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Preliminary buprenorphine sublingual tablet pharmacokinetic data in plasma, oral fluid and sweat during treatment of opioid-dependent pregnant women

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Abstract

Background—Buprenorphine is currently under investigation as a pharmacotherapy to treat pregnant women for opioid dependence. This research evaluates buprenorphine (BUP), norbuprenorphine (NBUP), buprenorphine-glucuronide (BUP-Gluc) and norbuprenorphine-glucuronide (NBUP-Gluc) pharmacokinetics after high dose (14–20 mg) BUP sublingual tablet administration in three opioid-dependent pregnant women.

Methods—Oral fluid and sweat specimens were collected in addition to plasma specimens for 24 h during gestation weeks 28 or 29 and 34, and 2 months after delivery. T_{max} was not affected by pregnancy; however, BUP and NBUP C_{max} and AUC_{0-24h} tended to be lower during pregnancy compared to postpartum levels.

Results—Statistically significant but weak positive correlations were found for BUP plasma and OF concentrations, and BUP/NBUP ratios in plasma and OF.

Conclusion—Statistically significant negative correlations were observed for times of specimen collection and BUP and NBUP OF/plasma ratios. BUP-Gluc and NBUP-Gluc were detected in only 5% of OF specimens. In sweat, BUP and NBUP were detected in only 4 of 25 (12 or 24 h) specimens in low concentrations (<2.4 ng/patch). These preliminary data describe BUP and metabolite pharmacokinetics in pregnant women and suggest that, like methadone, upward dose adjustments may be needed with advancing gestation.

Keywords

buprenorphine; pharmacokinetics; pregnancy; plasma; oral fluid

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1. Introduction

Buprenorphine (BUP) is a semi-synthetic opioid derived from the baine with partial agonist activity at the μ -opioid receptor. BUP is administered in low doses (0.3–0.6 mg) as an analgesic and in high doses (4–24 mg) as pharmacotherapy for opiate-dependence¹. BUP oral bioavailability is low (15%) due to extensive first pass metabolism²; however, sublingual (SL) administration achieves a bioavailability of 30–55%³. Phase I BUP N-dealkylation by cytochrome P450 3A4 (CYP3A4) produces norbuprenorphine (NBUP) primarily in the liver⁴. BUP and NBUP Phase II metabolism involves glucuronidation to buprenorphine-glucuronide (BUP-Gluc) and norbuprenorphine-glucuronide (NBUP-Gluc) by uridine diphosphate glucuronosyltransferase (UGT) 1A1, 2B7 and 1A3^{5, 6}.

SL BUP administration occurs with alcohol-based liquid preparations or tablet formulations, containing BUP only or BUP combined with naloxone in a 4:1 ratio (combination tablet to reduce medication diversion and intravenous abuse). Several high dose BUP pharmacokinetic studies evaluated liquid and tablet formulation bioequivalence^{7–11}, mono and combination tablet bioequivalence^{8, 12, 13} and different administration routes¹⁴. In these studies, only BUP^{7, 9–13} or BUP and NBUP^{8, 14} were quantified in plasma. None reported BUP- and NBUP-Gluc pharmacokinetics.

BUP tablets were evaluated for opiate-dependence treatment in pregnant women in Europe^{15, 16}, Australia¹⁷ and the United States¹⁸. To our knowledge, there are no published BUP pharmacokinetic data in this complex population. During pregnancy, absorption, distribution, metabolism and excretion of drugs may be modified. Absorption and distribution may be affected due to reduced gastric motility, increased total body water and fat, and changes in plasma protein binding¹⁹. Metabolism also can be affected by alteration of maternal hepatic enzyme activity²⁰ and fetal and placental metabolism^{21, 22}. CYP and UGT isoenzymes are present in fetal liver and placenta, although at lower concentrations compared to adult liver, limiting their contribution to metabolism. Previous studies documented that placenta was capable of Phase I metabolism transforming BUP to NBUP^{21, 23}, and that NBUP could be glucuronidated by the fetus²⁴. Glomerular filtration rate increases 50% in the first trimester and continues increasing throughout pregnancy²⁵, potentially raising excretion rates. These gestational changes may affect a drug's pharmacokinetics, possibly requiring dose adjustment. Opiate pharmacokinetics may be modified during pregnancy; plasma methadone concentrations are lower during pregnancy than postpartum, most likely due to enhanced metabolism²⁶. Morphine clearance at the time of delivery is higher and the terminal half-life shorter than for non-pregnant women²⁷.

We present the first SL BUP tablet pharmacokinetic data in plasma, OF and sweat of pregnant women during pregnancy and postpartum. Specimens were collected for 24h at 2 different stages of pregnancy and postpartum. OF and sweat are receiving increasing interest in clinical and forensic toxicology due to easier and non-invasive collection compared to blood/plasma. OF/plasma ratios for BUP and NBUP following controlled 14–20 mg SL BUP tablet administration were evaluated for the first time for up to 24 h in pregnant women. Although this is an observational study based on a small number of mothers, simultaneous plasma, OF and sweat collection in pregnant women receiving controlled BUP-assisted pharmacotherapy provided the opportunity to study BUP pharmacokinetic changes throughout pregnancy, BUP and metabolites' pharmacokinetics and disposition in these matrices, and their potential for monitoring BUP exposure

2. Materials and methods

2.1. Participants

Participants were pregnant women enrolled in a randomized, double-blind, double-dummy, flexible dosing, parallel-group controlled study comparing methadone and BUP for opiate addiction treatment during pregnancy²⁸. The Johns Hopkins Bayview Medical Center and National Institute on Drug Abuse Institutional Review Boards approved the study, and participants provided written informed consent. Study details were previously published²⁸. Briefly, inclusion criteria were 21–40 years old, 16–30 weeks estimated gestational age (EGA) based on sonogram, a *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) diagnosis of current opiate dependence, maintenance pharmacotherapy request, recent self-reported opiate use of more than 4 days in the past 7, and an opiate-positive urine specimen. Exclusion criteria were undocumented methadone-positive urine, current DSM-IV alcohol abuse or dependence, self-reported benzodiazepine use more frequent than 7 times a month or once weekly, currently taking another Axis I disorder medication, serious concurrent illness, previous diagnosis of preterm labor, evidence of fetal malformation, and human immunodeficiency virus or sickle-cell trait positive tests²⁸. Eligible applicants were stratified at study entry on cocaine use (yes/no), EGA (16–23 weeks and 6 days; 24–30 weeks) and opiate use (3 or less than 3, and greater than 3 times per day). Participants were assigned to one of two treatment groups (methadone or BUP) according to a computerized dynamic balanced randomization procedure²⁹.

2.2. BUP administration

Each pharmacokinetic session, women received SL BUP HCl (2 mg each, maximum 24 mg/day; manufactured by Reckitt-Benckiser Healthcare UK Limited, Hull, England) and matching placebo tablets totaling 12 tablets/day, along with 40 mL placebo cherry-flavored liquid, under supervision of clinical staff. Throughout the study, double-blind medication increase or decrease was determined by physicians based on medication compliance, participant request, urine toxicology results, and participant self-report of opioid withdrawal symptoms or craving; BUP doses ranged from 4 to 24 mg/day²⁸.

2.3. Specimen collection

Specimens were collected during the 28th or 29th and 34th gestation week, and 2 months after delivery. In the case of participant A, specimens also were collected 2.5 months postpartum. Plasma and OF specimens were obtained 0.5 h prior and 0.5, 1, 2, 3, 4, 6, 8, 12 and 23.5 h following the daily BUP dose. Two sweat patches were applied for 12 h (from 0.5 h prior to medication to 12 h post-dose, and 12 to 23.5 h post-dose) and one for 24 h (0.5 h pre-dose to 23.5 h post-dose).

Blood samples (3 mL) were collected in heparinized Vacutainer tubes. Specimens were centrifuged and plasma transferred and frozen at –20°C until analysis. OF specimen collection utilized Sarstedt Salivette® collection devices (Nümbrecht, Germany). The Salivette® swab was placed into the mouth and chewed for approximately 45 sec, and the swab was centrifuged to recover clear OF. OF specimens were frozen at –20°C until analysis. Sweat collection utilized PharmCheck™ sweat patches (Fort Worth, TX, USA). Sweat patch specimens were stored frozen at –20°C until analysis.

2.4. Quantification of BUP and metabolites in plasma, OF and sweat

BUP, NBUP, BUP-Gluc and NBUP-Gluc were quantified in plasma by a previously published liquid chromatography tandem mass spectrometry (LCMSMS) procedure³⁰. Briefly, 1 mL 0.1% perchloric acid in water was added to 0.5 mL plasma. After centrifugation, the supernatant was subjected to solid-phase extraction (SPE) with Strata-XC

cartridges (Phenomenex, Torrance, CA, USA). Reverse-phase separation was achieved with a Synergi Polar-RP 80A, 75 × 2 mm, 4 μm column (Phenomenex, Torrance, CA, USA) within 10 min under gradient conditions. The assay was linear from 0.1 to 50 ng/mL for BUP and BUP-Gluc, and from 0.5 to 50 ng/mL for NBUP and NBUP-Gluc. Intra-day, inter-day and total assay imprecision (%RSD) were <16.8%, and analytical recoveries were 88.6–108.7%. Extraction efficiencies ranged from 71.1 to 87.1%. All compounds showed ion enhancement, except BUP-Gluc that demonstrated ion suppression. Variation among 10 different blank specimens was <9.1%.

OF specimens were analyzed by the plasma method³⁰ after validation for the OF matrix. OF calibration curves were linear from 0.1–500 ng/mL for BUP and BUP-Gluc, and 0.5–500 ng/mL for NBUP and NBUP-Gluc. Intra-day, inter-day and total assay imprecision (%RSD) were <10.2%, and analytical recovery ranged from 90.1 to 114.1%. Extraction efficiency was 74.1–77.0% and process efficiency 46.0–102.0%. BUP showed ion enhancement (33.8%), NBUP and BUP-Gluc ion suppression (–23.3 and –40.4%, respectively), and NBUP-Gluc no matrix effect. The variation among 10 different blank specimens was <5.7%.

BUP and NBUP were quantified in sweat by LCMSMS³¹. Sweat patches were mixed with 6 mL acetate buffer at pH 4.5, and the supernatant extracted with Strata-XC-cartridges (Phenomenex, Torrance, CA, USA). The chromatographic separation was achieved in gradient mode with a Synergi Polar-RP 80A, 75 × 2 mm, 4 μm column (Phenomenex, Torrance, CA, USA). Linearity ranged from 1 to 1,000 ng/patch. Intra-day, inter-day and total imprecision were <9.7%, analytical recovery 90.6–98.1%, and extraction efficiency >40.4%. BUP showed no matrix effect, and NBUP exhibited ion enhancement of 42.6%. Deuterated internal standard compensated for these effects (CV <7.5%, n=9).

2.5. Pharmacokinetics and statistical analyses

The pharmacokinetic parameters estimated were peak plasma or OF concentration ($C_{\max}$), time of peak plasma or OF concentration ($T_{\max}$), and area under the plasma concentration-time curve from predose to the time point of the last concentration measured (AUC_{0-24h}). $C_{\max}$ and $T_{\max}$ estimates were derived from the observed plasma and OF concentration-time data. The trapezoid rule was employed to calculate AUC_{0-24h} with GraphPadPrism 5 software (La Jolla, CA, USA).

Statistical analyses were performed with PASW Statistics 18.0 (IBM, Somers, NY, USA). Spearman correlations evaluated relationships between BUP, NBUP and BUP/NBUP ratios in plasma and OF, and between BUP and NBUP OF/plasma ratios and specimen collection times (h post-dose). Statistical probability (P) <0.05 was considered statistically significant. The Kolmogorov-Smirnov test determined if data distribution was normal.

3. Results

3.1. Participants and BUP dosing

Nine women met inclusion criteria, were randomized to BUP and completed the study through delivery. Three participated in 3–4 pharmacokinetic sessions during and after pregnancy, with plasma, OF and sweat collections for 24 h. Participants (A, B and C) were African-American, and 32, 30 and 28 years of age, respectively. Participant B gave birth to monozygotic twins, and A and C had single births. Pharmacokinetic session data are summarized in Table 1.

3.2. Plasma results

BUP, NBUP, BUP-Gluc and NBUP-Gluc were quantified in 100 plasma specimens; 95% were positive for BUP, 92% for NBUP, 97% for BUP-Gluc and 100% for NBUP-Gluc. BUP concentrations ranged from 0 to 35.2 ng/mL (median 1.3 ng/mL), NBUP 0–27.5 ng/mL (median 2.9 ng/mL), BUP-Gluc 0–32.1 ng/mL (median 1.7 ng/mL), and NBUP-Gluc 1.5–81.2 ng/mL (median 14.3 ng/mL) following 14–20 mg SL BUP. BUP and metabolite plasma concentration time curves showed two concentration maxima (Fig. 1), except for NBUP-Gluc in participant A pharmacokinetic session 4. $C_{\max}$ and $T_{\max}$ for the first peak were defined as $C_{\max 1}$ and $T_{\max 1}$, and for the secondary peak, $C_{\max 2}$ and $T_{\max 2}$. For BUP, $C_{\max 1}$ was always greater than $C_{\max 2}$; however, this was not consistently the case for BUP metabolites. Plasma pharmacokinetic parameters ($C_{\max}$, $T_{\max}$ and AUC_{0-24h}) for each session are included in Table 1.

In order to compare $C_{\max 1}$ and AUC_{0-24h} for the different pharmacokinetic sessions, parameters were divided by the corresponding BUP dose ($C_{\max 1}/\text{dose}$ and AUC_{0-24h}/dose). For BUP and NBUP, lower $C_{\max 1}/\text{dose}$ and AUC_{0-24h}/dose were observed during pregnancy than post-partum. For BUP- and NBUP-Gluc, data were more variable, although generally $C_{\max 1}/\text{dose}$ and AUC_{0-24h}/dose were lower during pregnancy than after delivery.

3.3. OF results

BUP was quantified in all OF specimens (n=100) with a wide range of concentrations (range 0.1–12,300 ng/mL, median 15.4 ng/mL), initially due to SL BUP contamination of the oral mucosa. NBUP was quantified in 94% of specimens at much lower concentrations (range 0–122 ng/mL, median 3.5 ng/mL). BUP and NBUP $C_{\max}$ and $T_{\max}$ in OF are shown in Table 2. BUP-Gluc was only measurable in 5 specimens at concentrations <0.6 ng/mL, and NBUP-Gluc was not detected at the method's LOQ of 0.5 ng/mL.

3.4. OF and plasma

BUP and NBUP results in OF and plasma are summarized in Table 3 and Figure 2. Statistically significant positive, but weak correlations were observed for BUP concentrations in plasma and OF ($P=0.008$, $r=0.294$, $n=81$), and for BUP/NBUP ratios in plasma and OF ($P=0.011$, $r=0.292$, $n=75$). Negative correlations were observed for BUP OF/plasma and NBUP OF/plasma ratios and times of collection ($P=0.000$, $r=-0.75$, $n=78$; and $P=0.000$, $r=-0.515$, $n=79$, respectively). BUP and NBUP OF/plasma ratios were highly variable 0.5 h post-dose, with less variation for the rest of the time course.

3.5. Sweat results

Of a total of 25 sweat specimens collected, BUP and NBUP were quantified in only 4 specimens at low concentrations. One was from participant B, BUP (1.8 ng/patch) and NBUP (2.4 ng/patch) in the 24 h sweat patch from pharmacokinetic session 3. From participant C, NBUP was detected in the 24 h sweat patch from pharmacokinetic sessions 1 (1.9 ng/patch) and 3 (1.2 ng/patch), and BUP in the 24h sweat patch from PK session 2 (<1.0 ng/patch).

4. Discussion

BUP and metabolite pharmacokinetics after high dose (14–20 mg) SL BUP tablet administration were evaluated at different stages of gestation and postpartum in a small group of opioid-dependent pregnant women. Plasma, OF and sweat specimens were collected for 24 h in 3 different pharmacokinetic sessions at gestation weeks 28 or 29 and 34, and 2 months after delivery. The objectives were to evaluate if BUP pharmacokinetics

were altered across pregnancy, and to compare BUP and metabolite disposition in three matrices, plasma, oral fluid and sweat.

Several plasma BUP pharmacokinetic studies were published after high-dose SL BUP tablet administration to adult male and non-pregnant female, experienced^{7–9, 12} or naïve¹³ opioid users. BUP plasma T_{max1} in the present study, 1.6 ± 0.8 h, agreed with those noted in previous studies, 0.75 to 1.2 h^{9, 12, 13}. Dose-adjusted BUP C_{max1} in these other studies was 0.19–0.65 ng/mL/mg, and dose-adjusted AUC BUP was 1.9–4.4 h*ng/mL/mg^{7–9, 12, 13}. Dose-adjusted BUP C_{max1} and AUC_{0–24h} in the present study during gestation and postpartum were different; values were lower for gestational weeks 28–29 (0.1–0.3 ng/mL/mg, 1.1–2.0 h*ng/mL/mg) and 34 (0.1–0.2 ng/mL/mg, 0.1–1.7 h*ng/mL/mg), as compared to 2 months after delivery (0.2–2 ng/mL per mg, 1.4–14.1 h*ng/mL per mg).

Plasma NBUP pharmacokinetic parameters (T_{max} , C_{max} and AUC) were reported in just one previous study by Harris et al.⁸. After 16 mg SL BUP (n=8), mean plasma NBUP T_{max} was 1.44 ± 0.86 h, C_{max} 2.54 ± 1.29 ng/mL and AUC 32.64 ± 7.63 h*ng/mL⁸. In the present study, after 14–20 mg dose, NBUP T_{max1} was similar at 28 or 29 and 34 gestation week and 2 months after delivery (1.6 ± 0.7 h), while C_{max1} and AUC_{0–24h} values were lower for gestational weeks 28–29 (1.8–5.7 ng/mL/mg, 18.8–83.0 h*ng/mL/mg) and 34 (0.8–5.5 ng/mL/mg, 7.2–92.9 h*ng/mL/mg), as compared to 2 months after delivery (3.4–27.5 ng/mL per mg, 32.5–397.8 h*ng/mL per mg), as occurred for BUP.

The observed variations in BUP and NBUP pharmacokinetic parameters could be explained by the physiologic changes that occur throughout pregnancy. C_{max} for BUP and NBUP tended to be lower in pregnancy, especially at the 34th gestational week. It is well known that the apparent volume of distribution (V_d) increases throughout pregnancy²⁰; and therefore, these V_d changes may decrease C_{max} . BUP AUC_{0–24h} also tended to decrease during pregnancy, most likely because CYP3A4 and UGT activity, such as UGT2B7, is increased in this period^{20, 32, 33}, accelerating BUP elimination. These UGT activity changes also may reduce NBUP AUC_{0–24h}. BUP and NBUP C_{max} and AUC_{0–24h} changes in participant B who delivered monozygotic twins, were much higher after delivery than for participants A and C who had single births.

To our knowledge, these are the first published plasma BUP- and NBUP-Gluc pharmacokinetic data. We found no consistent BUP and NBUP-Gluc C_{max} and AUC_{0–24h} changes in pregnancy compared to postpartum. BUP metabolite plasma levels could be decreased in pregnancy due to increased glomerular filtration rate (GFR) compared to postpartum levels²⁵. Kacinko et al.³⁴ examined 24-h BUP and metabolite urinary excretion in the same 3 participants. In all participants, cumulative BUP metabolite excretion, mainly NBUP-Gluc, was higher in sessions before birth compared to postpartum. BUP metabolite levels also could be higher during pregnancy due to increased BUP metabolism^{20, 32, 33}. Inter-individual variations were noted, requiring further study of these possible-contributing factors.

All participants showed a secondary peak for BUP and metabolites about 8 h after dosing, except NBUP-Gluc in participant A 2.5 months after delivery. McAleer et al.¹³ also reported a secondary peak for BUP 10 h post-dose after 16 mg SL BUP. Cone et al.³⁵ suggested a BUP depot effect in the oral mucosa following SL administration. Thus, BUP may be released from this oral depot and produce a secondary peak for BUP and metabolites. As reported by others^{8, 13}, fluctuating terminal BUP plasma concentrations, possibly due to enterohepatic recirculation, also were observed in the present study.

BUP concentrations were much higher in OF than plasma due to oral contamination from SL administration and the oral mucosal BUP depot³⁵. A statistically significant but weak

correlation was noted for BUP plasma and OF concentrations, and between BUP/NBUP plasma and OF ratios. The low coefficient of correlation ($r=0.2$) was most likely due to OF contamination from SL BUP and/or the contribution from the oral mucosal BUP depot. BUP and NBUP OF/plasma ratios decreased with time of collection post-dose; however, high inter-individual variations were observed (Table 3, Fig. 2). These results suggest that it is not possible to predict plasma concentrations from OF levels. As expected, BUP-Gluc and NBUP-Gluc were not detected in most OF specimens at the method's LOQs 0.1 ng/mL for BUP-Gluc and 0.5 ng/mL for NBUP-Gluc. Drug and metabolite incorporation into OF occurs mainly by passive diffusion from blood, with the extent of transfer dependent on the drug's physicochemical properties (polarity, molecular weight and protein binding). BUP- and NBUP-Gluc transfer into OF is expected to be low due to their high polarity and molecular weight >500 Da.

BUP and NBUP were detected in just 4 sweat specimens and in low concentrations. Concheiro et al.³¹ reported BUP and NBUP concentrations up to 2.3 and up to 1 ng/patch, respectively, in sweat patches worn for 7 days from a BUP-maintained opioid-dependent woman receiving 15.6 mg/day. Kintz et al.³⁶ reported BUP concentrations of 1.3–153.2 ng/patch and NBUP in just one case at 3.1 ng/patch, in sweat patches worn for 5 days by 16 participants receiving 0.4–6 mg BUP/day. A sweat patch wear period of less than 24 h is insufficient to sensitively detect BUP exposure. BUP is a highly potent opioid and doses are low, even during daily opioid-dependence treatment.

This study had several limitations. This was an additional component of a clinical trial that compared methadone and BUP treatment in opioid-dependent pregnant women²⁸; the study is underpowered as only 3 subjects entered the pharmacokinetic component. However, the data are unique in assessing pharmacokinetic data at two different gestational weeks and postpartum in the same women, and in plasma, oral fluid and sweat. These preliminary data suggest that BUP and metabolite pharmacokinetics are modified during pregnancy.

BUP and metabolites T_{max} were not affected by pregnancy; however, BUP and NBUP C_{max} and AUC_{0-24h} tended to be lower during pregnancy compared to postpartum levels. These data suggest that, like methadone, pregnant opioid-dependent women may require increased BUP dose during gestation and decreased dose postpartum. Yet, across all patients in the primary study, participants did not report nor were they observed to have symptoms or signs of over- or under-medication resulting in BUP dose changes up to 4 weeks post-partum³⁷. Thus, additional research is needed to confirm these preliminary results. The disposition of BUP and metabolites in alternative matrices, OF and sweat, were studied in order to determine their utility in monitoring BUP exposure, and to improve interpretation of results as compared to plasma. OF was useful to monitor BUP exposure, although BUP and NBUP plasma concentrations could not be deduced from OF concentrations due to high variability in concentrations. Sweat patch testing showed that a collection period of greater than 24 h was necessary to identify BUP exposure.

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Figure 1.

Plasma buprenorphine (BUP), norbuprenorphine (NBUP), buprenorphine-glucuronide (BUP-Gluc) and norbuprenorphine-glucuronide (NBUP-Gluc) pharmacokinetic profiles corrected for dose (14–20 mg) for pregnant opioid dependent women participants A, B and C at 28–29th and 34th gestational week and 2 months after delivery.

Figure 2.

Buprenorphine (BUP) and norbuprenorphine (NBUP) oral fluid to plasma ratios (OF/plasma) median, minimum and maximum, at collection times 0.5, 1, 2, 3, 4, 6, 8, 12 and 23.5 h post-dose (14–20 mg). Total number of specimens n=100.

Table 1

Plasma pharmacokinetic parameters for buprenorphine (BUP), norbuprenorphine (NBUP), buprenorphine-glucuronide (BUP-Gluc) and norbuprenorphine-glucuronide (NBUP-Gluc) following 14–20 mg SL BUP to three pregnant opiate-dependent women at gestational weeks 28 or 29 and 34, and 2 and 2.5 months post-partum.

Analyte	Subject	PK session	Dose (mg)	Days in TX	Collection time	C _{max1} (ng/mL)	T _{max1} (h)	C _{max2} (ng/mL)	T _{max2} (h)	AUC _{0-24h} (h*ng/mL)
BUP	A	1	14	26	29 GW	1.7	1	1	12	15.1
		2	14	61	34 GW	1.1	2	0.5	8	9.3
		3	18	159	2 moPP	5.2	1	0.9	12	25.8
		4	18	176	2.5 moPP	7.4	0.5	1.6	8	38.6
	B	1	16	39	29 GW	3.8	2	3.2	8	32.5
		2	18	74	34 GW	3.8	2	2.1	6	30.7
		3	18	148	2 moPP	35.2	1	31.5	8	253.1
	C	1	14	70	28 GW	3.7	1	0.9	8	20.5
		2	18	112	34 GW	2.5	2	1.6	8	2.4
NBUP	A	1	14	26	29 GW	1.8	3	1.8	8	18.8
		2	14	61	34 GW	0.8	2	0.6	6	7.3
		3	18	159	2 moPP	3.4	1	2.2	8	32.5
		4	18	176	2.5 moPP	5	1	1.4	23.5	37.0
	B	1	16	39	29 GW	5.6	2	6.4	6	79.8
		2	18	74	34 GW	5.5	2	7	8	92.9
		3	18	148	2 moPP	27.5	1	22.2	8	397.8
	C	1	14	70	28 GW	5.7	1	4.2	12	83.0
		2	18	112	34 GW	5.4	1	6.0	4	7.2
BUP-Gluc	A	1	14	26	29 GW	3.6	1	1.3	8	16.2
		2	14	61	34 GW	1.7	0.5	0.7	12	10.4
		3	18	159	2 moPP	8.7	1	3.6	8	45.9
		4	18	176	2.5 moPP	10.2	1	1.1	8	25.7
	B	1	16	39	29 GW	32.1	1	3.6	6	62.1
		2	18	74	34 GW	11.8	2	19.1	8	121.9
		3	18	148	2 moPP	31.0	0.5	7.4	8	89.8
	C	1	14	70	28 GW	8.7	1	1	8	28.7
		2	18	112	34 GW	7.2	1	2.4	23.5	53.2
NBUP-Gluc	A	1	14	26	29 GW	14.2	1	8.6	8	141.6
		2	14	61	34 GW	8.3	2	6.6	12	109.9
		3	18	159	2 moPP	16.7	1	18.6	6	241.6
		4	18	176	2.5 moPP	16.9	1	-	-	153.3
	B	1	16	39	29 GW	81.2	1	22.6	6	394.3
		2	18	74	34 GW	31.4	2	48.8	8	543.3
		3	18	148	2 moPP	64.8	2	65.2	12	1202

Analyte	Subject	PK session	Dose (mg)	Days in TX	Collection time	C _{max1} (ng/mL)	T _{max1} (h)	C _{max2} (ng/mL)	T _{max2} (h)	AUC _{0-24h} (h*ng/mL)
	C	1	14	70	28 GW	22.1	1	14.4	6	337.1
		2	18	112	34 GW	32.4	1	35.7	6	516.0
		3	20	209	2 moPP	49.6	1	35.3	4	370.7

Tx: treatment; GW: gestation week; moPP: months post-partum

Table 2

Pharmacokinetic parameters in oral fluid for buprenorphine (BUP) and norbuprenorphine (NBUP), following 14–20 mg SL BUP in 3 pregnant opioid-dependent pregnant women at different times during gestation and post-partum.

Participant	PK session	Dose (mg)	Days in TX	Collection time	BUP		NBUP	
					C _{max} (ng/mL)	T _{max} (h)	C _{max} (ng/mL)	T _{max} (h)
A	1	14	26	29 GW	7,120	0.5	53.1	0.5
	2	14	61	34 GW	12,300	0.5	54.2	0.5
	3	18	159	2 moPP	7,560	0.5	100	0.5
	4	18	176	2.5 moPP	6,020	1	122	0.5
B	1	16	39	29 GW	3,450	0.5	52.8	0.5
	2	18	74	34 GW	3,208	0.5	55.6	0.5
	3	18	148	2 moPP	2,760	0.5	39.8	0.5
C	1	14	70	28 GW	3,510	0.5	43.9	0.5
	2	18	112	34 GW	2,840	1	37.4	1
	3	20	209	2 moPP	672	1	8.9	1

Tx: treatment; GW: gestation week; moPP: months post-partum

Table 3

Median and range of buprenorphine (BUP) and norbuprenorphine (NBUP) oral fluid (OF)/plasma ratios 0.5, 1, 2, 3, 4, 5, 6, 8, 12 and 23.5 h post-BUP dose (14–20 mg) in 3 pregnant opioid-dependent pregnant women at gestation week 28–29 and 34, and 2 months after delivery (100 specimens).

Collection time (h post-dose)	BUP OF/Plasma (n=95)			NBUP OF/Plasma (n=92)		
	Median	Min	Max	Median	Min	Max
0.5	1.802	0.2	16.466	23.4	0	68.5
1	810	28.5	1,449	7.6	0.5	16.3
2	85.3	4.1	482	1.9	0.3	2.9
3	59.3	10.9	801	1.1	0.3	6.9
4	25.5	1.6	254	1.9	0.3	3.8
6	2.4	0.4	795	0.4	0	8.1
8	3.8	0.1	16.2	0.5	0.1	2.1
12	1.7	0.1	15.7	0.8	0.1	9
23.5	1.0	0	165	0.2	0.1	6.3