ORIGINAL ARTICLE

Can methadone concentrations predict the severity of withdrawal in infants at risk of neonatal abstinence syndrome?

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Aim: To assess the usefulness of cord and serum methadone concentrations at 2 days of age in predicting the severity of neonatal abstinence syndrome (NAS) in infants whose mothers received methadone during pregnancy.

Methods: After informed consent, infants were enrolled if they were delivered at 35 weeks gestation or greater. Relevant information was collected from maternal notes. A sample of cord blood was taken at delivery, with a follow up sample at 48 hours of age. The samples were analysed in batches, and the results were unavailable to the attending clinical staff. Infants were treated for NAS on clinical grounds according to a standardised scoring system.

Results: Twenty five of 36 eligible infants over the 21 month period of the study were enrolled. Of these, 12 required treatment for NAS. Maternal methadone dose did not predict the need for treatment. However, infants who required treatment had significantly lower methadone concentrations in cord blood than the group who did not receive treatment (31 *v* 88 ng/ml respectively; p = 0.029). Paired blood samples for methadone concentrations were available for 17 infants. All but one of the 12 infants who required treatment had undetectable concentrations of methadone in the postnatal sample, whereas the median postnatal methadone concentration in untreated infants was 23 ng/ml (p = 0.002).

Conclusions: Methadone concentrations taken from cord blood may identify infants at greater risk of neonatal withdrawal and therefore requiring treatment.

Neonatal abstinence syndrome (NAS) occurs in between 30%[1] and 80%[2] of infants whose mothers have been receiving opiates during pregnancy. There are inconsistent data in the literature suggesting that there is a relation between the maternal dose of methadone and the severity of neonatal withdrawal. Some studies have shown that infants are more likely to have withdrawal symptoms with increasing maternal doses,[3–5] whereas others have shown no such relation.[6 7] Similarly, studies of neonatal methadone concentrations have shown a good correlation with maternal dose[4 8] or have shown no relation.[6 7] More severe withdrawal has also been associated with more rapid decline in neonatal methadone concentrations,[6 8] although this is not a consistent finding.[7]

Some studies evaluating drug use have been in populations where illicit use of other substances is common.[2 4 7 8] In our local population, use of additional opioids, barbiturates, and benzodiazepines—either legal or illegal—was not as high as in other studies. Therefore we evaluated whether methadone concentrations in infants whose opiate exposure was almost exclusively methadone would predict the severity of neonatal withdrawal.

METHODS

The study received approval from the Auckland Ethics Committee. Infants were eligible if their mothers were under the care of the Auckland Regional Methadone Service and referred to the National Women's Hospital Assessment of Drugs and Alcohol in Pregnancy Team (ADAPT). An additional source of mothers was women under the supervision of the National Women's Hospital Pain Service, who were receiving methadone as part of their treatment for chronic pain in pregnancy.

Mothers were initially approached at antenatal visits by a midwife affiliated to ADAPT, and gave informed consent for participation in the study. Routine toxicology screens were not performed on the mothers unless there were concerns from the medical staff or caseworkers about undisclosed drug use. Information was prospectively collected about complications in the pregnancy, the delivery, and condition of the infant at birth.

Infants were not eligible if they were delivered prematurely at a gestation of less than 35 weeks, because of lower rates of withdrawal requiring treatment in the preterm population.[9] At delivery, a sample of blood was drawn from the umbilical cord. A further venous sample was taken from the baby at about 48 hours of age. Immediately after collection, the laboratory centrifuged the venous specimens to obtain serum, which was stored at −20°C until analysed in batches. After denaturation of the protein with acidified methanol, the methadone and an added internal standard (proadifen) were extracted from the basic solution using an organic solvent. The organic extract was then concentrated, and a portion analysed by capillary gas chromatography with thermionic detection. Samples were calibrated using a seven point linear calibration curve at 0, 25, 50, 75, 100, 150, and 200 ng/ml with a quantification limit of 7 ng/ml. The coefficients of variation at 100, 50, and 25 ng/ml were 6.9%, 7.4%, and 7.9% respectively. Owing to the delay between sample collection and analysis in batches, results were not available to the attending clinicians.

Data including pregnancy duration, complications in pregnancy, mode of delivery, and anthropometric measures at birth were collected. Infants were observed and scored for the severity of NAS using a standardised Finnegan scoring system,[10] modified for local use. A urine sample was obtained in the first 24 hours of life to exclude recent drug intake,

which could affect severity of withdrawal. Toxicology analyses included enzyme immunoassay and thin layer chromatography. A decision to treat was made clinically on the basis of the scoring system without knowledge of the methadone concentration results. Infants who required treatment were started on oral (or, rarely, intravenous) morphine and weaned as able at the discretion of one of two attending neonatologists (CAK and RSHR). There were no restrictions on breast feeding. Infants were discharged when they had minimal signs of NAS and were reliably taking sucking feeds.

Maternal methadone concentrations were not routinely performed. However, many mothers had trough concentrations measured within a few days of delivery so that their dose could be titrated accordingly. Maternal methadone concentrations were measured using a fluorescence polarisation immunoassay (Abbott TDx; Abbott Laboratories, Diagnostics Division, Abbott Park, IL, USA).

Study variables were analysed using the computer statistical software StatView version 5.0.1 (SAS Institute, Cary, North Carolina, USA). Continuous variables were analysed using a Student's *t* test or Mann-Whitney U test, depending on the distribution. Nominal variables were analysed using a χ^2 test.

RESULTS

Between August 1999 and May 2001, 36 infants were born to 34 mothers who were receiving methadone at the time of delivery: 31 were born to mothers under the ADAPT service, with the remaining five born to mothers receiving methadone for the treatment of pain disorders in pregnancy. Of the 36 eligible infants, the parents of four declined consent, five were not approached, and two withdrew from the study after birth, leaving 25 infants in the study group. Table 1 gives the relevant details of the mothers and infants. Urine toxicology results were available for 20 of the study infants. Although maternal reporting has been documented to underestimate true drug use,[11] in no case was previously undisclosed drug use identified. Four women reported intravenous morphine use in pregnancy, although only one was regularly using it up until three days before delivery. The other three women ceased morphine use in the first trimester, the second trimester, or six weeks before delivery. One woman under the care of the Pain Service had received intravenous pethidine in the 24 hours before delivery for management of renal colic. Only three women had a history of benzodiazepine use: one was receiving diazepam 7.5 mg/day; one was receiving 2 mg/day at the time of delivery after reducing from 13 mg/day; one used diazepam and amphetamines early in the pregnancy. Nine of the women admitted to cannabis use in pregnancy. The women under the care of the Pain Service were also receiving other drugs for the treatment of chronic pain including mexilitine (three), amitriptyline (four), and clonidine (one).

Treatment for NAS was required for 12 (48%) of the 25 infants in the study. Treatment was instituted at a median age of 35 hours (range 7–84), and the median duration of treatment was 15 days (range 11–28). There were no significant differences in the gestation, sex, or weight of infants who did or did not require treatment. There was no significant relation between the maternal dose of methadone and the need for treatment (47.5 *v* 65 mg for treated and untreated infants respectively; $p = 0.14$). Infants who received treatment had significantly higher scores at 24 hours of age than those who did not (six versus three; $p = 0.002$). The length of stay for infants who required treatment was 20 days (14–34) compared with six days (4–10 days) for the untreated group ($p < 0.0001$). There were no significant differences in feeding between the treated and untreated groups. Six of the untreated infants and three of the treated infants exclusively received breast milk, three infants in the untreated group exclusively received formula, and the remainder received a combination of breast milk and formula during their hospital stay.

Table 1 Relevant details of the study mothers and babies

Maternal age (years)	28 (20–45)
Methadone dose at delivery (mg)	55 (15–105)
ADAPT team care	21 (84%)
Antibodies to HCV (ADAPT mothers only)	15 (71%)
Known illicit opiate use (ADAPT mothers only)	1 (5%)
Hours between last dose and delivery	14 (1–33)
Gestation at delivery (weeks)	38 (35–41)
Males	17 (68%)
Birth weight (g)	2995 (2265–3675)
Apgar score at 1 minute	9 (6–10)
Apgar score at 5 minutes	10 (7–10)

Values are absolute numbers (%) or median (range).
HCV, Hepatitis C virus; ADAPT, Assessment of Drugs and Alcohol in Pregnancy Team.

Of the 25 infants whose mothers consented to participation in the study, 17 paired methadone samples were available. For seven infants, one or both samples were not taken or were insufficient for analysis. The results for another infant were erroneously analysed using an adult methadone concentration assay (where the calibration is set for significantly higher concentrations) and were therefore felt to be unreliable, leaving nine treated and eight untreated infants for whom both samples were available. The median age at which the postnatal sample was taken was 49 hours (range 41–59). For statistical analysis, undetectable methadone concentrations (< 7 ng/ml) were assigned a value of 0 ng/ml. There was a strong relation between cord methadone concentration and maternal dose (fig 1; $R^2 = 0.59$, $p < 0.0001$). As a group, infants who needed treatment had lower cord methadone concentrations than those who did not (31 (17–70) *v* 88 (0–130) ng/ml; $p = 0.029$). All infants who required treatment had cord concentrations below 53 ng/ml; of the untreated infants, all but two had concentrations above 58 ng/ml. The two untreated infants with concentrations lower than 58 ng/ml had cord concentrations that were undetectable and 33 ng/ml. At 48 hours of age, all but one of the nine infants who required treatment had undetectable concentrations of methadone in their serum; the remaining infant had a concentration of only 7 ng/ml. In contrast, only two infants who did not require treatment had undetectable postnatal concentrations, with the median concentration for this group being 23 ng/ml ($p = 0.002$) (fig 2).

Postnatal methadone samples were available for only 11 of the 17 mothers whose infants had paired methadone samples taken. Methadone concentrations are often performed on mothers about five days after delivery to allow titration of the methadone dose as indicated. The maternal concentrations (taken at a median of 119 hours after delivery) were significantly lower in the mothers of infants who received treatment than in those who did not (148 (range < 100–403) *v* 277 (range 166–496) ng/ml; $p = 0.03$). The maternal dose of methadone at delivery for treated infants was 48 (15–100) mg/day, whereas mothers of the untreated infants were receiving a median of 65 (20–105) mg/day ($p = 0.14$)

DISCUSSION

This study shows that neonatal methadone concentrations may be useful in predicting the severity of withdrawal in

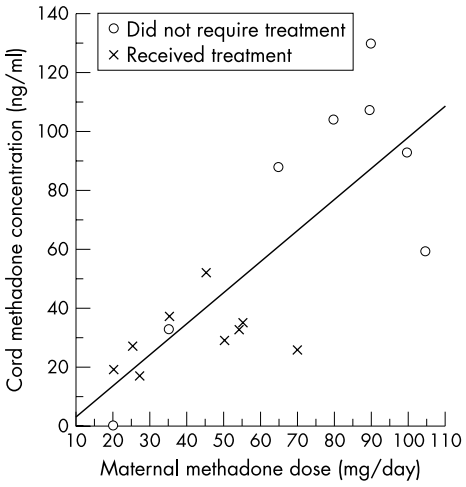

Figure 1 Relation between maternal methadone dose and cord methadone concentration. $R^2 = 0.59$, $p < 0.0001$.

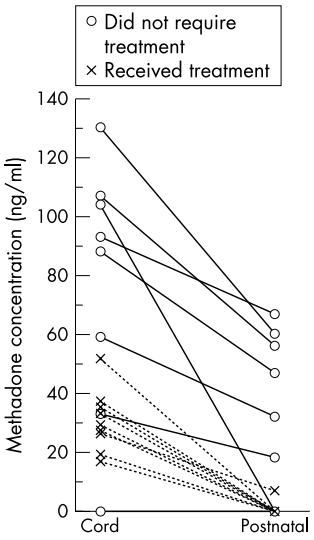

Figure 2 Cord and postnatal (48 hour) methadone concentrations.

babies exposed to methadone without significant other opiate or polydrug use. Infants who require treatment have lower cord concentrations than untreated infants, and undetectable or very low concentrations at 48 hours. Rosen and Pippenger[6] reported that infants with serum methadone concentrations greater than 0.06 μg/ml (60 ng/ml) appeared to be protected from withdrawal, and in our study no infant with a cord concentration higher than this required treatment. They also found that the half life of methadone in infants who had more severe withdrawal was shorter than in those whose symptoms were mild.[6] Similarly, Doberczak *et al*[8] observed an association of severe central nervous system signs with the rate of decline of neonatal plasma methadone concentrations between postnatal days 1 and 4. We are unable to accurately calculate the half life in our study population and therefore cannot determine whether it is the cord concentration, the rate of elimination from the neonate, or a combination of the two that determines the severity of withdrawal.

Despite a relation between maternal dose and cord methadone concentrations, our study also confirms that the maternal methadone dose is a poor predictor of severity of withdrawal. Indeed, in this study, there was a trend towards an inverse relation, with withdrawal being less likely with higher maternal doses, which is at odds with some literature.[1 4 12 13]

Most of the study infants have some symptoms on the first day, and babies with higher scores at 24 hours are more likely to require subsequent treatment. Most infants were treated by 36 hours, 10 of the 12 treated infants were on treatment by 48 hours, and the remaining two infants were treated at 67 and 84 hours. Other studies have reported that withdrawal has peaked at a later age.[8 9] As our hospital provides a regional service for infants who are exposed to maternal methadone, and almost all infants are seen in our follow up clinic, we are confident that infants who did not require treatment in the newborn period did not subsequently develop significant NAS.

More severe withdrawal has been reported with infants exposed to methadone than other shorter acting opiates.[14–17] Urine toxicology did not reveal any illicit use, but neonatal urine samples taken in the first few hours may only detect substances ingested by the mother over the preceding days or weeks, depending on the rate of elimination of the drug. However, urine analysis provides a more rapid result for a toxicology screen than either meconium or hair samples. Meconium production begins at the start of the second trimester, and therefore substances to which the fetus is subsequently exposed in the pregnancy may be detected.[11 18] Hair samples may detect drug exposure over the third trimester, but their usefulness may be limited by the amount of available hair, technical factors, and the observation that analysis of hair samples may not be as sensitive as meconium samples.[11] However, these assays are not routinely available at our laboratory, and, in the context of a relationship of trust with the mothers, we elected not to undertake more detailed testing.

Although there were no significant differences in feeding practices between the treated and untreated infants, it is possible that there were higher concentrations of methadone excreted in the breast milk of the mothers whose infants did not require treatment. The median dose of the three women who exclusively breast fed and whose babies developed NAS severe enough to warrant treatment was significantly lower than the six exclusively breast fed infants in the untreated group (20 *v* 80 mg/day, $p = 0.019$), but whether this affects the initial cord concentration, the quantity of methadone in the milk, or both cannot be determined, as methadone concentrations in maternal milk were not evaluated. The excretion of methadone in human milk is variable and related to maternal plasma concentrations, but is not thought to be significant enough to prevent NAS,[19] despite reports describing withdrawal in infants with sudden cessation of breast feeding.[20] We were unable to determine the quantity of milk, and therefore the potential dose of methadone, the babies received. As most infants who needed treatment were started on it within 48 hours, when milk production was still establishing, it also seems unlikely that this would have prevented significant withdrawal in most untreated infants. Interestingly, the only three infants who were exclusively formula fed did not have NAS severe enough to warrant treatment.

Cord methadone concentrations may be a useful predictor of the likelihood of severe withdrawal requiring treatment. Low concentrations may indicate a baby at greater risk of withdrawal, but clinical assessment through a standardised scoring system is still required to determine the need for treatment. Measuring methadone concentrations in our population at 48 hours is unlikely to be clinically useful, as 10 of 12 babies treated (83%) in this study had already been started on treatment by this age. Further studies should be performed to validate the positive predictive value and clinical usefulness of cord methadone concentrations.

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