The wellbeing of infants exposed to Buprenorphine via breast milk at 4 weeks of age

Well Established

Infants born to mothers maintained on buprenorphine may experience less severe Neonatal Abstinence Syndrome (NAS) compared to those born to mothers maintained on methadone.

Low levels of buprenorphine are transferred from mother to baby via breast milk.

Newly Expressed

Babies in this study exposed to buprenorphine via breast milk appear to have progressed normally over the first four weeks postnatally, maintaining appropriate weight and sleep routines.

Abstract

Background: Buprenorphine has been available in Australia since 2000 as an alternative pharmacotherapy to methadone for the treatment of opioid dependence. However, there is little information in the literature regarding the effect of buprenorphine on the well-being of infants exposed to buprenorphine via breastmilk, following discharge from hospital.

Objective: The aim of the present study was to examine the wellbeing of infants exposed to buprenorphine via breast milk up to four weeks postnatally.

Methods: Approximately four weeks after birth, information on the feeding and sleeping patterns, skin colour, infant elimination patterns and hydration, and Neonatal Abstinence Scores of infants (n=7) exposed to buprenorphine via breast milk, were collected via both observation and documentation.

Results: Infants were progressing well, with normal sleep patterns and skin colour, and two mothers had minor concerns regarding infant elimination patterns. Four infants were exclusively breastfed and three were receiving supplement, with a range of 260ml-700ml of formula over 24 hours. The sleep patterns following feeding ranged from 1.55 hours to 3.33 hours, with a median of 2.12 hours.

Conclusion: No adverse effects were detected in infants exposed to buprenorphine via breastmilk up to four weeks postnatally. Further research using larger samples to assess possible developmental effects over longer periods of time is required.

Background

In Australia the two main types of pharmacotherapy for treatment of opioid dependence are methadone (available since 1969) and buprenorphine (available since 2000). Buprenorphine is a partial opiate receptor agonist with a long half-life and mild withdrawal profile. It produces opiate-like agonist effects whilst at the same time preventing withdrawal and reducing craving for opiates by antagonist actions at μ opiate receptors. It is taken sublingually. Norbuprenorphine is a major metabolite of buprenorphine and animal studies indicate that it makes a significant contribution to the opioid receptor actions of buprenorphine. [1, 2]

Two buprenorphine products are registered in Australia for the treatment of opioid dependence. These are a product containing only buprenorphine (Subutex®), and a combined product containing buprenorphine and naloxone (Suboxone®).[3] Buprenorphine has been ascribed a Lactation Risk category of L3, (i.e. moderately safe), largely on the basis that there are no controlled studies on breastfeeding. [4] Buprenorphine in either form is not recommended for use during pregnancy and breastfeeding in Australia. In the event that an opioid dependent woman becomes pregnant whilst on buprenorphine they are advised to transfer to methadone. Nevertheless, some women choose to remain on buprenorphine.

A number of studies have compared buprenorphine to methadone in terms of neonatal outcomes and Neonatal Abstinence Syndrome (NAS) and have concluded that buprenorphine has a less severe NAS and neonatal outcomes in the normal range. [5-8] Following therapeutic doses of buprenorphine, others have examined the concentrations of buprenorphine and norbuprenorphine in the foetal circulation at birth [9], and reported low levels of transfer from mother to infant. We have previously reported the estimated dose exposure of the neonate to buprenorphine and its metabolite norbuprenorphine via breastmilk. [10] Overall, these results

suggest that the therapeutic dose would be unlikely to cause any adverse effect to the infant. [10] Only one previous case study has examined the buprenorphine levels contained in breastmilk at 4 weeks after birth[11]. All other studies examining buprenorphine concentrations in breast milk have been undertaken in the first two weeks of life. [12-15] As such, little is known of how breastfeeding infants of mothers receiving buprenorphine fare after separation from hospital.

The aim of the present study was to examine the effect on the well-being of infants exposed to buprenorphine via breast milk up to four weeks postnatally.

Methods

The study was approved by the Women and Newborn Services Ethics Committee of King Edward Memorial Hospital (Ref. no. 1552/EW). The methodology has been fully described previously. [10] Participants were recruited from women attending the Women and Newborn Drug and Alcohol Service antenatal clinic at King Edward Memorial Hospital, Perth, Western Australia. Opioid dependent women were recruited if they were being treated with buprenorphine and were intending to breastfeed. The women were treated with doses between 2.4 – 24 mg once per day, with a median dosage of 7 mg of buprenorphine per day. All women gave written informed consent to their participation in the study and all were taking buprenorphine sublingually (Subutex®).

Descriptive data on length of gestation, APGAR scores at 1 minute and 5 minutes, birth weight, head circumference, length, admissions to the special care nursery, treatment required and perinatal NAS scores were obtained from medical records. The NAS scores provided represent the highest NAS score recorded during the infants' stay in hospital. These data are summarised in Table 1 and have been reported previously. [10]

Three weeks after birth, infants were weighed at a post natal home visit and data were collected on progress in breastfeeding since birth. This included current feeding status, dates of cessation of breastfeeding if relevant and reasons for cessation of breastfeeding. Mothers were asked to describe their baby's feeding pattern by choosing from *Only one breastfeed per day, About half feeds are breastfeeds, Nearly all feeds are breastfeeds, occasional formula* and *All breastfeeds.* Data on supplements provided to infants other than formula were not collected. Breastfeeding problems such as perceived low supply were also documented. Weight and sleeping patterns formed the primary data collected at this visit. Infants were weighed using a Medela Babyweigh ™ Scale, model 040.7012 (Medela Inc., McHenry, IL, USA). Sleeping patterns were recorded over a 24 hour period by the mother. Data were also collected on general infant well-being measures such as skin colour and infant elimination patterns. We are not aware of any evidence relating to skin colour or hydration issues attributed to buprenorphine exposure. Colour was assessed visually with a view to identifying skin mottling, an indicator of Neonatal Abstinence Syndrome. As the research assistant only visited the mother for a period of up to 2 hours it was not possible to assess elimination patterns formally. Elimination was assessed according to the mothers' accounts of urination and stooling patterns, and any particular concerns of the mothers were noted. Infants were assessed for NAS using the modified Finnegan Scale.[10, 16] Mothers were requested to choose a 24 hour period in the ensuing week during which they would collect expressed breastmilk at each breastfeed and record the sleeping and feeding routines of their infants. The 24 hour time period began with the breastfeed immediately preceding the morning dose of buprenorphine. Documentation and breastmilk collection methods were explained to the mothers and equipment for milk collection was provided. Mothers expressed milk manually. The levels of buprenorphine found in the breast milk have been reported previously. [10]

The research assistant visited the women at home again approximately one week later to further document the infants' weight, visually assess skin colour, and obtain mothers' descriptions of elimination patterns. Assessments were made for NAS, and records of sleeping and feeding routines were collected. Mothers provided a urine sample at this visit which was later screened for illicit drugs other than buprenorphine in pathology laboratories at Sir Charles Gairdner Hospital, a Western Australian tertiary hospital. Two mothers were negative for all drugs, another two were negative for amphetamines, cocaine and opiates, two were positive for benzodiazepines, and four were positive for tetrahydrocannabol (cannabis).

Data Analysis

Due to the small number of participants in this study, this article reports descriptive data on each of the infants.

Results

Twenty women were approached for this study and initially 15 agreed to participate. Eight women became ineligible after birth as they chose not to breastfeed, withdrew consent, or could not be contacted. The final number of participants in the study was seven. The median gestational age of the infants was 39 weeks. The infants had normal Apgar scores at one and five minutes and the median birth weight was 3.13 kilograms which is less than the Australian mean birth weight of 3.37 kilograms [17], but within normal limits. The median (range) infant head circumference was 35 (34-37) cm and median length was 49 (48-55) cm. Four infants out of seven received a NAS score of eight or higher during the perinatal period, with two of those scoring 15 or above. A score equal to or greater than eight for three consecutive scorings indicates the need for pharmacologic management. One of the infants with NAS $\geq$15 had a generalised sepsis which was treated with antibiotics and resolved before discharge. The other was treated with morphine which is the current preferred

treatment in Australia [18, 19]. The mean peak in NAS scores was at 2.5 days following birth. Three of these infants were admitted to a special Level 2 nursery, although only one required pharmacological treatment with morphine. This infant was still being treated with morphine on discharge from hospital. At discharge, five infants were exclusively breastfed and two were supplemented with formula. Table 1 summarises infant characteristics at birth and follow-up.

Infant wellbeing was assessed in terms of weight gain, sleeping patterns, skin colour and elimination and hydration patterns. When visited at three weeks postnatally, the median weight gain from birth was 1.19 kilograms. Sleep patterns and the relationship between breastfeeding and sleeping were recorded by the mothers over the 24 hours of data collection and results are contained in table 1. The longest duration of sleep recorded following breastfeeding was 3.33 hours. Over a twenty four hour period, the highest number of hours slept was 20 hours. Skin colour was assessed to be healthy, although some mottling was observed in one infant. One mother expressed concern about loose stools and a second mother expressed concern about constipation. Despite these concerns, all mothers indicated that their infants were progressing well at the time of the study. There were no signs of dehydration and infants were exhibiting normal stooling patterns. All infants were maintaining weight at or above the birthweight percentile.

One infant with NAS was still being treated with morphine at five weeks of age. None required referral to other health professionals, although two mothers intended to visit the Child Health Nurse for advice on immunisation and this was reinforced by the research assistant. Four infants were being exclusively breastfed at four weeks postnatally. The

remaining three were supplemented with formula with amounts ranging from 260-700 mL per day, although one mother received help with lactation from the visiting midwife and when contacted some weeks later on a different matter pertaining to the study, reported she was breastfeeding for the majority of feeds. One mother was receiving support from the breastfeeding centre at King Edward Memorial Hospital. Two mothers were encouraged to contact the King Edward Memorial Hospital breastfeeding clinic or the Australian Breastfeeding Association for further support with breastfeeding.

Discussion

This study contributes to the body of knowledge around the effect on infant wellbeing of exposure to buprenorphine, with a particular focus on the first month after birth. At four weeks of age, four out of seven infants (57%) in this study were exclusively breastfed. This is lower than the 71% of infants in the general population of Australia exclusively breastfed at one month of age [20], but is higher than that reported in a study of mothers of infants with NAS syndrome, where only 25% of eligible mothers chose to breastfeed and more than half stopped within one week.[21] The World Health Organisation recommends six months of exclusive breastfeeding for infants. [22] However, in the general Australian population, only 14% of infants are fully breastfed at six months of age. [20] In one Australian study of 152 illicit drug users, the mean duration of breastfeeding for illicit drug users has been reported to be eight to ten weeks. [23]

There are several observational short-term studies reporting that breastfeeding whilst 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. [11, 24-28] In the current study, peak NAS scores occurred at a mean of 2.5 days following birth, which concurs with previous studies. [25, 26] The lack of adverse infant effects associated with

breastfeeding over the first weeks following birth is supported by the findings of this study which found that by four weeks of age the highest NAS score was eight, with all other babies scoring at very low levels. Treatment should begin within two to four hours if the total score over two consecutive scorings is twelve or higher. Whilst in hospital, one infant received a NAS score of 20, but was also suffering from an infection requiring antibiotics at the time. Another infant scored 15 and was treated with morphine in hospital.

At four weeks of age, the median weight of infants was 4.32 kilograms, with a mean weight gain from birth of 1.19 kilograms. All infants were within the recommended weight quintiles for their age. [29]

Infant elimination and hydration patterns were explored verbally with the mothers. There is acknowledged variability in the frequency of stooling in infants. [30] However, despite minor concerns, mothers in this study reported their infants were exhibiting normal elimination patterns, producing clear or pale yellow urine between six and eight times per day [31] and yellow seedy stools at least once every three days. [32] The constipation reported by one mother may have been associated with the introduction of a formula supplement as the differences in fat digestion and absorption between breast milk and formula can result in harder stools. [33, 34] Despite these concerns, infants were settled and feeding well, with all infants receiving some proportion of their feeds as breast milk. Four mothers had received or intended to seek help from breastfeeding support services for assistance with breastfeeding issues. Seeking advice and support indicates the mothers' resolve to continue at least some form of breastfeeding. The mothers also demonstrated other appropriate mothercrafting skills, with all mothers demonstrating acceptable levels of confidence in their handling of the baby, anticipating the baby's needs and recognising the baby's cues.

Sleeping patterns recorded by the mothers revealed the median number of hours slept per 24 hour period to be 15 hours. There is an acknowledged wide range of normal sleeping behaviour in infants in the first three months of life when neurological systems remain immature and limit infants' capacity to regulate sleep [35, 36]. However, despite concerns with infant sleep being one of the most common complaints among new parents [36], none of the mothers in the current study raised concerns about frequent waking of their infants.

The strength of this study is that it adds to the sparse data on infants exposed to buprenorphine in utero and via breastmilk, [5, 10-14] and extends previous findings to the important first 4 weeks after discharge from hospital, during which time breastfeeding routines which have a lifetime effect are established .[37]

One of the limitations of this study is the small sample size. Only seven mothers participated although at recruitment antenatally 15 indicated that they intended to breast feed and agreed to be involved. Prenatal intentions have been reported to be one of the strongest predictors of initiation and duration of breastfeeding. [38] This did not appear to be the case for eight of the mothers approached to be in this study and the reasons for modifying their intentions after delivery are unclear. Another limitation is that the amount of breastmilk each infant consumed is unknown as they were not weighed before and after each feed. The short follow-up period must also be considered. Hence our findings need to be interpreted cautiously. A recent follow-up home visiting study of illicit drug using mothers and their infants reported that six months follow-up was too short, and recommended that well supported programs of much longer duration be considered. [23] The ideal would be a pathway of care and support that was sufficiently resourced and flexible to accommodate individual needs over varying periods of time.

During 2010, 46,078 opioid dependent Australians received pharmacotherapy, almost 70% with methadone, and the remainder with some form of buprenorphine. [39] Approximately 33% were female and the majority were of child bearing age. Hence it is likely that more pregnant women on buprenorphine will be required to make choices about their treatment during pregnancy and lactation. These women need evidence based information to guide them in their important decisions during this vulnerable period.

Breastfeeding confers considerable benefits to the newborn baby. These include nutritional, gastrointestinal, immunological and neurodevelopmental benefits to the baby and psychosocial benefits for the mother. [40-43] Improved cognitive skills, lower infection rates and impacts on behaviour have also been noted [40]. Before recommending that a mother not initiate or cease breastfeeding there must be good evidence that it poses a real risk to the infant.

Conclusions

Overall, results from this study are consistent with previous studies that report no adverse effects in newborns exposed to therapeutic dose of buprenorphine in utero and via breast milk. Infants followed for four weeks post separation from hospital were feeding well, following normal sleep patterns, and had good skin colour. Despite some minor concerns, the infants were exhibiting normal elimination patterns. Exposing infants to buprenorphine via breast milk over the first four weeks of life appears to be safe. However, it is possible there were other unmeasured adverse effects of buprenorphine, and therefore further research is required to assess the developmental trajectories and duration of breastfeeding of infants of women on buprenorphine maintenance treatment.

Funding and Conflict of Interest

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Permission

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TABLE 1. INFANT CHARACTERISTICS AT BIRTH AND FOLLOW-UP

Infant #	Gest-ation (weeks)	Sex	APGAR scores (1min, 5min)	Head Circ. (cm)	Length (cm)	Time in level 2 nursery (days)	NAS score in hos-pital	NAS score at follow-up	Age at follow-up (months)	Weight at birth[§] (kg (per centile))	Weight at follow-up[§] (kg (percentile))	Exclusive breast feeding	Mean sleep following breastfeed (hours sleep / # of feeds (hours))	Total sleep in 24 hours (hours)
1	39.6	M	9, 9	34	49	0	9	2	0.98	3.130 (10-25%)	4.322 (50-75%)	no (390mL)[♯]	1.86	13
2	39	F	9, 9	35	50	1	8	0	0.62	3.185 (25-50%)	3.930 (50-75%)	yes	3.33	20
3	38.1	F	9, 9	35	50	17	20*	2	0.58	3.180 (25-50%)	3.220 (25-50%)	yes	2.14	15
4	39.6	F	9, 9	34	48	14	15**	2	1.18	3.105 (10-25%)	3.652 (10-25%)	no (260mL)[♯]	2.12	17
5	40.5	M	7, 9	37	55	0	12	0	1.37	3.800 (50-75%)	5.048 (95%)	yes	2.71	16.25
6	39	M	9, 9	35	48	0	3	2	1.85	2.970 (10-25%)	5.500 (75%)	yes	1.78	12.5
7	38.4	F	9, 9	34	49	0	8	8	1.25	2.975 (10%)	4.606(50-75%)	no (700mL)[♯]	1.55	13
Median (range)	39.17 (38.1-40.5)	3M/ 4F		35 (34-37)	49 (48-55)	(0-17)	(3-20)	(0-8)	1.18 (0.58-1.85)	3.13 (2.98-3.8)	4.32 (3.2-5.5)		2.12 (1.55-3.33)	15 (12.5-20)

* infection requiring antibiotics, **morphine for NAS, [§]weight-for-age percentile, [□]approximate volume of formula supplement/day.

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