Published in final edited form as:

Am J Obstet Gynecol. 2017 October ; 217(4): 459.e1–459.e6. doi:10.1016/j.ajog.2017.06.029.

An Evidence-Based Recommendation to Increase the Dosing Frequency of Buprenorphine During Pregnancy

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Abstract

Background—Dose-adjusted plasma concentrations of buprenorphine are significantly decreased during pregnancy compared to the non-pregnant state. This observation suggests that pregnant women may need a higher dose of buprenorphine than non-pregnant individuals in order to maintain similar drug exposure (plasma concentrations over time after a dose). The current dosing recommendations for buprenorphine during pregnancy address the total daily dose of buprenorphine to be administered but the frequency of dosing is not clearly addressed. Based on buprenorphine's long terminal half-life, once daily or twice daily dosing has generally been suggested.

Objective—To assess the impact of dosing frequency on buprenorphine plasma concentration time course during pregnancy.

Study Design—We have utilized three data sources to determine an optimal frequency for dosing of buprenorphine during pregnancy: data from a pharmacokinetic study of 14 pregnant and post-partum women on maintenance buprenorphine in a supervised clinical setting; data from pregnant women attending a buprenorphine clinic; and data from a physiologically based pharmacokinetic (PBPK) modeling of buprenorphine pharmacokinetics in non-pregnant subjects.

Results—Among the fourteen women participating in the pharmacokinetic study during and after pregnancy, plasma concentrations of buprenorphine were < 1ng/ml (the theoretical concentration required to prevent withdrawal symptoms) for 50–80% of the 12 hour dosing interval while at steady state. Among 62 women followed in a opioid agonist treatment program, where dosing frequency is determined in part by patient preference, 10 (16 %) were on once daily

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Disclosure: The authors report no conflicts of interests.

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dosing, 10 (16%) were on twice daily dosing, 28 (45%) were on thrice daily dosing and 14 (23%) were on four times daily dosing. A physiologic based pharmacokinetic (PBPK) model in non-pregnant subjects demonstrated that dosing frequency impacts the duration over which the plasma concentrations are below a specified plasma concentration threshold.

Conclusion(s)—A more frequent dosing interval i.e. TID or QID dosing may be required in pregnant women to sustain plasma concentrations above the threshold of 1ng/ml to prevent withdrawal symptoms and to improve adherence.

Keywords

Buprenorphine; Dosing Frequency; Pregnancy; Pharmacokinetics

Introduction

The Substance Abuse and Mental Health Services Administration (SAMHSA) recommends protocols for the induction, stabilization and maintenance phases for buprenorphine¹. In general, an induction dose is initiated and titrated according to patient symptomatology primarily using the Clinical Opioid Withdrawal Scale (COWS) score. Once a suitable dose is identified to prevent withdrawal symptoms, a stabilization regimen follows for 1–2 weeks as the patient acclimates to the buprenorphine therapy and thereafter the long-term maintenance phase begins for an indefinite time period.

Sublingual (SL) buprenorphine is increasingly being prescribed for pregnant women on opioid agonist therapy for an opioid use disorder (OUD)². Pregnancy is associated with a numerous physiological changes and many recommendations applicable to men and non-pregnant women are not appropriate for pregnant women³. Recently, we and others have reported that buprenorphine exposure is lower during pregnancy than during the post-partum period and that buprenorphine dosing regimens during pregnancy may need to be re-evaluated^{4,5}. In our report⁵ we focused on the total dose of buprenorphine that should be administered to obtain comparable drug exposure, but here we will focus on the need to change the frequency of dosing as well.

The currently recommended dosing frequency for buprenorphine in non-pregnant subjects is a single daily dose due to its long half-life⁶. Some have suggested that doses every 2–3 days may even be sufficient for some patients⁷. The elegant work of Greenwald et al.^{8,9} clearly demonstrated that craving is directly linked to buprenorphine plasma concentrations. The occupancy of mu opioid receptors in the brain appears to be linked not only to withdrawal but also to satiety, and there appears to be hierarchical plasma concentration thresholds for these different outcomes. A plasma concentration above 1ng/ml appears to eliminate cravings (i.e. withdrawal) in most subjects⁹. The observations of Greenwald et al. suggest that any dosing regimen recommendation should therefore assure that plasma concentrations remain above 1ng/ml during an entire dosing interval^{8,9}. With a once daily dose, this implies that the plasma concentration of buprenorphine should stay above the 1ng/ml threshold, until the next dose is administered 24 hours later. Likewise, with a twice daily (BID) dosing regimen, the buprenorphine plasma concentration should be above 1ng/ml for the entire 12 hours until the next dose is administered. In this report we provide evidence that in pregnant

women, the buprenorphine concentration is not sustained above 1ng/ml for a large part of a dosing interval even with a BID dosing regimen. We have previously reported that a given dose of buprenorphine results in lower plasma concentrations in pregnant women than in non-pregnant women. Our objective in this report is to demonstrate that dosing frequency also impacts plasma concentrations.

Material and Methods

Pharmacokinetic Data

The methodology and analytical methods of the pharmacokinetic study data used in this report have been previously published and are briefly summarized here⁵. The University of Pittsburgh IRB approved this protocol. Blood samples were obtained 11 times over a dosing interval of 12 hours in 14 pregnant women on a stable BID dose of SL buprenorphine for at least 7 days. All but one of these 14 women underwent the pharmacokinetic study at least once during pregnancy in the 2nd and/or 3rd trimesters and again in the postpartum state. The plasma concentrations of buprenorphine were determined using high-performance liquid chromatography with tandem mass spectrometric detection (LCMS-MS). The lower limit of quantification was 0.05 ng/ml and calibration curves were linear, ranging from 0.05–50 ng/mL. The plasma concentration vs time data were dose-normalized (ng/ml per mg dose) enabling concentration x time data from women on different doses to be combined and expressed as ng/ml per mg of buprenorphine administered. The median dose-adjusted plasma concentration values were then multiplied by the desired dose that was to be plotted in the figures in the results section. This process was repeated for each cohort i.e. 2nd trimester, 3rd trimester and postpartum.

Data from the Magee Womens Hospital Pregnancy Recovery Center (PRC)

These data include patients who were seen over a 9-month period from July 2014 to April 2015. All patients seeking care in the PRC were scheduled for an initial evaluation visit where their pertinent medical and substance use histories were assessed. On the first day of buprenorphine induction, the patients were expected to be demonstrating mild to moderate withdrawal symptoms from their opioid use disorder as they were instructed to not take opioids for at least 8 hours prior to the visit. Based on their histories, patients were started on 4–8 mg SL buprenorphine and observed in the clinic for 4–6 hours, while being evaluated for withdrawal symptoms using the Clinical Opioid Withdrawal Scale (COWS) score. Based on their symptomatology over the 4–6 hours, the patient's initial buprenorphine dose was supplemented until all withdrawal symptoms were alleviated for a sustained period. The subjects were then sent home with a take-home dose equivalent to the dose administered during the period of observation. On the next day of induction, the dose was adjusted based on COWS scores and symptoms reported by the patient from the previous night. Though the total daily dose is generally fixed (most often 16 mg daily), the patients were given the opportunity to split the total daily dose to best reduce their symptoms of withdrawal.

Physiologically based pharmacokinetic (PBPK) modeling

PBPK modeling incorporates a drug's physiochemical properties, in-vitro drug metabolism estimates, human physiological variables and population variability estimates to predict drug

exposure¹⁰. Because population PBPK models incorporate anatomical, physiological and metabolic attributes, any physiological alterations induced by pregnancy, disease, age, gender, genetic polymorphism, and other pathophysiologic conditions can be captured by the model. Buprenorphine PBPK modeling and simulations were conducted using SimCyp® population-based simulator v15.1 (Simcyp limited, Sheffield, UK). WinNonlin software (Phoenix WinNonlin®: version 6.4, Pharsight Corp, Mountainview, CA) was used to simulate steady-state exposure after administration of the SL formulation. Systematic and extensive literature search in MEDLINE through PubMed was performed to identify published physicochemical properties, plasma protein binding, in-vitro disposition and metabolism profiles of buprenorphine. Similar strategies were used to identify published clinical trials involving buprenorphine administration. Details of the development and validation of the model are discussed elsewhere¹¹. In summary, after developing a PBPK model from IV buprenorphine, we utilized data from Ciraulo et al.¹² for building a sublingual model for the 8 mg dose. The sublingual model was assessed at doses of 4, 8, 16 and 24 mg. for intra-study validation Model naïve data from Harris et al.¹³ and McAlear et al.¹⁴ were used for the inter-study validation of the buprenorphine sublingual PBPK. In addition, data from Compton et al.¹⁵ and Greenwald et al.^{8,9} were used for further validation of sublingual buprenorphine during steady state following multiple-doses. The accuracy of the predicted means of from the area under the plasma concentration-time curves (AUC) were within 75–125% of the observed means for doses of 4–24 mg.

Results

We utilized data from 14 women from a prior PK study who were on twice daily SL buprenorphine maintenance therapy. All but one of these 14 women underwent intensive pharmacokinetic sampling at least once during pregnancy in the 2nd and/or 3rd trimesters and again in the postpartum state. The demographic characteristics of the subjects have been previously report and are provided here (Table 1) in an abbreviated form.

Median plasma concentrations after doses of 4, 8 and 12 mg BID are depicted in Figures 1a, 1b and 1c. Figure 1a depicts the median buprenorphine plasma concentrations from 7 women studied during the 2nd trimester. Each of the dose-normalized concentrations was multiplied by the specific dose selected to be displayed in the Figures. At all doses depicted in Figure 1a (2nd trimester), median plasma concentrations were less than 1 ng/ml within 4 hours of drug administration. Even with the 12 mg BID dose, plasma concentrations remained below 1ng/ml for nearly 8 hours until the next dose was to be administered. Figure 1b depicts median buprenorphine plasma concentrations from the 11 women studied during the 3rd trimester. Median plasma concentrations in the women on the 4 mg BID dose were below 1ng/ml within 2 hours after dosing. Among those women on the 8 BID dose, median plasma buprenorphine concentrations were below 1 ng/ml by 8 hours after the dose. Among those women on the 12 mg BID dose, median plasma concentrations exceeded the 1ng/ml level throughout the 12 hour dosing interval except for a brief period at the 10th hour after dosing.

Figure 1c depicts median buprenorphine plasma concentrations from the 10 women studied in the postpartum state. Nine of these women were studied at least once during pregnancy.

As expected, plasma concentrations during the postpartum period were higher than during pregnancy. Had these women been taking a 4 mg dose twice daily, plasma concentrations would have been < 1 ng/ml within 4 hours after the dose was administered; however, those on the higher doses sustained concentrations > 1 ng/ml throughout the entire dosing period.

The data presented in Figures 1a, 1b and 1c indicate that many of these women appear to have plasma concentration < 1 ng/ml (sub-therapeutic as defined by Greenwald) for a large part of the dosing interval. The duration of time where plasma concentrations are less than 1 ng/ml in Figures 1a, 1b and 1c is summarized in Table 2. During pregnancy, the average (2nd and 3rd trimester data) duration below 1 ng/ml is 10, 6 and 4 hours respectively for doses of 4, 8 and 12 mg BID respectively. In the postpartum period, the duration below 1 ng/ml is 8, 0 and 0 hours respectively for doses of 4, 8 and 12 mg BID. The plasma concentrations are reported as medians indicating that in some women, plasma concentrations would be higher than those depicted in the figures, but an equal number would be lower than the median value depicted in the figures.

At the Pregnancy Recovery Center (PRC) at Magee Womens Hospital, women are provided their total maintenance dose and are given the opportunity to administer their medication at an individualized frequency that minimizes craving/withdrawal for that patient. Figure 2 demonstrates that in this clinic, the majority of the 62 women represented in the figure take the medication 3–4 times daily. The total daily dose ranged from 4 to 32 mg but the median dose is 16mg daily.

The third source of support for a dosing regimen change comes from physiological-based pharmacokinetic modeling (PBPK) and simulations performed. We have performed PBPK modeling of buprenorphine in non-pregnant subjects who, of course, have higher plasma concentrations than non-pregnant subjects as demonstrated in Figures 1a–c. PBPK modeling is able to predict plasma concentrations that would be achieved with various dosing regimens. Figure 3 shows simulated data in 100 virtual non-pregnant subjects to illustrate the impact of dosing frequency on plasma concentrations. The absolute concentrations are not the focus of this example but rather the focus is to demonstrate the relationship between dosing frequency and plasma concentrations time course with a fixed total daily dose. In these simulations a total daily dose of 6 mg is administered to virtual subjects. The frequency of dosing in the 3 scenarios is 6mg QD, 3 mg BID and 2 mg TID. It is assumed for the sake of this discussion that a concentration of 1 ng/ml is required to sustain satiety and prevent withdrawal symptoms. Despite the fact that the total daily dose (6 mg) and cumulative 24 hour exposure (AUC) are identical (AUC equals 26 ng/ml/hour for the QD, BID and TID dosing intervals), the time that the trough concentrations (the concentrations prior to the next dose) are above 1 ng/ml, in this example, varies by dosing frequency. With the 6mg daily dose, mean plasma concentrations exceed the 1 ng/ml threshold for the first 7.7 hours but after that time the concentrations are lower than 1 ng/ml for the rest of the 24 hour study period i.e. 16.3 hours. With the 3mg BID dose, plasma concentrations are below 1 ng/ml between hours 5.3–12 and from hour 17.3–24; a total 14.4 hours. With the 2 mg TID dosing interval, mean concentrations are below 1 ng/ml between hours 4.4–8, 12.4–16 and 20.4–24 for a total of 10.8 hours daily. Plasma concentrations with the TID regimen are below the 1 ng/ml threshold a shorter length of time than either of the other two dosing

frequencies (see Table 3). This example demonstrates the impact of dosing frequency on plasma concentrations when the total daily dose is constant; in this example, 6 mg daily.

Comments

We have provided evidence to support a change in the dosing frequency of SL buprenorphine in pregnant women. This recommendation is based on 3 different analyses: previously published pharmacokinetic data from an intensive sampling pharmacokinetic study⁵; data from patients in a hospital based opioid agonist treatment program and simulations using a physiological based pharmacokinetic (PBPK) modeling of buprenorphine. The fact that the 3 sources support the same conclusion is a strength of this study providing both scientific and practical perspectives to the recommendation. A weakness of this study is the small sample size which adds to the variance in plasma concentrations depicted in Figure 1.

The elegant work of Greenwald et al.^{8,9} has demonstrated a strong relationship between plasma concentrations of buprenorphine and occupancy of the mu opioid receptor. At concentrations < 1ng/ml, mu opioid receptor occupancy in non-pregnant subjects is too low to prevent symptoms of withdrawal. Thus, the objective of therapy in non-pregnant individuals should be to sustain plasma concentrations >1ng/ml throughout the duration of the dosing interval. The precise plasma concentration required in pregnant women to prevent symptoms of withdrawal may be higher or lower than that seen in non-pregnant subjects. There are no similar pharmacodynamic data relating mu opioid receptor occupancy to plasma concentrations and satiety in pregnant women, but there is no reason to challenge the general principals presented by the work of Greenwald et al.^{8,9}. We suggest an approach that acknowledges that pregnant women receiving buprenorphine will most likely require similar levels of buprenorphine to saturate the mu opioid receptors in the brain and that receptor occupancy determines to some extent the degree of satiety and withdrawal symptoms. Using actual data from our published study on the pharmacokinetics of SL buprenorphine, we have shown here that the plasma concentrations after doses of 4–12 mg BID are below 1ng/ml in many pregnant subjects for a considerable time between doses. We have previously reported that with comparable doses, buprenorphine plasma concentrations during pregnancy are lower than in the non-pregnant state⁵. We have therefore suggested in our prior work that care providers and insurers should take into account the differences in buprenorphine pharmacokinetics during pregnancy when adjusting buprenorphine doses or when considering requests from care providers for higher than standard doses⁵. It should not be assumed that a higher dose requirement is necessarily indicative of diversion in this specific population.

In the current report we demonstrate that the dosing frequency as well as the total daily dose of buprenorphine will affect plasma concentration time profiles. The half-life of SL buprenorphine in non- pregnant subjects is long and in one study ranged from 24–69 hours and this has led to the strategy of once daily or even less frequent dosing^{6,7}. Even in non-pregnant subjects the plasma concentrations after a single 24 mg daily dose decrease rapidly and are lower than 1ng/ml within 12 hours of drug administration¹². There are limited data describing the half-life of buprenorphine in pregnancy. The plasma concentration vs time

curves that we report here clearly indicate that at steady state, plasma concentrations decrease rapidly after a SL dose is administered to pregnant women. This rapid decrease suggest that even with higher doses and more frequent dosing, pregnant women may have plasma concentrations below the threshold for withdrawal for a significant portion of a dosing interval.

We suggest that the long terminal half-life of buprenorphine reported in the literature should not be the determinant of the dosing frequency in pregnant women. Precedence for this approach is evident in the dosing of other agents. For example, the half-life of tacrolimus is approximately 36 hours in normal healthy adults, yet it is administered on a twice daily basis in transplant patients^{16,17}. The rationale for this regimen is related to the fact that levels are below therapeutic range within 12–24 hours post dosing and subsequently decline at a much slower rate. This may be related to slow release of the tacrolimus from a peripheral tissue site. Buprenorphine is a lipophilic drug with a long half-life, but the plasma concentrations may fall rapidly after a dose to a level below the therapeutic threshold desired as demonstrated in this manuscript. Although buprenorphine avidly binds to the mu opioid receptors in the brain, these receptors become increasingly available by 4 hours after dosing and symptoms of withdrawal begin to be manifested^{8,9}. Thus, reliance on plasma concentrations as surrogates of mu opioid receptor binding appears reasonable and supports our recommendation that dosing frequency also be considered in the process of dosing pregnant women during the induction, stabilization and maintenance phases.

In the initial months of our buprenorphine clinic most women were placed on BID dosing. Clearly, blood levels in many of the women were sub-therapeutic with this dosing regimen. The clinicians treating these women responded to the patients' request for more frequent dosing and that adjustment seems to have been well-received. Many of the women select a dosing frequency of TID or QID based on their symptomatology during the day. The total daily dose is not changed but the frequency of dosing is in large part determined by the patient. This is consistent with the analyses presented here.

Higher doses would be needed in order to sustain concentrations above the 1ng/ml threshold if administered on a daily or BID dosing regimen compared with a TID or QID regimen. Although there does not appear to be a relationship between dose at delivery and the risk of NAS¹⁸, maternal dose alone may not fully represent the fetal exposure to buprenorphine. There does appear to be a relationship between the quantity of buprenorphine in meconium and the risk of NAS^{18,19}, so the potential benefit of a lower dose should not be discounted. More relevant to the patient and her provider however is the possibility that a split dose will lead to greater occupancy of the mu opioid receptor for much of the day, which may result in a more satisfied and adherent patient. This approach provides the patient more confidence that she can control her disease, enhances trust in her care providers and makes it less likely she will crave additional illicit drugs despite being treated with buprenorphine.

The practical implications of our recommendation relate to dosing during the induction, stabilization and maintenance periods. As the induction dose is being established, a careful history from the woman can assist in determining whether a higher dose is needed or whether more frequent dosing would reduce symptoms of withdrawal. If the woman is

having symptoms long before her next scheduled dose, consideration should not be limited to raising the daily dose alone but consideration should also be given to splitting the current total daily dose into 3–4 divided doses given at regular intervals. Clearly, more data are needed to clarify the relationship between plasma concentrations of buprenorphine and symptoms of withdrawal during pregnancy. Studies are needed to prospectively evaluate the recommendations proposed here.

Acknowledgments

Funding Source: Funding for grant HD047905 from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. Dr. Bastian was a T32 Scholar on NIH/NICHD HD071859 Training Grant

Thanks to the staff at the Pregnancy Recovery Center for their assistance on this project.

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Figure 1a.

Figure 1b.

Figure 1c. **Figure 1.**

Figure 1a. Median Buprenorphine Concentrations According to Dose During the 2nd Trimester

Figure 1b. Median Buprenorphine concentrations According to Dose During 3rd Trimester

Figure 1c. Median Buprenorphine Concentrations According to Dose During the Postpartum Period

Figure 2.
Buprenorphine Dosing Frequency at the Magee Pregnancy Recovery Center (PRC)

Figure 3.
PBPK-Simulated Plasma Concentrations in Non-Pregnant Subjects Receiving 6 mg
Buprenorphine Daily
PBPK – Physiologic Based Pharmacokinetic
Values are means.

Table 1

Characteristics of Subjects Undergoing PK Analysis

	2 nd trimester	3 rd trimester	Postpartum
Number of subjects	7	11	10
Age (year)	27 ± 5	28 ± 5	29 ± 6
BMI	29 ± 4	29 ± 4	25 ± 5
Smoker-current (%)	5 (71)	8 (73)	7 (70)
Weeks	22 ± 2.5	34 ± 2.2	7 ± 4.2 postpartum
BID dose in mg (range)	8 ± 3.1 (2–12)	10 ± 3.7 (2–16)	8 ± 0

Values are mean ± SD

Table 2

Time That Dose-Normalized Plasma Concentrations Are Below 1ng/ml During Intensive Sampling PK Study in Subjects During Pregnancy and Postpartum State

	Hours below 1ng/ml		
	4mg dose	8 mg dose	12 mg dose
2 nd trimester	10	8	8
3 rd trimester	10	4	0
Pregnancy average (2nd and 3 rd trimesters)	10	6	4
Postpartum	8	0	0

Table 3

Impact of Dose Frequency on Time That Target Concentration Not Achieved Based on PBPK Simulation in Non-Pregnant Subjects

Dose and Frequency	Hours Plasma Concentrations < 1ng/ml
6 mg QD	16.3
3 mg BID	14.4
2 mg TID	10.8