Estimated Dose Exposure of the Neonate to Buprenorphine and Its Metabolite Norbuprenorphine via Breastmilk During Maternal Buprenorphine Substitution Treatment

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Abstract

Objective: The aim of the present study was to estimate the dose of buprenorphine and its primary metabolite norbuprenorphine that a breastfed infant would receive during maternal maintenance treatment with buprenorphine.

Study Design: Seven pregnant opioid-dependent women taking buprenorphine (median, 7 mg/day; range, 2.4–24 mg) and who intended to breastfeed were recruited. After lactation was established, several milk samples were collected from each subject over a 24-hour dose interval, and buprenorphine and norbuprenorphine concentrations were measured by liquid chromatography–tandem mass spectrometry. The average concentration ($C_{avg}$) across the dose interval was estimated as for both buprenorphine and norbuprenorphine (as buprenorphine equivalents). Absolute infant dose (AID), defined as $C_{avg} \times$ daily milk intake, and relative infant dose (RID), defined as $100 \times$ AID/weight-adjusted maternal daily dose, via milk were calculated, assuming a milk intake of 0.15 L/kg/day. The infant’s health and progress were assessed directly and by questionnaire on the study day.

Results: Mean (95% confidence interval) norbuprenorphine concentration in milk and AID values (1.94 [0.79–3.08] µg/L and 0.29 [0.12–0.46] µg/kg/day, respectively) were approximately half those for buprenorphine (3.65 [1.61–5.7] µg/L and 0.55 [0.24–0.85] µg/kg/day, respectively). Similarly, the mean RID values were 0.18% (0.11–0.25%) for norbuprenorphine and 0.38% (0.23–0.53%) for buprenorphine. The breastfed infants showed no adverse effects, were all in good health, and were progressing as expected.

Conclusion: Thus the dose of buprenorphine and norbuprenorphine received via milk is unlikely to cause any acute adverse effects in the breastfed infant.

Introduction

Buprenorphine is a partial opiate agonist used for maintenance treatment of adults, including pregnant women addicted to opiates. It is initially metabolized by N-dealkylation to norbuprenorphine, primarily by hepatic cytochrome P450 3A4.1 Subsequently, both compounds are conjugated by uridine diphosphoglucuronosyl transferases (UGTs), with UGT1A1 and UGT2B7 primarily conjugating buprenorphine2,3 and UGT1A1 and UGT1A3 conjugating norbuprenorphine.4 In the context of this study, norbuprenorphine is of interest as rodent studies suggest that it has approximately 25% of the analgesic activity5 and approximately 10 times the respiratory depressant activity of buprenorphine.5

The aim of the present study was to estimate the dose of buprenorphine and its primary metabolite norbuprenorphine that a breastfed infant would receive during maternal maintenance treatment with buprenorphine. When we commenced this study in 2008, there was one published case report suggesting that infant exposure to buprenorphine and norbuprenorphine via milk was very low,7 and since then...
there has been a second report documenting similar low-dose exposure in six mother–infant nursing pairs. Our study essentially doubles the database available for assessment of the safety of buprenorphine use during lactation.

Subjects and Methods

Seven pregnant opioid-dependent women participating in a buprenorphine substitution treatment program were recruited in their third trimester from the Women and Newborn Drug and Alcohol Service antenatal clinic at the King Edward Memorial Hospital, Subiaco, WA, Australia. The women gave written informed consent to their participation in the study according to protocols approved by the Women and Newborn Services Ethics Committee (protocol number 1552/EW) and were intending to breastfeed. The women were visited at home 3 weeks after birth and provided with a sample collection kit consisting of labeled sample tubes, a data collection sheet, and information forms. The mothers were educated on sample collection and labeling procedures by the research assistant. The infants were weighed at this visit. Most of the women were taking buprenorphine daily, but one was on a twice-daily schedule. This mother arrived with her prescribing doctor to have her buprenorphine adjusted to daily to reduce the expressing commitment to 24 hours. The research assistant visited the women at home when advised of collection being completed to further check on the infant’s well-being, quality control sample collection, and documentation and to transport samples to the laboratory. The research assistant also recorded data on sleep patterns, advice provided on breastfeeding, and general impressions of the infant, mother, and home. Identified problems and referrals were also recorded. A 2-page questionnaire was delivered to the mother requesting information on the commencement of breastfeeding and duration of breastfeeding. Mothers were asked to rate their breastfeeding pattern as “all breastfeeds,” “nearly all breastfeeds,” “about half are breastfeeds,” or “only one breastfeed per day.” If mothers had ceased breastfeeding they were asked for the reason, and this was recorded in the questionnaire. The questionnaire also asked about any pharmacological treatment required for their baby. At this visit the women were paid $80 for their involvement in the study. Data were obtained on maternal age, weight, birth, and buprenorphine dose. Infant data included gestational age, 1-minute and 5-minute Apgar scores, evidence of the neonatal abstinence syndrome (NAS) in hospital and at follow-up, birth weight, and weight at follow-up and breastfeeding. The Modified Finnegan Scale was used to assess severity of NAS.

Reference standards of buprenorphine, buprenorphine-\(d_4\), norbuprenorphine, and norbuprenorphine-\(d_3\) were obtained from Cerilliant Corp. (Round Rock, TX). Buprenorphine and norbuprenorphine in milk (1 mL) were quantified by an ultra-performance liquid chromatography (UPLC)–electrospray interface–tandem mass spectrometry (MS/MS) assay. Unknown samples (1 mL each) and standards (1 mL each containing 0.0, 0.1, 0.25, 1, 2, 5, and 10 \(\mu\)g/L buprenorphine and norbuprenorphine) were spiked with 5 ng each of buprenorphine-\(d_4\) and norbuprenorphine-\(d_3\), alkalinized with 1 mL of 2% (wt/vol) \(\text{Na}_2\text{B}_4\text{O}_7\), and extracted into 10 mL of diethyl ether (catalog number 1.00926.5000, Merck Chemicals Australia, Kilsyth, VIC, Australia) by shaking vigorously for 5 minutes. After centrifugation at 1,500 \(g\) for 5 minutes, the diethyl ether layer was back-extracted into 1.5 mL of 0.05 M HCl by shaking for 2 minutes. After centrifugation as above, the HCl layer was aspirated, mixed with 1 mL of 2 M \(\text{NH}_3\text{COOCH}_3\) (adjusted to pH 9.2), and extracted into 10 mL of diethyl ether as above. After centrifugation, the diethyl ether layer was evaporated to dryness under a stream of \(\text{N}_2\) and reconstituted in 0.1 mL of the mobile phase, and 7-\(\mu\)L aliquots were injected onto the UPLC-MS/MS system. Assays used an Agilent Zorbax Eclipse XDB-C18 narrow-bore (2.1-\(\times\)150-mm; particle size, 5\(\mu\)m) column (Agilent Technologies Australia, Forest Hill, VIC, Australia) with a mobile phase of 30% (vol/vol) \(\text{CH}_3\text{CN}\), 30% (vol/vol) methanol, and 40% (vol/vol) 4\(\times\)3 m aqueous \(\text{NH}_3\text{COOCH}_3\) (previously adjusted to pH 3.2 with acetic acid) and pump rate of 0.25 mL/minute.

Analyses were performed using a Waters Acquity UPLC apparatus (Waters Corp., Milford, MA) coupled to a Waters Quattro Premier XE MS/MS instrument running in electrospray interface (electrospray ionization positive) mode. Under these conditions, buprenorphine and norbuprenorphine had retention times of 1.6 and 2.3 minutes, respectively. Data acquisition and processing were carried out using the Waters Masslynx and Quanlynx software. The \(m/z\) transitions used were from 468 to 468 for buprenorphine, 472 to 472 for buprenorphine-\(d_4\), 414 to 414 for norbuprenorphine, and 417 to 417 for norbuprenorphine-\(d_3\). For milk the intra-day relative SD (RSD) values at 0.25 \(\mu\)g/L and 10 \(\mu\)g/L were 6.4% and 7.4%, respectively, for buprenorphine and 3.7% and 1.8%, respectively, for norbuprenorphine (\(n=5\)). Similarly, for milk the inter-day RSDs at 0.25 \(\mu\)g/L and 10 \(\mu\)g/L were 6.1% and 7.8%, respectively, for buprenorphine and 3.7% and 2.6%, respectively, for norbuprenorphine. The limit of quantification (RSD <20%) for both analytes in milk was 0.1 \(\mu\)g/L. Correlation coefficients for the individual standard curves were 0.997 or better, and no interferences were found in blank milk samples. Quality control sample(s) were included with each batch of assays and had to be within ±15% of the nominal value for the batch to be accepted.

The milk concentration–time datasets were subjected to noncompartmental pharmacokinetic analysis using Topfit version 2.0 to calculate area under the curve (AUC) for 0–24
hours and average concentration ($C_{\text{avg}}$), defined as AUC for 0-24 hours/24, across the 24-hour dose interval. All norbuprenorphine AUC and $C_{\text{avg}}$ data have been reported as “buprenorphine equivalents” after multiplying the raw concentration data from UPLC-MS/MS by the molecular weight ratio of buprenorphine/norbuprenorphine (467.6/413.6 = 1.1306). Milk creatocrit was measured as previously described, and absolute infant dose (AID), defined as $C_{\text{avg}} \times$ daily milk intake, and relative infant dose (RID), defined as $100 \times$ AID/weight-adjusted maternal daily dose, via milk were calculated according to the method of Bennett, assuming a milk intake of 0.15 L/kg/day. Differences in median milk buprenorphine (µg/L), norbuprenorphine (µg/L), and creatocrit (%) between paired fore-milk and hind-milk samples were examined using Wilcoxon’s Rank Signed test (SigmaPlot version 11.0, Systat Software Inc., San Jose, CA). Results are summarized as mean (95% confidence interval or range) or median (range or interquartile range) as appropriate.

**Results**

The characteristics of the mothers and their infants are summarized in Tables 1 and 2. The mothers’ mean age was 31 years, with a mean weight of 72.8 kg. Three births were by cesarean section, whereas the others were spontaneous vaginal deliveries. Median sublingual buprenorphine dose was 7 mg, with a range from 2.4 to 24 mg once daily. The urine drug screen conducted on the study day revealed that two subjects were negative for all drugs, whereas another two were negative for amphetamines, opiates, and cocaine, two were positive for benzodiazepines, and four were positive for THC. Their infants were four girls and three boys, with normal Apgar scores. Three infants required transfer to a special Level 2 nursery. Four infants had NAS scores of 9 and above, but only one required pharmacological treatment with morphine. On discharge from the hospital, five infants were exclusively breastfed, and two were supplemented with formula. At follow-up two had NAS scores of 2, and one had a score of 8. The mean age and weight were 1.12 months and 4.32 kg, respectively, on the study day. All were tracking according to their expected weight-for-age percentiles from birth to the study day and were exhibiting normal sleep patterns. All mothers indicated that their infants were progressing well at the time of study, although one mother expressed concern about loose stools, and a second mother expressed concern about constipation. One infant was still being treated with morphine at 5 weeks of age. All mothers were coping well and confident with mothercrafting. Four mothers reported they were exclusively breastfeeding at follow-up, whereas two were supplementing with formula but reported they were breastfeeding for the majority of feeds. One mother reported she was breastfeeding approximately half of all feeds. However, this mother received help with lactation and was breastfeeding for the majority of feeds some weeks later.

The concentrations of buprenorphine and norbuprenorphine (raw data from UPLC-MS/MS) in milk samples collected for the individual mothers across the 24-hour dose interval are shown in Figure 1A and B, respectively. Table 3 summarizes the $C_{\text{avg}}$ milk concentrations achieved as well as the AID and RID for buprenorphine and norbuprenorphine (as buprenorphine equivalents; see Subjects and Methods). Mean norbuprenorphine $C_{\text{avg}}$ in milk (1.94 µg/L) and its mean AID (0.29 µg/kg/day) values were approximately half those for buprenorphine (3.65 µg/L and 0.55 µg/kg/day, respectively). Similarly, even after normalization to maternal dose, the mean RID values were 0.18% for norbuprenorphine and 0.38% for buprenorphine. When buprenorphine and norbuprenorphine (as buprenorphine equivalents) $C_{\text{avg}}$ milk concentrations were summed and normalized per 10 mg of daily buprenorphine dose, the mean (95% confidence interval) data were 6.0 (4.9–7.1) µg/day/L x 10 mg.

The mean maximum concentration ($C_{\text{max}}$) of buprenorphine in milk was 9.1 (4.8–13.4) µg/L at 4.2 (2.1–6.3) hours after dosing, whereas for norbuprenorphine (as buprenorphine equivalents) the maximum concentration was 2.1 (0.9–3.3) µg/L at 4.0 (2.1–5.8) hours after dosing. If the later $C_{\text{max}}$ concentrations are used for infant dose assessment, one obtains AIDs of 1.4 (0.7–2) µg/kg/day and 0.32 (0.14–0.5) µg/kg/day for buprenorphine and norbuprenorphine, respectively, and RIDs of 1.21 (0.66–1.75%) and 0.25 (0.19–0.3%) for buprenorphine and norbuprenorphine, respectively.

Four patients contributed data from which drug concentrations in paired fore-milk and hind-milk samples could be compared using the Wilcoxon Rank Signed test (paired sample analysis, n = 16). Subjects 2 and 6 contributed five samples each, subject 3 contributed four samples, and subject 4 contributed two samples. For buprenorphine, the median (interquartile range) concentration (1.8 µg/L [1.3–6.2 µg/L]) in fore-milk was not significantly different from that (1.9 µg/L [1.6–6.1 µg/L]) in hind-milk. Similarly, for norbuprenorphine,

<table>
<thead>
<tr>
<th>Study number</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Birth</th>
<th>Buprenorphine dose (mg/day)</th>
<th>Drug screen result$^a$</th>
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<tbody>
<tr>
<td>1</td>
<td>27.4</td>
<td>62.4</td>
<td>SVD</td>
<td>10</td>
<td>THC</td>
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<td>SVD</td>
<td>24</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>4</td>
<td>26.8</td>
<td>66.3</td>
<td>CS</td>
<td>6</td>
<td>THC, benzodiazepines</td>
</tr>
<tr>
<td>5</td>
<td>34.7</td>
<td>70.4</td>
<td>CS</td>
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</tr>
<tr>
<td>6</td>
<td>35.9</td>
<td>68</td>
<td>SVD</td>
<td>6</td>
<td>THC</td>
</tr>
<tr>
<td>7</td>
<td>30.9</td>
<td>73.9</td>
<td>SVD</td>
<td>7</td>
<td>THC</td>
</tr>
<tr>
<td>Mean (range)</td>
<td>31 (27.4–35.9)</td>
<td>72.8 (62.4–100.4)</td>
<td>7 (2.4–24)$^b$</td>
<td></td>
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</tbody>
</table>

$^a$Screen by immunoassay for amphetamines, benzodiazepines, cocaine, opiates, and tetrahydrocannabinol (THC).

$^b$Median (range).

CS, delivery by cesarean section; SVD, spontaneous vaginal delivery.
the concentration (2.1 µg/L [0.6–3.2 µg/L]) in fore-milk also was not significantly different from that (2.1 µg/L [0.7–4.2 µg/L]) in hind-milk. However, there was also no significant change in median (interquartile range) creamatocrit values from fore-milk samples (6.3% [3.7–6.7%]) compared with hind-milk samples (6.2% [5.6–7.1%]).

Discussion

The urine drug screen results indicated that all subjects were, apart from buprenorphine, opiate-free. Benzodiazepines (not prescribed) were detected in two subjects, and four had used THC. In our experience, this pattern of drug use is typical of opiate-dependent mothers maintained on buprenorphine.

Drug transfer into milk occurs primarily by passive diffusion, and lipid solubility of the drug and co-transfer in milk lipid are important factors in this process. The lack of any increase in buprenorphine or norbuprenorphine concentrations in hind-milk versus fore-milk was unexpected. Nevertheless, our opportunity to detect any such increase was limited by the similarity of the fat content (creamatocrit) in the fore-milk versus hind-milk samples. We have no explanation for the lack of increase of creamatocrit in hind-milk samples.

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There was wide inter-subject variability in milk $C_{avg}$. This was 10.3-fold for buprenorphine (range, 0.83–8.27 µg/L) and
TRANSMISSION OF BUPRENORPHINE IN BREASTMILK

Table 3. Values for Average Concentration in Milk, Absolute Infant Dose, and Relative Infant Dose of Buprenorphine and Norbuprenorphine

<table>
<thead>
<tr>
<th>Study number</th>
<th>Milk C\text{avg} (\mu g/L) over 24 hours</th>
<th>Absolute infant dose (\mu g/kg/day)</th>
<th>Relative infant dose\textsuperscript{b}</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Buprenorphine</td>
<td>Norbuprenorphine\textsuperscript{a}</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>1</td>
<td>6.75</td>
<td>2.34</td>
<td>1.01</td>
</tr>
<tr>
<td>2</td>
<td>1.75</td>
<td>2.44</td>
<td>0.26</td>
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<td>3</td>
<td>8.27</td>
<td>4.96</td>
<td>1.24</td>
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<td>4</td>
<td>2.3</td>
<td>1.59</td>
<td>0.35</td>
</tr>
<tr>
<td>5</td>
<td>0.83</td>
<td>0.45</td>
<td>0.12</td>
</tr>
<tr>
<td>6</td>
<td>2.9</td>
<td>0.60</td>
<td>0.44</td>
</tr>
<tr>
<td>7</td>
<td>2.76</td>
<td>1.18</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Mean (95% CI) 3.65 (1.61–5.7) 1.94 (0.79–3.08) 0.55 (0.24–0.85) 0.29 (0.12–0.46) 0.38 (0.23–0.53) 0.18 (0.11–0.25)

\textsuperscript{a}Expressed as buprenorphine equivalents.

\textsuperscript{b}Equal to absolute infant dose as a percentage of daily weight-adjusted maternal dose (which was calculated in \mu g/kg/day from data in Table 1).

\text{C\text{avg}} average concentration, CI, confidence interval.

11-fold for norbuprenorphine (range, 0.45–4.96 \mu g/L) as illustrated in Figure 1 and the corresponding data in Table 2. Nevertheless, when the C\text{avg} data were expressed per 10-mg buprenorphine dose (mean [range] of 4.0 [1.75–6.75] \mu g \times \text{day}/L \times 10\text{mg} for buprenorphine and 2.0 [2.44–0.99] \mu g \times \text{day}/L \times 10\text{mg} for norbuprenorphine), it is clear from the reduced spread in the dose-normalized data (3.9-fold for buprenorphine and 2.5-fold for norbuprenorphine) that dose accounts for a large proportion of inter-subject variability in milk C\text{avg}. The residual variability in milk C\text{avg} presumably represents the true between-subject variability plus that due to unexplained sources. A limitation of our study is the use of an estimated value of 0.15 L/kg/day for infant milk intake, which may have reduced both inter-subject variability in both measured drug concentrations and in estimates of infant dose.

The mean AID of 0.55 \mu g/kg/day for buprenorphine was almost twice that of 0.29 \mu g/kg/day for norbuprenorphine. However, there is no pediatric dose available for comparison, as use of buprenorphine in children is not recommended because of lack of clinical safety and efficacy data in patients under 18 years of age. The mean RID values of 0.38% and 0.18% for buprenorphine and norbuprenorphine, respectively, are well below the 10% limit\textsuperscript{13} below which breastfeeding is acceptable for many drugs. Our data are similar to those of Lindemalm et al.,\textsuperscript{5} who reported a median AID of 0.42 \mu g/kg/day and 0.33 \mu g/kg/day and median RID of 0.2% and 0.12% for buprenorphine and norbuprenorphine, respectively, in six mother–infant pairs. This confirmation is encouraging, given that the infants in the latter study were only 5–8 days old and were studied in a maternity ward where it was possible to measure the daily milk intake for each infant and thus individualize the calculation of infant dose. In addition, our data also compare with the AIDs of 0.77 \mu g/kg/day for buprenorphine and 0.08 \mu g/kg/day for norbuprenorphine and RIDs 1.3% for buprenorphine and 0.14% for norbuprenorphine, which can be calculated (assuming infant weight of 4.25 kg and maternal weight of 70 kg) from the dose and drug concentration data from the single case reported by Marquet et al.\textsuperscript{7} The buprenorphine and norbuprenorphine concentrations we measured in milk were also within the range reported in one subject over a 4-day period.\textsuperscript{20} However, these authors did not report infant dose estimates.

When C\text{max} concentrations of buprenorphine or norbuprenorphine in milk were used to calculate AID and RID, as the worst case scenario for potential infant exposure, mean AID for buprenorphine increased 2.5-fold to 1.4 \mu g/kg/day, and mean RID increased 3.2-fold to 1.2%; AID and RID for norbuprenorphine were virtually unchanged. The increased exposure to buprenorphine (assessed as RID) at the time of C\text{max} is still well within the usual safety margin (exposure <10%). It is our view that the use of C\text{avg} in calculation of infant dose best reflects infant exposure across the whole dose interval.

Our data show that RIDs (calculated using C\text{avg}) for both buprenorphine and norbuprenorphine combined are less than 1% of the maternal weight-adjusted dose and support the inference that this amount of exposure by mouth is unlikely to be a cause of adverse effects in the breastfed infants. In agreement with a previous study\textsuperscript{6} the limited assessment of the breastfed infants in our study found no drug-related adverse effects and satisfactory developmental progress. However, we note that only four of the seven infants were exclusively breastfed, as this would limit our ability to detect adverse effects. Our study essentially doubles the database available for assessing the infant dose of buprenorphine use during lactation. There are also several observational short-term studies showing that breastfeeding while taking buprenorphine as a maintenance treatment causes no adverse effects in the breastfed infant, although a mild abstinence syndrome is sometimes seen in the first few weeks after birth.\textsuperscript{2,5,6,19} Nevertheless, the amounts of buprenorphine and norbuprenorphine in milk are not sufficient to prevent withdrawal.\textsuperscript{2,19}

Conclusions

We conclude that the dose of buprenorphine and norbuprenorphine that a breastfeeding infant receives via milk is generally less than 1% of the weight-adjusted maternal dose and unlikely to cause any acute adverse effects in the infant. The possibility that long-term developmental outcomes might be affected by infant exposure to these drugs in milk cannot be excluded, and future studies on this topic are desirable. Nevertheless, mothers receiving sublingual buprenorphine maintenance treatment should be encouraged to breastfeed as there are many benefits of breastmilk for their infants.\textsuperscript{22} Regular clinical assessment of infants in this population is
recommended to ensure that any adverse effects to prescribed medications and/or other drugs used by their mothers are minimized.

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Disclosure Statement

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References


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