Methadone distribution and excretion into breast milk of clients in a methadone maintenance programme

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Aims Methadone is widely used in maintenance programs for opioid-dependent subjects. The aims of the study were to quantify the distribution and excretion of methadone in human milk during the early postnatal period and to investigate exposure of breast fed infants to the drug.

Methods Blood and milk samples were obtained from 12 breast feeding women who were taking methadone in daily doses ranging from 20–80 mg ($0.3–1.14\ \mathrm{mg\ kg}^{-1}$). Blood was also obtained from eight of their infants. Methadone concentration in these samples was quantified by h.p.l.c. The infants were observed for withdrawal symptoms.

Results The mean (95% CI) milk/plasma ratio was 0.44 (0.24–0.64). Exposure of the infants, calculated assuming an average milk intake of $0.15\ \mathrm{l\ kg}^{-1}\ \mathrm{day}^{-1}$ and a bioavailability of 100% was 17.4 (10.8–24) $\mathrm{\mu g\ kg}^{-1}\ \mathrm{day}^{-1}$. The mean infant dose expressed as a percentage of the maternal dose was 2.79 (2.07–3.51)%. Methadone concentrations in seven infants were below the limit of detection for the h.p.l.c. assay procedure, while one infant had a plasma methadone concentration of $6.5\ \mathrm{\mu g\ l}^{-1}$. Infant exposure to methadone via human milk was insufficient to prevent the development of a neonatal abstinence syndrome which was seen in seven (64%) infants. No adverse effects attributable to methadone in milk were seen.

Conclusions We conclude that exposure of breast fed infants to methadone taken by their mothers is minimal and that women in methadone maintenance programs should not be discouraged from breast feeding because of this exposure.

Keywords: methadone, human milk, milk:plasma ratio, neonatal abstinence syndrome, infant exposure

Introduction

The number of persons attending methadone maintenance clinics in Australia has increased from approximately 2000 in 1985 to more than 16 000 in 1995 [1]. A significant number of these are women of child bearing age who may wish to breast feed their infants. A recent retrospective study in New Zealand found that some 60% of mothers taking methadone were breast-feeding when discharged from hospital [2].

Methadone is a synthetic opioid drug used in maintenance programs worldwide for the treatment of opioid dependence. It is usually administered in a single oral dose each day. The drug has a half-life of around 27 h in tolerant individuals [3], and is metabolized in the liver by *N*-demethylation, ring cyclisation and conjugation [4]. The metabolites are excreted in the bile and urine [4]. Methadone is highly lipid soluble and 89% protein bound. It is a weak base with a pKa of 8.25, an octanol:water (pH 7.2) partition coefficient of 120 [5], and a molecular weight of 309.4. Predicted milk:plasma (M/P) ratios of around 0.65 [5] are supported by published data with M/P values ranging from 0.05 to 1.9 [6–9]. Current recommendations on breast-feeding during methadone therapy are based on four studies ($n=$ 14), which were published 11–23 years ago [6–9]. Although reviewers [10–12] generally have considered that breast feeding is safe during low dose methadone therapy (20 mg or less day^{-1}), there is one case report where methadone may have contributed to the death of an infant [13]. In addition, it has been suggested that the methadone dose requirement may need to be increased during pregnancy [6], and in recent years there has been a general move to the use of higher daily doses in methadone programs [14]. There is also acknowledgment that a Neonatal Abstinence Syndrome (NAS), which is known to occur in 60–90% of infants born to mothers taking methadone [7, 15–18], is not ameliorated by breast-feeding [2]. This suggests that the amount of methadone in milk is insufficient to maintain the methadone concentrations to which the foetus has been exposed *in utero*. In the present study we report new data characterizing the distribution/excretion of methadone in human milk in 12 women taking daily doses of methadone hydrochloride ranging from 20–80 mg in the early postnatal period. Eleven of their breast-fed infants were observed for signs of NAS during this time.

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Methods

Materials

Desipramine hydrochloride and methadone hydrochloride reference standards were obtained from Ciba-Geigy Australia Limited and Wellcome Australia Limited respectively.

Patients

Twelve breast-feeding women who were participants in a methadone maintenance program were enrolled in the study. Their mean age was 31 years (range 20–38 years) and their mean body weight was 63.1 kg (range 53–78 kg). They were maintained on a mean single daily oral dose of methadone hydrochloride (Methadone Syrup®; 5 mg ml^{-1}, Wellcome Australia Ltd) of 43.3 mg (range 20–80 mg). Their infants, who had a mean gestational age of 38.9 weeks (range 36–41 weeks) and a mean weight of 3.1 kg (range 2.37–3.78 kg) were a mean of 6.7 days (range 3–26 days) post partum at the time of the study. During the week following their birth, the infants were monitored every 4 h and assessed for withdrawal symptoms using a Neonatal Abstinence Syndrome (NAS) scoring system adapted from Finnegan *et al.* [19], and treated with phenobarbitone according to hospital guidelines when appropriate.

Study protocol

The study design was approved by the Research and Ethics Committees of the King Edward Memorial Hospital, Centre for Women's Health. Written informed consent was obtained from all participants. Two milk samples (10–20 ml) were collected using a manual breast pump, one immediately before and one after the infant was breast fed, and a mean methadone milk concentration obtained from these. A heparinized venous blood sample (6 ml) was obtained from the mother usually immediately following the post-feed milk sample. In eight cases, immediately following the final milk sample collection, a heparinized venous blood sample (0.5–1 ml) also was taken from the nursing infant. Breast milk sampling times were calculated from the time of last dose to the mid-point of the feed.

H.p.l.c. analysis of methadone in plasma and milk

Aliquots of plasma (1 ml) were mixed with desipramine (internal standard; 0.01 ml of a 16 mg l^{-1} solution in methanol) in 10 ml screw-capped disposable polypropylene tubes. NaOH (0.2 ml, 1 M) was added to the plasma and the samples were extracted with 9 ml of 1% v/v isoamyl alcohol in hexane by shaking vigorously for 5 min. After centrifugation (5 min at 1500 *g*), 8.5 ml of the organic phase was aspirated to a clean tube and back-extracted into 0.2 ml of 0.05 M HCl by shaking vigorously for 1 min. After further centrifugation, the organic phase was aspirated and discarded and 0.04 ml aliquots of the acid phase were injected directly onto the h.p.l.c. Unknown samples were interpolated from a linear plot of the peak height ratio for methadone : desipramine versus known concentrations of methadone in plasma. The plasma standard curve was linear

over the range 0.005–0.8 mg l^{-1} with a correlation coefficient of 0.999. The within-run coefficients of variation (CV) for the assay were 7.3% and 3.2% at 0.05 and 0.8 mg l^{-1} respectively ($n=8$). The inter-day CV was 5.5% at 0.4 mg l^{-1} ($n=8$). The limit of detection (peak height 3 × baseline noise) was 0.005 mg l^{-1} but was higher for some infant plasma samples where limited sample volumes were available. Aliquots of milk were analysed by the method of addition so as to avoid differential variation in recovery of methadone and desipramine which occurs when milk samples, having different lipid contents, are extracted. Internal standard (0.01 ml of a 16 mg l^{-1} solution of desipramine in methanol) was added to 1 ml aliquots of milk in 10 ml disposable polypropylene tubes. Each sample was assayed in triplicate with the addition of 50, 100, and 200 ng of methadone respectively. NaOH (0.2 ml, 1 M) was added to each tube and the samples were extracted as described for plasma above. For each individual sample a standard curve relating added methadone concentration and peak height ratio (methadone : desipramine) was constructed and the concentration of methadone in the sample was obtained from the x-axis intercept. The within-run CVs for the milk assay were 6.6 and 8.1% at 40 and 400 μg l^{-1} respectively ($n=5$).

H.p.l.c. analyses were carried out on a system comprising a GBC Model LC 1610 Autosampler, Waters 6000A Solvent Delivery System, Waters 486 Tunable u.v. absorbance detector and a Goerz Model SE120 BBC chart recorder. Analytes were separated on a Merck LiChrospher® 60, RP-Select B (5 mm × 250 mm) column using a mobile phase of 42% v/v acetonitrile in 0.01% w/v NaCl and 0.01% w/v H$_3$PO$_4$, pumped at a flow rate of 1 ml min^{-1}.

Calculation of infant dose

The absolute infant methadone dose was calculated from the average of the pre- and post-feed milk concentrations assuming an infant milk consumption of 0.15 l kg^{-1} day^{-1} [20], and a bioavailability of 100%. The relative dose of methadone, expressed as percentage of maternal dose received by a nursing infant, was calculated from the absolute dose × 100, divided by the maternal dose where both doses are expressed in mg kg^{-1} day^{-1}.

Statistical evaluation of data

Data have been summarized as mean (95% CI) or mean (range) as appropriate. Methadone concentration in pre- and post-feed milk samples were compared using a paired Student's *t*-test. Relationships between maternal plasma methadone concentration and the time after birth at which the NAS score was ≥8 on two subsequent 4 hourly observations, or when phenobarbitone treatment was started (shorter time interval used) were investigated by linear regression and correlation analyses.

Results

The daily maternal methadone dose ingested, methadone concentrations in maternal plasma and milk, and milk/plasma (M/P) ratios are shown in Table 1. Maternal daily

Table 1 Maternal methadone dose, concentrations of methadone in milk and plasma, and M/P ratio.

Patient	Methadone dose★ (mg kg^{-1} day^{-1})	Methadone concentration (μg l^{-1}) in Milk†	Plasma$^{\xi}$	M/P ratio
RA	0.30	65	155	0.42
LG	0.33	112	121	0.93
DM	0.38	52	164	0.32
LR	0.42	39	208	0.19
RP	0.52	49	375	0.13
JE	0.53	88	393	0.22
CW	0.67	82	204	0.40
DH	0.70	94	351	0.27
TI	0.70	197	165	1.19
EM	0.78	164	536	0.31
JM	0.92	218	603	0.36
KM	1.14	232	462	0.50

★as methadone base.

†average of pre- and post-feed measurements; mean sampling time 1.9 (1.0–2.8) h after last dose. Time of sampling calculated from the time of last dose, to the midpoint of the feed.

$^{\xi}$mean sampling time 2.8 (1.7–3.9) h after last dose.

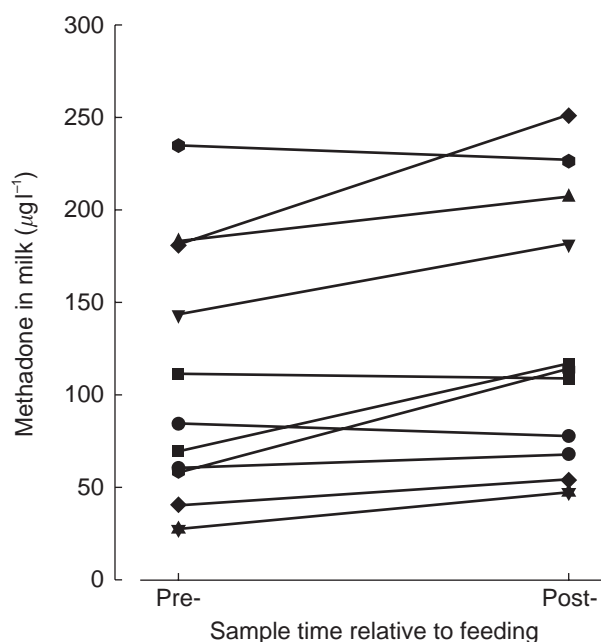**Figure 1** Concentration of methadone in pre- and post-feed milk samples from 11 patients.

dose varied over a 3.8-fold range. The mean concentrations (95% CI) for methadone in plasma and milk were 311 (207–416) μg l^{-1} and 116 (72–160) μg l^{-1} respectively, yielding a mean M/P ratio of 0.44 (0.24–0.64). In 11 of the patients, it was possible to assess the change in methadone concentration between the pre- and post-feed milk samples (Figure 1). The mean time between the two samples in these patients was 1.15 h (0.67–1.63). Overall, the post-feed milk methadone concentration was significantly ($P = 0.01$) higher, by a mean of 26 (7–43) μg l^{-1} or 33% (10–56%), than that in the pre-feed milk. Patient DM was excluded from the latter sub-analysis because her pre- and post-feed milk samples were obtained from two successive feeds that were 6 h apart.

Table 2 summarizes the demographic characteristics of the infants, doses of methadone consumed (absolute and relative to maternal dose), plasma methadone concentrations, as well as details of the occurrence of NAS. The mean absolute infant dose (methadone base) was 17.4 (10.8–24) μg kg^{-1} day^{-1}, while the mean relative infant dose as a percentage of maternal dose was 2.79 (2.07–3.51)%. Blood samples were collected from eight infants and plasma methadone concentration was below the assay limit in seven infants and measurable at 6.5 μg l^{-1} in the remaining infant. Of the twelve infants in the study, eight required observation in the Special Care Nursery. Seven (64%) were assessed as having NAS, and six of these required treatment (phenobarbitone) for their symptoms. There was no significant correlation or regression between time to NAS/phenobarbitone treatment and either maternal plasma methadone concentration, or estimated infant methadone dose in milk.

Table 2 Infant demographics, absolute and relative doses of methadone from milk, infant plasma methadone concentrations, and occurrence of abstinence syndrome.

Infant of patient	Gestation (weeks)	Gender/ Age (days)	Weight (g)	Methadone dose (μg kg^{-1} day^{-1})	% Maternal dose	Plasma methadone (μg l^{-1})	Abstinence syndrome (Y/N)
RA	38	M/4	2950	9.7	3.23	<15.0	Y
LG	36	M/7	3110	16.8	5.09	—	N
DM	40	M/5	3455	7.8	2.05	—	Y
LR	40	M/4	3180	5.9	1.40	<30	N
RP	39	F/4	2490★	7.4	1.42	<5	Y
JE	39	M/4	3580	13.2	2.49	6.5	N
CW	37	M3	2370★	12.3	1.84	—	N
DH	38	F/5	2690	14.1	2.01	<10	Y
TI	40	M/26	3630	29.6	4.23	—	N
EM	41	M/5	3780	24.6	3.15	<5	Y
JM	39	F/7	2680	32.7	3.55	<25	Y
KM	40	F/6	3325	34.8	3.05	<20	Y

★small for gestational age.

Discussion

In this particular group of women, who were inpatients and in the early post partum period (with the exception of TI), there were logistic difficulties in obtaining multiple paired plasma and milk samples. Thus we were only able to make single point observations of M/P distribution for each of the 12 patients. While multiple sampling within a dose interval and the use of area under the curve measurements in plasma and milk is generally recommended [21], it is critical only for drugs with a short $t_{1/2}$. Since methadone has a long $t_{1/2}$ of around 27 h [3], single point sampling is adequate. In the present study we have shown that post-feed methadone concentrations in milk were 33% higher on average than those in the pre-feed samples. This increased partitioning of the drug into milk is most likely to be attributable to the increase in milk lipid content that occurs during feeding. Average milk concentration measurements (pre- and post-feed) were therefore used in the calculation of M/P and infant dose.

All of the infants studied were 7 days of age or less, with the exception of the infant of TI who was 26 days of age. Milk composition changes from the initial high protein, low fat of colostrum to that of mature milk in 2–3 weeks [22]. The distribution of methadone into immature milk may thus differ from that of mature milk. This may explain the higher M/P and percentage of maternal dose obtained for the infant of TI. The mean M/P ratio of 0.44 (0.24 − 0.64) in the present study, was approximately half of the M/P ratio of 0.83 reported by Blinick *et al.* [7], was similar to data from two patients (0.32, 0.61) reported by Pond *et al.* [6], and was within the range in another two patients (0.05, 1.2) reported by Kreek *et al.* [8, 9]. In all of these studies the dose range and infant ages were similar. Daily infant exposure to methadone was 17.4 (10.8–24) $\mu g\,kg^{-1}$ in absolute dose terms and this corresponded to a mean of 2.79 (2.07–3.51)% relative to the maternal daily dose. This exposure is less than half the average daily infant exposure of 40 $\mu g\,kg^{-1}$ reported by Blinick *et al.* [7], but is similar to an average daily exposure of 10 $\mu g\,kg^{-1}$ which can be calculated from the data of Kreek *et al.* [9].

There has been one report in the literature of an infant death possibly related to methadone ingestion via breast milk [13]. The plasma methadone level in this infant was 400 $\mu g\,l^{-1}$. This is 13 times greater than the highest minimum detection limit for plasma methadone in the eight infants in this study. Moreover, six of the infants in the present study experienced withdrawal symptoms severe enough to warrant phenobarbitone therapy. Two large studies, one involving 40 women on a methadone program [2], the other 196 drug dependent women [15], have reported a significant correlation between maternal methadone dose and neonatal withdrawal symptoms. Our study did not support this finding, but this may be because of its small sample size.

Our results show that only small amounts of methadone pass into breast milk in the early postpartum period, despite methadone doses ranging up to 80 mg day^{-1}. Infant exposure via breast milk was minimal (mean exposure 2.79% of maternal dose and detected in plasma of only one infant) and was insufficient to prevent NAS in 64% of infants. We recommend that women on a methadone maintenance program should not be discouraged from breast feeding. However further studies are required in women who are breast feeding older infants and those who are maintained on larger daily methadone doses.

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