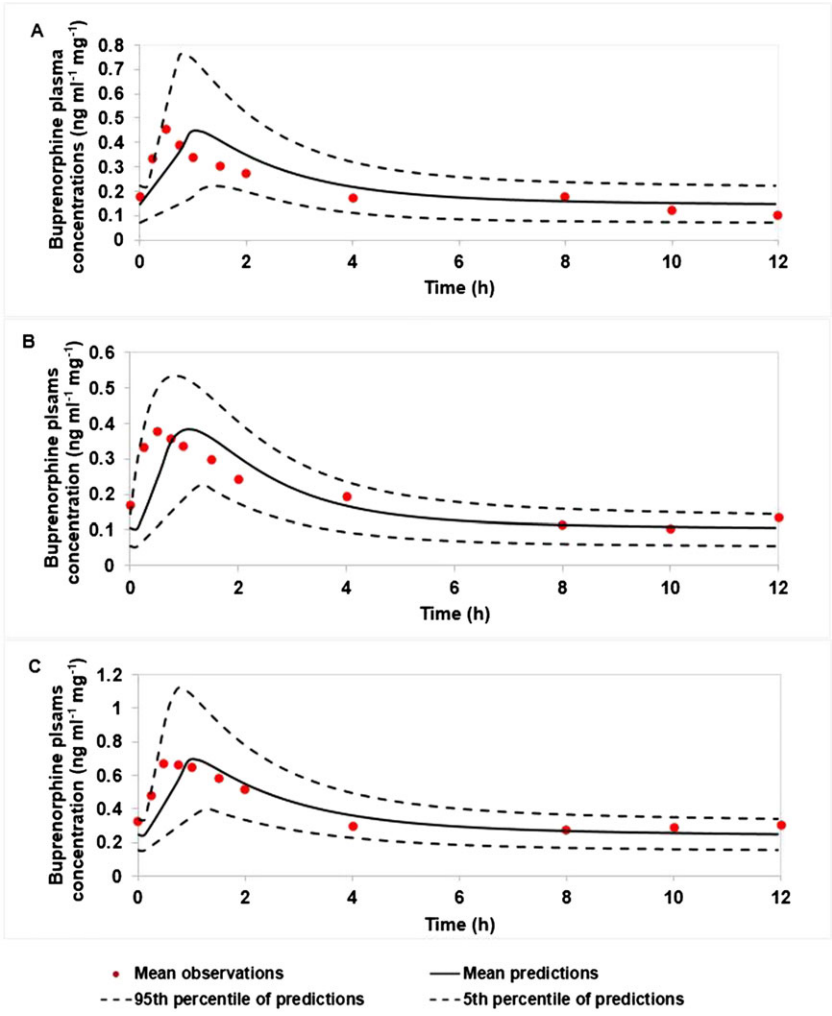

Figure 4

Predicted and observed dose normalized concentration–time profiles at steady-state following administration sublingual twice daily buprenorphine. A, B, and C represent interstudy validation by plotting mean predictions, 5th–95th percentiles of predictions against clinical observed mean concentrations during 2nd trimester, 3rd trimester, and *postpartum* respectively as observed by Bastian *et al.* [19]

Table 3

Goodness of fit of buprenorphine sublingual model in pregnancy and *postpartum* [pharmacokinetic parameters are expressed as mean (standard deviation)]

Interstudy validation	Period	Study	AUC_{0-12}/D ng•h ml^{-1}	Diff[a] %	CL/F l h^{-1}	Diff[a] %	C_{max}/D ng ml^{-1}	Diff[a] %	C_{av}/D ng ml^{-1}	Diff[a] %	T_{max}[b] h	Diff[a] %
Bastian *et al.* [19]	T2	Observed (n = 8)	2.34 (1.82)		607.83 (270.79)		0.52 (0.2)		0.19 (0.15)		0.43 (0.19)	
		Simulations (n = 100)	2.19 (1.19)	–6.4	523.16 (174.33)	–13.9	0.44 (0.15)	–15.4	0.18 (0.10)	–5.3	1.1 (0.2)	155.8
	T3	Observed (n = 13)	2.26 (1.29)		568.12 (282.75)		0.50 (0.2)		0.19 (0.11)		0.92 (1.08)	
		Simulations (n = 100)	1.73 (0.78)	–23.4	647.66 (204.43)	14.0	0.39 (0.12)	–22.0	0.14 (0.06)	–26.3	1.1 (0.2)	19.6
	PP	Observed (n = 13)	4.16 (2.29)		301.27 (136.98)		0.77 (0.30)		0.35 (0.19)		0.75 (0.28)	
		Simulations (n = 100)	3.84 (1.08)	–7.7	280.22 (77.65)	–7.0	0.69 (0.16)	–10.4	0.32 (0.1)	–8.5	1.1 (0.3)	46.7

AUC_{0-12}/D, dose normalized area under plasma concentration–time curve from time 0 to 12 h; CL/F, oral clearance; C_{max}/D, dose normalized maximum concentration; C_{av}/D, dose normalized average concentration; T_{max}, time to reach maximum concentration; T2, 2nd trimester; T3, 3rd trimester; PP, *postpartum*

[a]Diff (difference)% = (predicted - observed mean value)/observed mean value*100

[b]T_{max}: The patient number used to calculate T_{max} were n = 7, 12,12 for 2nd trimester, 3rd trimester, and *postpartum* respectively. Three patients were excluded for T_{max} calculation as the T_{max} was observed at 12 h after a dose.

$C_{av}/D = AUC_{0-12}/12$

in the late stage of pregnancy has also been reported by other groups [24, 42]. The physiological changes incorporated into the custom pregnancy population model are provided in Table 2. As there are currently no conclusive data on the involvement of ABC (ATP binding cassette) and SLC (solute carrier) drug transporters in the disposition of BUP [43], we assumed that BUP only passively diffuses across the placenta and is not metabolized by the placenta. Several groups have developed maternal–fetal PBPK models and various compartment structures have been used to model the fetal–placental unit [23, 27]. Still, the primary challenge in building a comprehensive fetal compartment is the limited information on the fetal physiological development and drug exposure in the fetus during pregnancy. In SimCyp, the fetal–placental unit is considered as a combined compartment in the pregnant women. The fetal–placental unit is simplified as a homogenous organ with the assumption that the components of the unit have similar characteristics of blood perfusion and drug partitioning [44].

In the BUP PBPK model developed, we used the corrected Poulin and Thiel method to estimate BUP distribution between blood and tissue. Both corrected Poulin and Thiel method and Rodgers and Rowland method utilize drug specific properties such as lipophilicity, pKa and plasma protein binding to estimate drug partitioning among the components of tissue and plasma including water, neutral lipid and phospholipids. The main difference between the two methods is that the approach of Rodgers and Rowland divides tissue water into extracellular and intracellular parts and contains an added acidic phospholipid component for basic drugs. The Rodgers and Rowland method also incorporates differences in pH of biological fluids and tissues and helps in modelling of active transporter uptake and efflux activity, whereas this ability is not present in the Paulin and Theil method. In general, the Rodgers and Rowland method has a better predictive performance, but the prediction by this method is not optimal for highly lipophilic and/or highly protein bound drugs with minimal to no transporter involvement [45]. During base model building phase, the Rodgers and Rowland method was tested to predict BUP volume of distribution at steady state, but due to poor prediction results, the corrected Paulin and Theil method was used from that point forward. BUP is a highly lipophilic drug and is extensively bound to plasma proteins with no transporter mediated disposition characteristics, and the corrected Paulin and Theil method is the preferred method for modelling this particular drug.

In general, the model performed well in predicting BUP exposures within 25% of the observed mean values. Currently there is no guidance on the appropriate variance for goodness of fit or validation criteria for model predictions. We considered a 50% deviation as reasonable, considering the variability in the physiological parameters and disposition of BUP in this population. Although our model predicted the plasma concentration *vs*. time profiles fairly well, the model underestimated the time to maximal concentration (t_{max}); the predicted t_{max} values lagged the actual values by about half an hour. This might be attributable to the fact that patients in the published clinical study broke the SL tablet into small pieces to reduce the nausea and discomfort of holding the medication under the tongue [19]. Published studies in nonpregnant populations did not control for this variable.

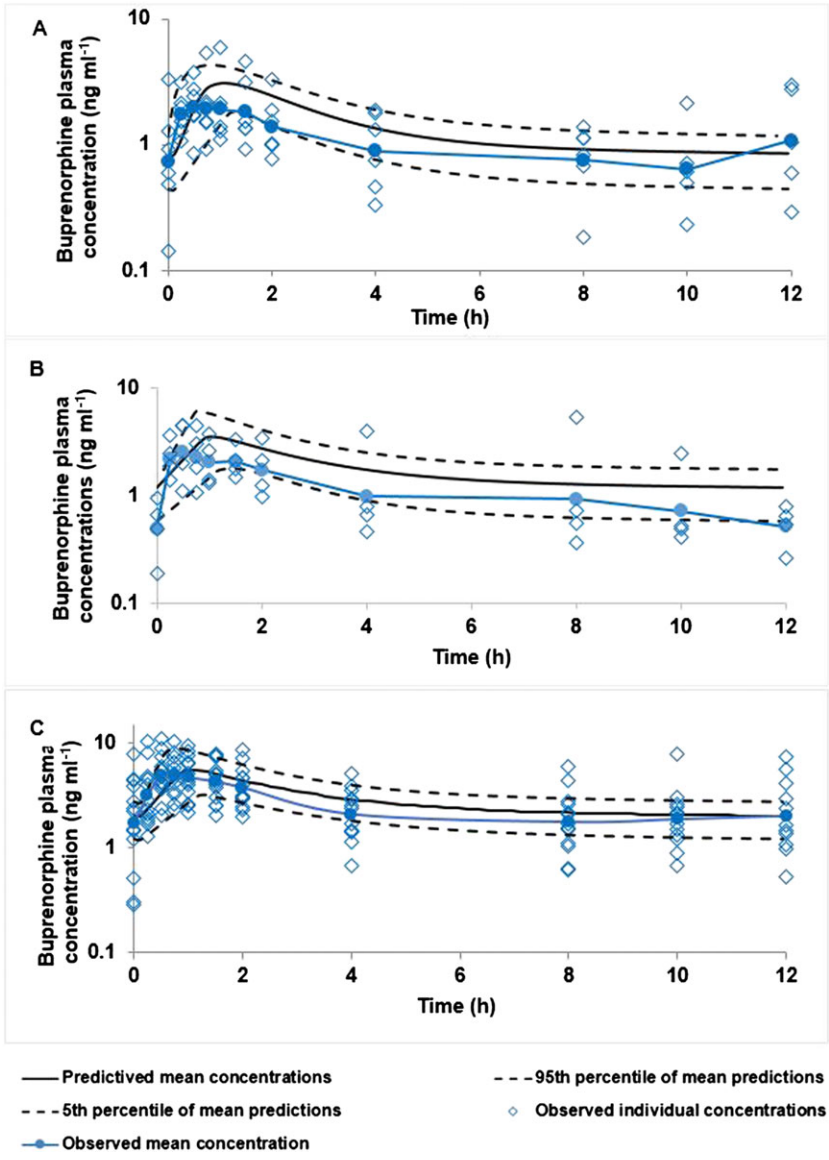

Figure 5

Predicted and observed concentration–time profiles at steady-state following administration of 8 mg sublingual twice daily buprenorphine. A, B, and C represent interstudy validation by plotting mean predictions, 5th -95th percentiles of predictions against clinical observed mean concentrations, and observed individual concentrations during 2nd trimester (Figure 4A), 3rd trimester (Figure 4B), and *postpartum* (Figure 4C) as reported by Bastian *et al.* [19]

Breaking up a tablet decreases the disintegration and dissolution time, and leads to a faster drug absorption, which probably reduced the time to the peak concentrations in the clinical study. The assumption was affirmed by model simulations, as increases of K_a or decrease of lag time shortened the t_{max} without affecting AUC or C_{max}.

Plasma clearance of BUP in healthy volunteers is around 60 l h^{-1} after an IV injection [46–49]. Comparing the clearance of BUP with hepatic blood flow in healthy subjects (1.5 l min^{-1}), the estimated BUP hepatic extraction ratio is ~0.67, which indicates BUP to be an intermediate to high hepatic clearance drug. For an intermediate to high hepatic clearance drug, both the intrinsic hepatic clearance and hepatic blood flow will affect drug clearance. Cardiac output increases from 35% to 50%, and the activity of CYP3A4 increases from 35% to 38% during pregnancy. Therefore, the higher clearance of BUP during pregnancy is probably due to higher intrinsic clearance and the increased hepatic blood flow. The increased BUP clearance during gestation leads to a lower systemic exposure in pregnant women.

In clinical practice, most drug dosing regimens are prescribed based on drug specific half-life. In nonpregnant patients, BUP is recommended to be administered as a single daily dose due to its long half-life (31–35 h) after SL administration [50]. Using positron emission tomography scan, Greenwald *et al.* have reported that the occupancy of μ-opioid receptors in the brain is correlated with plasma concentrations of BUP [18]. A plasma concentration of BUP of 1 ng ml^{-1} is associated to 50% μ-opioid receptor occupancy, a minimum requirement to inhibit drug withdrawal. The

Table 4

Pharmacokinetic parameters of buprenorphine (BUP) during pregnancy and *postpartum* following 8 mg twice daily BUP sublingual (SL) administration (geometric mean ± standard deviation)

	Our in-house clinical study			Model Prediction		
PK parameters	**2nd trimester**	**3rd trimester**	***postpartum***	**2nd trimester**	**3rd trimester**	***postpartum***
No. of subjects	4	4	10	100	100	100
Dose regimen	8 mg twice daily					
AUC_{0-12} (ng*h ml^{-1})	15.38 ± 14.81	12.41 ± 6.51	27.93 ± 20.18	16.21 ± 9.50	13.00 ± 6.21	29.62 ± 8.65
CL/F (l h^{-1})	519.96 ± 288.83	644.75 ± 362.26	286.42 ± 145.65	523.16 ± 174.33	647.66 ± 204.43	280.22 ± 77.65
C_{max} (ng ml^{-1})	3.80 ± 1.4	2.62 ± 0.57	5.40 ± 2.46	3.36 ± 1.17	3.01 ± 1.00	5.39 ± 1.31
T_{max} (h)	1.00 ± 3.75	0.47 ± 0.6	0.91 ± 3.6	1.10 ± 0.2	1.09 ± 0.26	1.04 ± 0.27

T_{max}, time to reach maximum concentration; C_{max}, maximum concentration; AUC_{0-12}, area under plasma concentration–time curve from time 0 to 12 h; CL/F, oral clearance

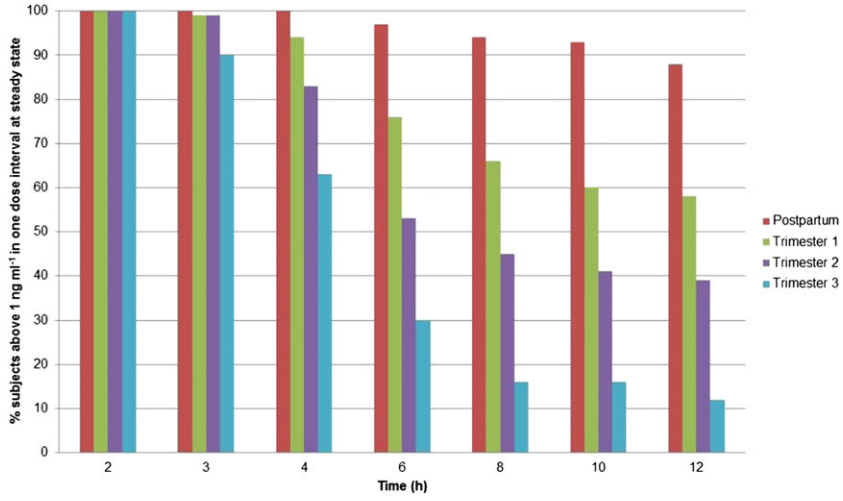

Figure 6

Percent of 100 virtual subjects with buprenorphine plasma concentration above 1 ng ml^{-1} in one dosing interval at steady-state following administration of 8 mg sublingual twice daily during *postpartum*, 1st, 2nd, 3rd trimester

recommended plasma concentration of BUP of 1 ng ml^{-1} as a threshold for withdrawal suppression is based on a study in nonpregnant subjects [18], and no similar pharmacokinetic–pharmacodynamics studies have been conducted in pregnant women. If we use plasma concentration of 1 ng ml^{-1} of BUP as a threshold for 50% of μ-opioid receptor occupation [18], among 100 virtual subjects, 40 subjects would be subtherapeutic in the 1st trimester in about 10 h after dosing, 47 subjects would be subtherapeutic in the 2nd trimester in about 6 h after dosing and 37 subjects would be subtherapeutic in the 3rd trimester in about 4 h following administration of 8 mg SL BUP. The model predictions demonstrate the need for an increase in dose or dosing frequency to maintain efficacy of BUP for opioid addiction in pregnancy. The model predictions are in agreement with the current clinical practice in pregnant women. At the Pregnancy Recovery Center at Magee-Womens Hospital, among 62 pregnant women followed up in an opioid agonist treatment programme, 68% of the patients chose a three or four times dosing per day to maximally suppress craving/withdrawal symptoms [20].

Recruitment of pregnant women on opioid maintenance therapy during the 1st trimester of pregnancy is difficult and as there are few such data on BUP PK profiles in the 1st trimester. The PBPK modelling study provided us additional information during 1st trimester that we were unable to obtain from our clinical study. We have also used the PBPK model to simulate the duration over which the plasma concentration of BUP will be above 1 ng ml^{-1} (the threshold to suppress drug withdrawal) with various dosing regimens across three trimesters. Such information enables optimization of BUP dosing during pregnancy.

We verified our SL BUP PBPK pregnancy model by using data from our clinical study data as there are no other published data on BUP PK in pregnancy. We are currently recruiting for a larger prospective BUP clinical study in pregnant women (NCT02863601), and we will be able to further

validate this PBPK model upon study completion. In addition, we have collected cord blood samples at delivery in the prior study as well in the on-going BUP study to further optimize and validate the estimates of BUP fetal exposure.

In conclusion, using the SL BUP PBPK model, we are able to predict maternal plasma concentrations of BUP in pregnant women across various gestational ages. The PBPK model predicted a decrease in BUP exposure during pregnancy and these results are aligned with published clinical study. We have also demonstrated the clinical implication of the SL BUP PBPK model in optimization of BUP dosing in pregnant women by predicting the duration over which the plasma concentrations will be below the threshold for inhibiting drug withdrawal over a dosing interval. The model predictions demonstrate the need for an increase in dose or dosing frequency to maintain efficacy for opioid addiction during pregnancy.

Competing Interests

There are no competing interests to declare.

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Appendix A

Table A1

Physiochemical and pharmacokinetic parameters used to develop buprenorphine profile in Simcyp[a] [28]

Parameter	Value	Reference/ Source
Physicochemical		
MW (g mol^{-1})	467.64	Pubchem/ DrugBank
Log $P_{o:w}$	4.98	[51]
Compound type	Diprotic base	
pKa1, pKa2	9.62, 8.31	[51]
B/P	0.55	[52]
f_u	0.03	[53]/ Parameter optimization
Absorption		
Absorption model	1st order absorption model	
f_a	0.80	Parameter estimation tool

(continues)

Table A1

(Continued)

Parameter	Value	Reference/ Source
K_a (h^{-1})	2.34	Parameter estimation tool
Lag time (h)	0.7	Parameter estimation tool
Q_{gut} (l h^{-1})	8.12	Predicted
f_{uGut}	1	User input
Permeability predicted via	PSA	
	PSA (Å):62.16	Pubchem/ DrugBank
	HBD: 2	Pubchem/ DrugBank
Distribution		
Distribution model	Full PBPK model	
Prediction method of V_{ss}	Method 1 (Corrected Poulin-Theil)	
Predicted V_{ss} (l kg^{-1})	2.48	
Elimination		
Clearance type	Enzyme kinetics	
***In vitro* metabolic system**	Recombinant	
CYP3A4		[54]
V_{max} (pmol min^{-1} pmol of isoform^{-1})	10.4	
K_m (μmol h^{-1})	13.6	
CYP2C8		[54]
V_{max} (pmol min^{-1} pmol of isoform^{-1})	1.4	
K_m (μmol l^{-1})	12.4	
UGT1A1		[55]
Cl_{int} (μl min^{-1} pmol of isoform^{-1})	0.0162	
UGT1A3		[55]
Cl_{int} (μl min^{-1} pmol of isoform^{-1})	0.0155	
UGT2B7		[55]
Cl_{int} (μl min^{-1} pmol of isoform^{-1})	0.0116	

[a]For detailed information please refer to Kalluri *et al.* [28].
MW, molecular weight; log$P_{o:w}$, logarithm of the octanol to water partition coefficient, pKa, negative logarithm of the acid dissociation constant, B/P, blood to plasma partition coefficient; f_u, Plasma fraction unbound; PSA, polar surface area; HBD, number of hydrogen bond donors; V_{ss}, apparent volume of distribution at steady state; Cl_{int}, intrinsic clearance

Table A2

Key pharmacokinetic parameters of buprenorphine in nonpregnant subjects (range, or mean ± SD)

PK parameter	Value	Reference
CL ($l\ h^{-1}$)	50–62.5	[46–49]
Bioavailability of SL dose	36 ± 13%	[49]
T_{max} (h)	0.75–1.5	[56–58]
C_{max} ($ng\ ml^{-1}$, mean ± SD) following 8 mg single SL dose	2.88 ± 1.14	[59]
$AUC_{0\text{-}inf}$ ($ng*h\ ml^{-1}$, mean ± SD) following 8 mg single SL dose	28.39 ± 10.22	[59]

CL, clearance, T_{max}, time to reach maximum concentration, C_{max}, maximum concentration, $AUC_{0\text{-}inf}$, area under plasma concentration–time curve from time 0 to infinity; SD, standard deviation; SL, sublingual

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