Distribution of *R*- and *S*-methadone into human milk during multiple, medium to high oral dosing

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Aims To measure the interdose milk to plasma ratio (M/P) of *R*- and *S*-methadone during multiple dosing in lactating mothers taking medium to high doses of methadone (>40 mg daily), and to assess likely infant exposure.

Methods Eight mother/child pairs were studied, initially during their postpartum hospital stay (immature milk), and where possible again after 15 days (mature milk). The women were on a methadone maintenance programme with daily doses of ≥ 40 mg day^{-1}. Venous blood was collected at 0, 1, 2, 4, 6, 8, 12, and 24 h and milk was collected from both breasts at 0–4, 4–8, 8–12, 12–16, 16–20, and 20–24 h after dose. *R*- and *S*-methadone were quantified by h.p.l.c. The areas under the plasma and milk concentration-time curves (AUC) were estimated and M/P_{AUC} was calculated. The relative infant dose of both enantiomers was estimated as the product of drug concentration in milk and an average daily milk intake of 0.15 l kg^{-1}.

Results For immature milk ($n=8$) the M/P_{AUC} for *R*-methadone was 0.68 (95% CI 0.48, 0.89) and for *S*-methadone 0.38 (0.26, 0.50). For mature milk ($n=2$) the M/P_{AUCs} for *R*-methadone were 0.39 and 0.54 and for *S*-methadone 0.24 and 0.30, respectively. The estimated doses of *R*- and *S*-methadone that would be received by the infant via immature milk were 3.5% (2.05, 5.03%) and 2.1% (1.3, 2.8%), respectively, of the maternal dose (assuming 50% of each enantiomer in the dose). The relative infant dose for *R*- plus *S*-methadone together was 2.8% (1.7, 3.9%).

Conclusions Breastfeeding during medium to high dose methadone appears to be 'safe' according to conventional criteria because the dosage is $<10\%$. However because the absolute dose received by the infant is dependent on the maternal dose rate, the risk-benefit ratio should be considered for each individual case. The doses of methadone received via milk are unlikely to be sufficient to prevent the neonatal abstinence syndrome.

Keywords: enantiomers, methadone, milk, pharmacokinetics

Introduction

Methadone is used in programs for the treatment of opiate addiction. Many women with drug addiction become pregnant, and breast feed their infants after delivery. A recent retrospective study at Christchurch Women's hospital showed that about 60% of known methadone users were discharged breastfeeding [1]. The dose of methadone for patients in maintenance treatment programs has increased considerably in recent years, and many patients are on doses in excess of 100 mg day^{-1}. Maternal dosage at delivery appears to relate strongly to the severity of neonatal withdrawal [1]. Furthermore, abrupt cessation of breastfeeding during high maternal dosing, has been associated with the neonatal abstinence syndrome [2]. This suggests that breastfeeding may protect against the withdrawal syndrome. While there are published data on methadone distribution in milk [3–5], there are few data for women on medium to high

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doses. Furthermore there are no reports of the relative distribution of the *R*- and *S*-enantiomers of methadone. Perhaps the most likely unwanted side-effects of methadone in breastfed infants would be sedation and/or depression of respiration. In this regard, *R*-methadone is of interest because of its potency as a competitive antagonist at the μ opioid receptor (some 10 times that of *S*-methadone) [6]. Methadone can also block the reuptake of serotonin in the brain [7] and again the *R*-enantiomer has the greater potency. However, *S*-methadone is also of interest as it has significant noncompetitive antagonist activity at the NMDA receptor [8] which is excitatory for functions such as respiration [9]. Hence, an understanding of the transfer of both enantiomers of methadone into milk is important. Methadone is metabolized by demethylation to inactive metabolites. The aim of this study was to examine the M/P_{AUC} for the *R*- and *S*-enantiomers of methadone during methadone maintenance at moderate to high doses in the early postpartum period (immature milk), and again at >15 days postpartum (mature milk), and to assess likely infant exposure.

Methods

Subjects

Eight women were recruited from Christchurch Women's Hospital. They were established methadone users, who were, or were about to be, breastfeeding their infants. The study was approved by the Canterbury Area Health Board Ethics Committee and written informed consent was obtained from each participant.

Drug dosage and administration

Each woman received their standard dose of methadone (Physeptone® 10 mg tablets) at around 09.00 h on the day of the study, with the exact time being noted. The women were studied during multiple dosing when they could reasonably be expected to be at steady-state. It was assumed that the mothers were not taking extra methadone, although with this patient group this cannot be assured.

Blood and milk collection

Blood was sampled via an indwelling catheter just prior to the dose administration, and again at 1, 2, 4, 6, 8, 12, and 24 h. All the milk from both breasts was expressed by electric or manual breast pump over the periods 0–4, 4–8, 8–12, 12–16, 16–20, and 20–24 h (or as close as possible to these times) after drug dosing. The total volume of each milk sample was measured and an aliquot was retained for measurement of methadone. The remaining milk was discarded. For both blood and milk samples, exact times were recorded if they were different from those stated in the protocol. The samples were stored at −80° C prior to analysis of methadone content.

Chemicals

Reference standards of *R*- and *S*-methadone were a gift from Professor L. Christrup at the Danish School of Pharmacy, Copenhagen, Denmark, racemic methadone was sourced from The Sigma Chemical Co., Mo, USA and ropivacaine from Astra Pharmaceuticals Pty Ltd, Sydney, Australia. All other chemicals were of analytical or h.p.l.c. grade.

Analytical methods

Extraction of R- *and* S-*methadone* The plasma method was based on a previous publication by Kristensen *et al.* [10] with modifications as below:

Plasma: Internal standard (ropivacaine, 0.4 μg) was added to 1 ml aliquots of patient plasma or spiked standard plasma samples containing 100–800 $\mu g\ l^{-1}$ racemic methadone. Samples were made alkaline with 1 ml 1 M Na_2CO_3 and extracted with 8 ml *n*-hexane by shaking vigorously for 5 min. After centrifugation at 1500 *g* for 5 min, the organic phase was transferred to a clean tube and evaporated to dryness under N_2 at 50° C. The residue was reconstituted in 0.2 ml of mobile phase and 0.08 ml aliquots were injected onto the h.p.l.c. column.

Milk: Individual milk samples often have a variable matrix composition that in our experience can sometimes alter recovery of a drug and/or the chosen internal standard. To avoid such problems, we used the 'method of addition' described below for the assay of methadone in milk. Internal standard (0.4 μg ropivacaine) was added to four 1 ml aliquots of each separate milk sample which were then spiked with racemic methadone to give additional concentrations of 0, 100, 200 and 500 $\mu g\ l^{-1}$, respectively. The samples were then made alkaline with 1 ml 1 M Na_2CO_3 and extracted with 8 ml *n*-hexane by shaking vigorously for 5 min. After centrifugation at 1500 *g* for 5 min, the organic phase was transferred to a clean tube, and back extracted into 1 ml 0.1 M HCl by shaking vigorously for 5 min. After a further centrifugation at 1500 *g* for 5 min, the organic phase was aspirated to waste. The acid phase was made alkaline with 1 ml 1 M Na_2CO_3 and re-extracted into 8 ml hexane by shaking as above. After a final centrifugation as above, the hexane phase was transferred to a clean tube and evaporated to dryness under N_2 at 50° C. The residue was reconstituted in 0.2 ml of mobile phase and 0.08 ml aliquots were injected onto the h.p.l.c. column.

H.p.l.c. analysis of R- *and* S-*methadone*

The h.p.l.c. system consisted of a Waters 515 pump, 717 autosampler, 996 photodiode array detector coupled to a Millenium data system. A ChromTech (ChromTech, Hagersten, Sweden) Chiral-AGP column (100 × 4 mm i.d.) and a mobile phase of 10% v/v acetonitrile in 10 mM H_3PO_4 (adjusted to pH 5 with NaOH) with the final addition of 0.05% v/v dimethyloctylamine, were used. The mobile phase was pumped at a flow rate of 1.3 ml min^{-1} and eluting compounds were detected by their u.v. absorbance at 200 nm. Under these conditions, approximate retention times were 3.5 min for ropivacaine, 6.2 min for *R*-methadone and 7.9 min for *S*-methadone.

Plasma *R*- and *S*-methadone concentrations were interpolated from a standard curve (linear regression analysis; peak height ratio analyte : ropivacaine (y-axis) *vs* analyte concentration (x-axis); $r^2 > 0.995$) run with each batch of samples. For each individual milk sample, a standard curve (peak height ratio analyte : ropivacaine (y-axis) *vs* added analyte concentration (x-axis); was determined by linear regression analysis ($r^2 > 0.995$) and, using the equation to the line, analyte concentrations were determined from the negative x-axis intercept. For the plasma assay, absolute recoveries at 50 and 200 μg l^{-1} were 94 ± 3.0% and 86 ± 8.0% and 95 ± 5.4% and 95 ± 4.9% for *R*-and *S*-methadone, respectively (mean ± s.d., $n = 5$). Absolute recoveries for the milk assay were generally high (≈80% or greater) but were not investigated in detail because the 'method of addition' individualizes recovery for each milk sample. The coefficients of variation (CV) for the plasma assay of *R*- and *S*-methadone were 5.8% and 6.0% (25 μg l^{-1}, intraday), 7.7% and 6.1% (25 μg l^{-1}, interday), 3.2% and 3.2% (300 μg l^{-1}, intraday) and 3.8% and 3.7% (300 μg l^{-1}, interday), respectively ($n = 5$). Similarly, CVs for the milk assay of *R*- and *S*-methadone were 4.4% and 4.2% (50 μg l^{-1}, intraday), 5.0% and 4.4% (50 μg l^{-1}, interday), 3.6% and 5.5% (300 μg l^{-1}, intraday) and 4.5% and 6.0% (300 μg l^{-1}, interday), respectively ($n = 5$). In both milk and plasma, the limit of quantification (CV < 20%) was 10 μg l^{-1} for *R*- and *S*-methadone and the limit of detection (signal : noise = 4) was 4 μg l^{-1} for *R*- and *S*-methadone.

Pharmacokinetic analysis

The area under the plasma concentration *vs* time curve from zero to 24 h was calculated for *R*- and *S*-methadone using the linear trapezoidal rule for the ascending part of the curve and the log–linear trapezoidal rule for the descending part of the curve. The AUC(0,24 h) for milk was calculated using rectangular areas (Σ milk concentration × collection interval in h). The dose of methadone that might be ingested by the infant during each milk expression was calculated by multiplying the average concentration in milk (AUC(0,24 h)/24 h) by 0.15 l kg^{-1} [11]. The relative exposure of the infant to each enantiomer was calculated by comparing the mother's dose (assuming 50% *R*- and 50% *S*-methadone content) with that of the infant, in each case correcting for the respective body weights.

Results

Eight women, aged 18–33 years (median 25.5), and weighing 48–83 kg (median 53) participated in the study. The doses of methadone ranged from 40 to 105 mg day^{-1} with four women having doses higher than the maximum studied previously during breastfeeding (80 mg day^{-1}) [5]. The demographic features of the women and their infants are shown in Table 1.

For immature and mature milk, the milk and plasma AUCs, M/P_{AUC}, average milk concentration, calculated infant dose per day, and infant dose expressed as a percentage of maternal dose corrected for weight for the enantiomers of methadone are shown in Table 2. For immature milk ($n = 8$), the mean M/P ratio for *R*-methadone was 0.68 (95% CI 0.48, 0.89), and for *S*-methadone 0.38 (0.26–0.50), while for mature milk ($n = 2$), the M/P ratio for *R*-methadone was 0.54 (c.f. 0.44 for immature milk in same subject) and 0.39 (c.f. 0.22), and for *S*-methadone 0.30 (c.f. 0.24), and 0.24 (c.f. 0.12). The estimated dose of *R*-methadone that would be received by the infant via immature milk was 3.5% (95% CI 2.0, 5.0%) of the maternal *R*-methadone dose, and 2.1% (1.3, 2.8) for *S*-methadone (referenced to maternal doses of each enantiomer). For mature milk, the weight-adjusted doses of *R*- and *S*-methadone were 1.9% and 2.5%, and 1.6% and 2.2%, respectively, in the two subjects studied.

Table 1 Maternal and infant demographics.

Subject	*Age (years)*	*Weight (kg)*	*Daily methadone dose (mg)*	*Infant age at test (days)*
1	26	52	75	5 (27⋆)
2	23	48	75	4 (18⋆)
3	18	54	90	7
4	27	83	75	8
5	33	52	40	1
6	25	75	90	7
7	26	49	105	11
8	23	64	90	5

⋆Second study (mature milk).

Table 2 Absolute maternal and infant doses, average milk concentration, M/P_{AUC}, and relative infant dose for *R*- and *S*-methadone.

Subject	*Daily maternal dose (mg kg^{-1})*	*M/P_{AUC}*		*Average milk methadone concentration (μg l^{-1})*		*Daily infant dose (μg kg^{-1})*		*Relative infant dose (%)*	
		R	*S*	*R*	*S*	*R*	*S*	*R*	*S*
Immature milk									
1	1.44	0.44	0.24	144	115	21.6	17.3	3.0	2.4
2	1.56	0.22	0.12	42	26	6.3	3.9	0.8	0.5
3	1.66	0.58	0.35	113	89	17.0	13.4	2.0	1.6
4	0.9	0.78	0.39	146	69	21.9	10.4	4.8	2.3
5	0.75	0.90	0.48	121	74	18.2	11.1	4.8	2.9
6	1.2	0.96	0.55	259	126	38.9	18.9	6.5	3.2
7	2.14	0.86	0.55	181	87	27.2	13.1	2.5	1.2
8	1.4	0.71	0.39	185	121	27.8	18.2	3.9	2.6
Mean		0.68	0.38					3.54	2.09
s.d.		0.25	0.15					1.83	0.91
95% CI		0.5, 0.9	0.3, 0.5					2.0, 5.0	1.3, 2.8
Mature milk									
1	1.44	0.54	0.30	89	76	13.4	11.4	1.9	1.6
2	1.56	0.39	0.24	135	119	20.3	17.9	2.5	2.2

The relative infant dose for the sum of *R*- and *S*-methadone in immature milk was 2.8% (1.7–3.9%). In the same subjects, the mean of the average plasma concentrations of *R*-methadone (222 μg l^{-1} (95% CI 171, 273 μg l^{-1})) was similar to that of *S*-methadone (246 μg l^{-1} (158, 334 μg l^{-1})).

Discussion

Four of the eight mothers studied had doses higher than those in mothers in previous reports [3–5]. However, their M/P-values were consistent with those of previous studies [3–5], suggesting that standard principles of passive diffusion apply, and that the ratio is not dose-dependent. In all subjects the mean M/P for *R*-methadone was significantly (80%) higher ($t=2.9$, $P=0.01$) than that for *S*-methadone. Consistent with this, the calculated dose of *R*-methadone received by the infant was higher than that of *S*-methadone, although the difference did not reach statistical significance.

The reason why the M/P for *R*-methadone is greater than that for *S*-methadone can be understood by reference to previous studies. In sweat, Kintz *et al.* showed that the $R:S$ ratio for methadone was generally >1 [12], indicating that the *R*-enantiomer transfers more readily from plasma to sweat. In addition, *R*-methadone also has a greater volume of distribution, clearance and half-life than *S*-methadone [13]. Thus, as suggested by Kristensen *et al.* [13], the most likely explanation for all of these changes derives from the fact that the plasma protein binding of *S*-methadone is significantly higher than that of *R*-methadone [14]. This leads to higher total plasma concentrations of S-methadone compared with R-methadone. The R-methadone will therefore have a larger apparent volume of distribution, a higher sweat to plasma ratio and a higher M/P ratio.

Decisions about breastfeeding during methadone ingestion are more complicated than for other drugs. For most drugs the aim is to subject the infant to as little drug as possible. An arbitrary cut-off level of predicted infant exposure of $<10\%$ the maternal dosage has been recommended [11]. If this is the criterion, then methadone might be considered 'safe', since the total dose received by the infant is $<5\%$. If mothers were taking extra, undeclared, methadone, the relative dose received by the infant would have been less. Therefore our results represent an 'at worst' case. Infant dose ultimately depends primarily on the concentration of drug in milk, which in turn is the product of M/P and maternal plasma drug concentration. Since M/P does not appear to be dose-dependent, one might reasonably expect that a higher maternal dose would result in increased plasma methadone concentrations and increased infant exposure. To test this hypothesis we have compared doses and plasma concentrations from the present study with those from a previous study [5] where lower doses were used. The total ($R+S$) methadone plasma concentration in the present study with a mean daily dose of 1.38 mg kg^{-1} (1.02–1.74) was 468 μg l^{-1} (335–501 μg l^{-1}). By comparison, patients in the study of Wojnar-Horton *et al.* [5] were taking a mean daily dose of 0.62 mg kg^{-1} (0.46–0.78 mg kg^{-1}) that gave a mean racemic methadone

plasma concentration of 311 $\mu g\,l^{-1}$ (207–415 $\mu g\,l^{-1}$). Despite the significantly greater plasma concentrations in the present study ($t=2.1$, $P<0.05$), the mean relative infant doses in both studies were identical (2.8%). Nevertheless, the absolute infant dose must increase as the maternal dose increases. This finding emphasizes the need to individualize the calculation of relative dose for each mother/child pair and also to measure the drug concentration in the infant's plasma when high methadone doses are necessary.

An additional complication is the neonatal withdrawal syndrome, that often occurs soon after delivery in infants exposed to methadone during pregnancy. These infants may require administration of descending doses of methadone to diminish the withdrawal syndrome. Breastfeeding in these infants may be thought of as a potential dosing source of methadone, which may protect against neonatal abstinence. Indeed we have observed neonatal abstinence occurring in infants after abrupt cessation of breastfeeding during high dose maternal ingestion, suggesting that methadone received via milk may be partially protective against withdrawal [2]. However, relying on delivery of methadone via milk assumes that the amount in the milk is adequate to prevent withdrawal, including subclinical withdrawal. Our results suggest that the doses received via milk may be insufficient to prevent withdrawal. This is supported by a previous observation that 58% of breastfeeding infants developed the neonatal abstinence syndrome during ongoing maternal methadone treatment [5]. Other drugs such as morphine and/or phenobarbitone are used in descending doses to treat the neonatal abstinence syndrome.

It was a pity that we could only study two of the mothers in both the early and mature milk periods. This is a difficult group of patients to study as they are not very reliable, particularly when out of hospital. However the results of the two suggested no great differences in the likely doses received by the infants.

In summary, the M/P_{AUC} of high doses of methadone is consistent with studies of lower doses, and is higher for *R*-methadone than *S*-methadone. Although the dose received by the infant during high dose therapy is less than a conventional cut-off value of 10% of the maternal dose corrected for weight, the absolute dose received is proportionally higher than with lower doses. However the amount received is likely to be insufficient to prevent the neonatal abstinence syndrome. Decisions about the safety of breast feeding during high dose therapy need to be made on an individual basis.

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