Published in final edited form as:
Am J Drug Alcohol Abuse. 2009 ; 35(3): 151–156. doi:10.1080/00952990902825413.

Management of Acute Postpartum Pain in Patients Maintained on Methadone or Buprenorphine During Pregnancy

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Abstract

Background—Empirical evidence is needed to guide adequate post-partum pain relief of methadone and buprenorphine stabilized patients.

Objectives—To first determine the adequacy of pain control using non-opioid and opioid medication in participants stabilized on buprenorphine or methadone before a vaginal delivery. Second, to compare the amount of non-opioid and opioid medication needed for adequate pain control for buprenorphine-and methadone-maintained patients during the immediate post-partum period.

Methods—Pain control adequacy and amount of non-opioid and opioid medication needed in buprenorphine- (n=8) and methadone-maintained (n=10) patients over the first five days post-partum were examined.

Results—Pain ratings and number of opioid medication doses decreased over time in both medication groups. While the buprenorphine and methadone groups began with similar mean daily ibuprofen (IB) doses, the buprenorphine group decreased its IB use, while the methadone group increased its IB use.

Conclusions and Scientific Significance—Patients treated daily with either buprenorphine or methadone can have adequate pain control post-partum with opioid medication and IB. Pain control is dependent on the opioid-agonist medication in use at delivery, and must be individualized.

Introduction

The treatment of acute pain in patients maintained on methadone or buprenorphine is a complex clinical issue (1). Unfortunately, for multiple reasons, the pain of many opioid-agonist-maintained patients is often under-estimated and under-treated (1). Because addiction causes neurophysiologic, behavioral, and social responses that worsen the pain experience (2), these patients must have adequate pain relief treatment. Acute pain treatment for a methadone-maintained patient should include using short-acting opioid analgesics in addition to the patient's daily methadone maintenance dose (2–4).

The unique pharmacological characteristics of buprenorphine (5), while beneficial for treatment, may also pose a potential complication for providing adequate post-partum pain relief. The current treatment options for acute pain in buprenorphine-maintained patients are based upon sound clinical experience (2,6,7) and lack empirical support (8).

Inadequate post-partum pain control can set the stage for adverse maternal and neonatal outcomes (9). Following routine vaginal birth, post-partum pain can be controlled by alternating the oral administration of short-acting opioids and non-opioids. Non-opioid drugs [e.g., non-steroidal anti-inflammatory agents (NSAIDs) and acetaminophen] have the advantage over opioid drugs by producing fewer side-effects (9). Case reports including a neonatal death due to rapid metabolism of codeine to morphine in the mother with subsequent absorption in the neonate from breast milk, highlights the need for caution in the use of this medication for post partum pain control (10,11).

Hyperalgesia is observed in patients with heroin use histories and is not altered by methadone or buprenorphine treatment. Thus, it may be that current opioid-dependent patients maintained on agonist treatment do not experience effects of the medication diminished by tolerance but a subjective state opposite to the effect of the drug (12). Hence, additional opioid medication may be needed to achieve adequate pain control. For example, on average, methadone-maintained women had increased pain and required up to 70% more oxycodone equivalents after cesarean delivery (8). Further, following cesarean delivery, buprenorphine or methadone treated women showed adequate pain control post-partum using a 24-hour PCA pump followed by opioids in combination with acetaminophen. However, the methadone-maintained patient required the addition of an NSAID to maintain adequate pain control (13).

The two primary objectives of this study were to determine: 1) the adequacy of pain control using non-opioid and opioid medication in participants stabilized on buprenorphine or methadone before a vaginal delivery; and, 2) the amount of non-opioid and opioid medication needed for adequate pain control for buprenorphine-and methadone-maintained patients during the immediate post-partum period. Based on the previous data (13), it was hypothesized that methadone-maintained patients would require greater doses of non-opioid medications to achieve adequate pain control compared to their buprenorphine counterparts over the first five post-partum days.

Methods

Participants

Secondary data analysis included women who delivered a child following admission to the labor and delivery unit at the Johns Hopkins Bayview Medical Center. Following delivery, participants were transferred to the adjacent post-partum unit. All study participants (14,15) were administered double-blind, double-dummy [2 dosage forms: sublingual (tablet) and oral (liquid)] study medication as a part of their comprehensive treatment at the Center for

Addiction and Pregnancy (CAP). Of *N*=20 participants, two cesarean-section deliveries already reported were excluded (13).

Medication administration

Each dosing day, participants received study medication (14,15 see for medication details). Upon hospitalization, participants received study medication at the bedside by trained nursing staff.

Pain ratings were collected by nursing staff every 4–6 hours. Post-partum pain medications were ordered as per standardized hospital order sheets. The orders allow the following medications to be ordered on an as-needed basis: an acetaminophen 500mg/oxycodone 5mg combination product (AOxy; e.g., Tylox™) was provided every 4–6 hours as needed for relief of moderate to severe pain and ibuprofen 400 –600 milligrams (e.g., Motrin™) was provided for pain relief every 4 to 6 hours as needed for mild to moderate pain.

Measures

Using a numerical rating scale, respondents selected a number between 0 “no pain” and 10 “the worst pain imaginable” that best describes current pain intensity. The multiple daily pain ratings were averaged across each calendar day to yield a single pain rating value for each day. The administration of AOxy was converted to a binary variable (yes *v*. no) indicating the presence or absence of the daily receipt of AOxy because the range of AOxy doses provided was extremely restricted due to the limited number of doses that could be provided in a 24-hour period. As one participant from the buprenorphine and methadone group received intravenous morphine over two and one days, respectively, this potential dependent variable was not analyzed.

Statistical Analyses

Given the small sample size, α was set at .05 for each of the three analyses. Although this choice of an error rate increases the cumulative error rate, a more conservative rate would run the risk of failing to detect a small but potentially important difference between the mothers in the two medication groups. Moreover, the simplest possible suitable linear model was employed to conduct the analyses. The primary explanatory variable in the statistical model was the binary variable representing Medication Group (buprenorphine *v*. methadone); a repeated-measures factor, Day, (representing observation days 1–5) was included in the statistical model, as was the Medication Group × Day interaction. Estimation and tests of significance were conducted using a mixed model approach. This model assumed a normal distribution for pain ratings and Ibuprofen dose, and a binomial distribution for receipt of AOxy (yes *v*. no), a Huynh-Feldt error structure, and error degrees of freedom determined by the Satterthwaite’s method (sometimes leading to fractional error *df*). Model-derived least squares means are reported for pain ratings and Ibuprofen dose, while model-derived probabilities for receipt of AOxy are reported for AOxy administration.

Results

Sample characteristics

The participant’s (*N*=18) characteristics are shown in Table 1.

Pain Medication

Pain Ratings—There was a main effect for Day, $F(4, 64) = 21.44$. $p < .0001$; neither the main effect for Medication Group, $F(1, 19.3) = .01$. $p > .9$, nor the interaction of Medication Group × Day was significant, $F(4, 64) = .36$. $p > .8$. The pain ratings fell from a mean rating

of 4.43 on Day_1 to a mean rating of 1.18 on Day_5 (Table 2). An a posteriori, Scheffé-adjusted test (Scheffé critical $F = 10.06$) of the linear trend was significant, $F(1, 64) = 76.9$, while the test of deviations from linearity failed to reach significance, $F(3, 64) = 3.0$, indicating that the decrease in pain ratings declined in an orderly fashion over the time period in question.

Receipt of AOxy—Similar to the pain ratings results, there was a main effect for Day, $F(4, 59.9) = 7.86$. $p < .0001$; neither the main effect for Medication Group, $F(1, 13.9) = .15$. $p > .7$, nor the interaction of Medication Group × Day was significant, $F(4, 59.9) = .01$. $p > .9$. The model-estimated probabilities of receiving AOxy on Days 1–5 (Table 2) show a pattern similar to that found for pain ratings. An a posteriori, Scheffé-adjusted test (Scheffé critical $F = 10.10$) of the linear trend was significant, $F(1, 59.9) = 25.6$, while the test of deviations from linearity was not significant, $F(3, 59.9) = 1.6$, indicating that the probability of receiving AOxy, like the pain ratings, declined in an orderly fashion over the time period in question.

Ibuprofen Dose—Similar to the pain ratings and receipt of AOxy, the main effect for Medication was likewise non-significant, $F(1, 32.8) = 3.50$. $p > .07$; and, in contrast to the findings for both the pain ratings and receipt of AOxy, the main effect for Day was not significant, $F(4, 46.1) = .69$. $p > .6$. However, the Medication Group × Day interaction effect did emerge as significant, $F(4, 46.1) = 3.11$, $p < .03$. Inspection of the respective means for the two medications groups over Days 1–5 (Table 2 and Figure 1) reveals that while the buprenorphine and methadone groups began Day_1 with similar mean doses of ibuprofen (*M*s = 1725 *v*. 1740, respectively), the buprenorphine group decreased its ibuprofen use from 1725 mg to 1525 mg, on average, while the methadone group increased its ibuprofen use from 1740 mg to 2040 mg, on average.

Discussion

The present sample of buprenorphine- and methadone-stabilized pregnant patients has characteristics and average medication doses similar to other such participants in previously-published studies (16,17,18).

Results show overall pain scores in the mild range of the scale and an orderly decline in average daily pain ratings following the use of pain medications for both buprenorphine- and methadone-maintained groups are consistent with the results reported in methadone and non-drug addicted post-partum patients (8) using the same subjective pain scale. The pain rating scale used in this study has reliability and validity compared to other pain scoring methods (19).

Also consistent with previous data (8), opioid medication was more likely to be received in the first post-partum day and then decreasingly used over time. The present data suggests that opiate analgesics can and should be a routine component of acute pain management for agonist treated post-partum patients. While it could be expected that buprenorphine's high affinity for the μ receptor might complicate pain management with opioid medications, there is considerable individual variability in response to these medications and combination of medications, and the present results suggest that buprenorphine patients do respond to additional opioid medication given for pain control.

The result showing that the buprenorphine group decreased its ibuprofen use over time while the methadone group increased its average ibuprofen use while both groups showed similar average pain scores suggests that the methadone but not buprenorphine group required additional medication to maintain low pain ratings. The results showing more non-opioid

use in the methadone compared to the buprenorphine groups are similar to our previously reported results with pain-management following cesarean-sections (13), and are consistent with recent observations that full agonist exposure leads to allodynia by possibly creating a shift in mu-opioid receptor (MOR)-G protein coupling from G(i/o) to G(s). This outcome is prevented by co-administration with an ultra-low-dose opioid antagonist (20). Thus, it is possible that patients receiving buprenorphine experience less post partum pain and therefore need less analgesic medications to manage pain.

Several study strengths deserve mention. First, the average pain scores of both groups were mild and decreased over time. These results demonstrate the utility of providing NSAIDs and acetaminophen/oxycodone combination products for pain resulting from vaginal delivery in the immediate post-partum period. Second, all care components were performed within one hospital and by one group of medical practitioners. Third, the individualized dosing of methadone or buprenorphine ensured dose adequacy for each participant and suggests that, on average, additional pain medication needs in the methadone-maintained group were not a result of under-dosing of methadone in this group or the presence of epidural for pain control during labor and delivery.

Several study limitations merit discussion. First, data were collected as part of a secondary observational study. A prospective trial would yield results supporting stronger conclusions in regard to the most optimal methods for pain control for methadone- or buprenorphine-stabilized post-partum patients as compared to non-dependent controls. However, current results do support the use of this one treatment regimen for pain control in agonist-stabilized patients. Second, the sample sizes of the medication groups are modest and limit the power to detect differences. However, this limitation is tempered by the fact that differences in the expected direction were observed on pain and medication usage outcome measures. Third, while this sample is similar to other agonist treated pregnant samples (17,18) the extent to which these pain and pain medication usage outcomes following a vaginal delivery generalize to the larger population of methadone or buprenorphine maintained patients is unknown.

In summary, these results suggest that routine pain management protocols are effective in reducing pain in buprenorphine- or methadone-maintained patients following a vaginal delivery. However, pain control must be individualized because most opioid-dependent patients require greater than typical doses for pain management (21) and pain control appears dependent on the maintenance opioid-agonist medication used prior to and at delivery.

Acknowledgments

We are indebted to the patients who participated in this study. We also thank the following individuals and groups (listed alphabetically) for their assistance with this study: Gad Alpan; Behavioral Pharmacology Research Unit clinic, dispensary and pharmacy staff; Center for Addiction and Pregnancy staff; Christian A. Chisholm, Robin E. Choo, Robin Clay; Ed Cone; Michael Crocetti; Data Safety Monitoring Board members (J. T. Christmas, Joseph Collins, Paul Fudala, Charles Gorodetzky, Karol Kaltenbach, and Sidney Schnoll); Robert Dudas; Meade Eggelston; Joan Hamilton; Cheryl Harrow; Marilyn A. Huestis; Judy Jakubowski; Lauren M. Jansson; Donald R. Jasinski; Chuka Jenkins; Johns Hopkins Bayview Medical Center General Clinical Research Center staff, Johns Hopkins Bayview Medical Center Labor and Delivery, Michael Lantz; pediatric, NICU and A2West staff; Sherri Kacinko; Tim Mudric; Tina Robilotto; Jenna Schulcz; Patricia Suess, Martha Velez and Vickie Walters. Dr. Johnson is now employed by Reckitt Benckiser (the manufacturer of buprenorphine).

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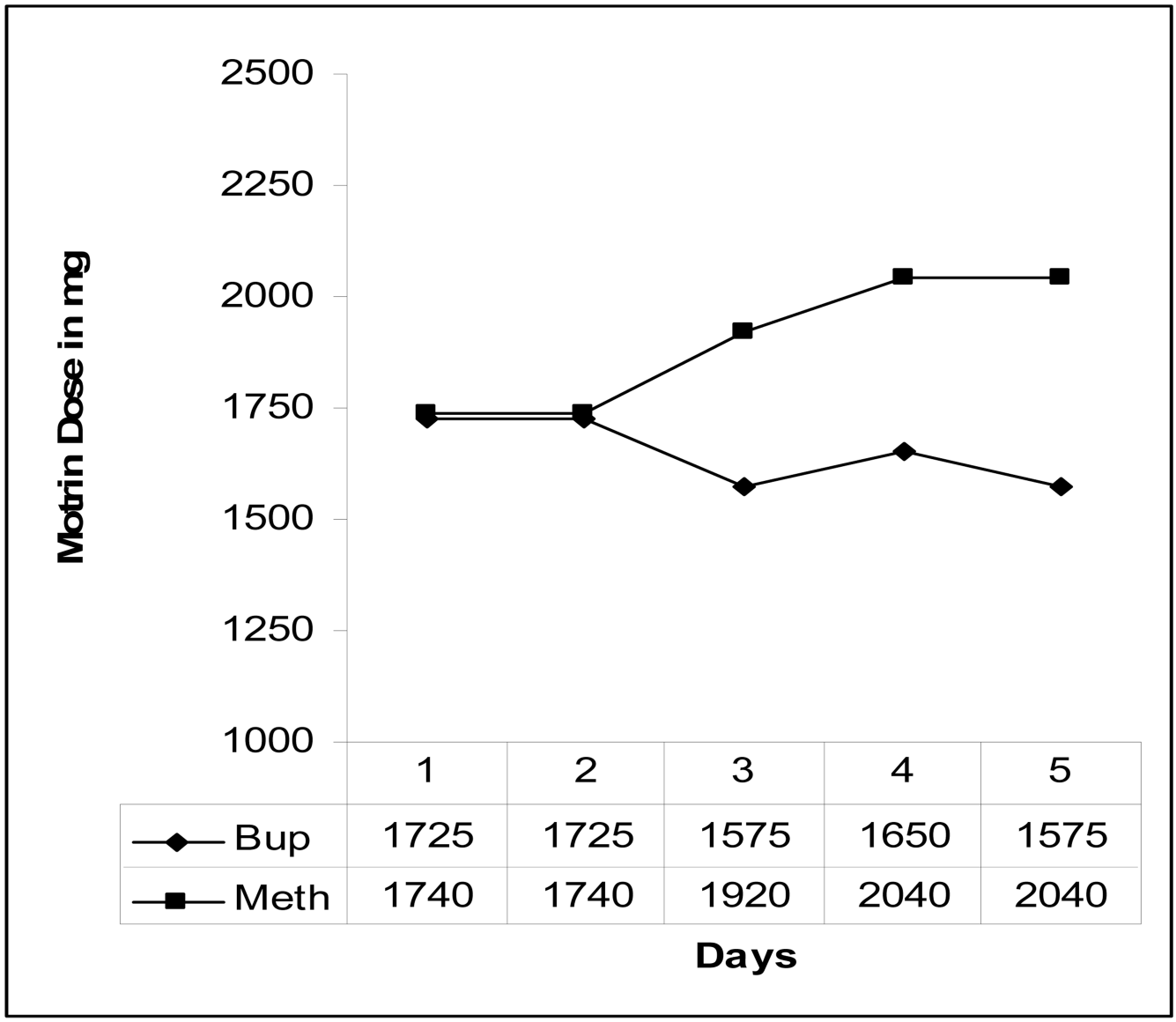

Figure 1.
The interaction between methadone and buprenoprhine maintenance and amount of Ibuprofen received each day.

Table 1

Sample Descriptive Statistics (*N*=18)

	Total Sample (*N* = 18)	**Buprenorphine Sample (*n* = 8)**	**Methadone Sample (*n* = 10)**	**Test Statistic $\chi^2(df)$ or $F(df, df)$**	***p***
Pre-Treatment Characteristics Mean (SD)					
Age (years) of mother	29.8(3.6)	29.6(3.4)	29.9(4.0)	$F(1,16) = .02$	.878
Years of education completed	10.8(1.5)	10.1(1.1)	11.3(1.6)	$F(1,16) = 3.17$	.094
Race					
White	4	1	3	$\chi^2(1) = .79$	.375
Black or other	14	7	7		
Marital Status					
Not-married	16	7	9	$\chi^2(1) = .03$	.867
Married	2	1	1		
Current employment					
FT homemaker	1	1	0	$\chi^2(2) = 2.55$	.279
Unemployed (seeking)	10	3	7		
Unemployed (not seeking)	7	4	3		
Total number of pregnancies					
3	2	1	1	$\chi^2(7) = 10.58$	.158
4	3	2	1		
5	3	1	2		
6	6	0	6		
7 or more	4	4	0		

	Total Sample (N = 18)	Buprenorphine Sample (n = 8)	Methadone Sample (n = 10)	Test Statistic $\chi^2(df)$ or $F(df, df)$	p
Cigarette smoking %	78	75	80	$\chi^2(1) = .06$	.800
Estimated gestational age (weeks) at time of prenatal care entry	22.6(4.0)	22.1(3.9)	22.9(4.1)	$F(1,16) = .16$	.693
Days of treatment in the study and CAP	105.7(29.2)	116.1(24.3)	97.3(31.2)	$F(1,16) = 1.96$	.181
Labor and Delivery					
Epidural received					
No	6	2	4	$\chi^2(1) = .45$	.502
Yes	12	6	6		
Estimated gestational age by last menstrual period	38.7(1.8)	38.9(1.6)	38.5(2.0)	$F(1,16) = .19$	.671
Maternal weight at delivery, in pounds	171.5(30.7) (N = 14)	171.0(28.7) (n = 6)	171.9(34.0) (n = 8)	$F(1,12) = .00$	.960
Dose of medication at delivery, in milligrams	---	18.8(3.7)	79.0(21.5)		
Positive drug screen for THC, mother at delivery*					
No	17	8	9	$\chi^2(1) = .85$	.357
Yes	1	0	1		

Note. Missing data occurred because weights were not obtained before delivery due to health care provider error.

*All other toxicological screens were negative at delivery.

Table 2

Model-derived Parameter Estimates for Pain Ratings, Receipt of AOxy, and Ibuprofen Dose (*N*=18)

Mean Pain Ratings					
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Day Main Effect	4.43(.36)	2.84(.56)	2.27(.55)	2.19(.46)	1.18(.35)
Probabilities for Receipt of AOxy					
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Day Main Effect	.89(.06)	.77(.11)	.27(.12)	.27(.12)	.16(.08)
Mean Ibuprofen Dose in milligrams					
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Medication × Day					
Buprenorphine	1725(96.5)	1725(119.0)	1575(123.4)	1650(151.3)	1575(139.9)
Methadone	1740(86.3)	1740(106.5)	1920(110.4)	2040(135.3)	2040(125.1)

Note. Results are not different if epidural status was included in the model.

Am J Drug Alcohol Abuse. Author manuscript; available in PMC 2010 August 23.