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Transfer of methylamphetamine and amphetamine into breast milk following recreational use of methylamphetamine

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The extent of drug transfer into milk during recreational intravenous use of methylamphetamine has not previously been studied.

WHAT THIS STUDY ADDS

- We have shown that methylamphetamine transfers into breast milk.
- The amount a breastfed infant would receive varied over 2.5-fold range.
- A 48-h withholding period for breastfeeding is recommended following recreational use.

AIMS

To investigate the transfer of amphetamines into breast milk following their recreational use and estimate drug exposure for the breastfed infant.

METHODS

Two breastfeeding mothers who were occasional recreational users of intravenous amphetamines were studied. A urine sample was collected 4 h after dose, and milk samples were collected over 24 h. Drug in urine was qualitatively identified by gas chromatography-mass spectrometry and quantification in milk was by high-performance liquid chromatography. Absolute infant dose via milk was estimated.

RESULTS

The urines contained predominantly methylamphetamine together with smaller amounts of amphetamine. In the 24 h after dose, average concentrations in milk were 111 μg l^{-1} and 281 μg l^{-1} for methylamphetamine and 4 μg l^{-1} and 15 μg l^{-1} for amphetamine in cases 1 and 2, respectively. Absolute infant doses for methylamphetamine plus amphetamine (as methylamphetamine equivalents) were 17.5 μg kg^{-1} day^{-1} and 44.7 μg kg^{-1} day^{-1}, respectively, for cases 1 and 2.

CONCLUSION

These limited data suggest that breastfeeding should be withheld for 48 h after recreational amphetamine use.

Introduction

Amphetamines are among the most widely abused compounds among recreational drug users in Western Australia, and use is reportedly increasing [1]. Although methylamphetamine and amphetamine (usually as a metabolite of methamphetamine) are the most frequently identified drugs of this class, other related compounds such as methylenedioxymethylamphetamine and methylenedioxyethylamphetamine are also occasionally detected by urinalysis (L. J. Dusci, personal communication).

Numerous and extensive studies have demonstrated the advantages of breastfeeding for both infants and mothers. However, the American Academy of Pediatrics considers breastfeeding to be contraindicated if the mother is using amphetamine(s) [2]. This recommendation is presumably based on the notion that exposing developing infants to psychoactive drugs has a high risk of causing adverse effects. Others have suggested that amphetamines should be contraindicated because the dose injected by a drug abuser is uncontrolled and unknown, and could cause acute adverse effects such as poor feeding, stimulation and insomnia in the breastfed infant [3]. Furthermore, drug use may reduce the mother's ability to provide optimal care for her infant.

Based on theoretical grounds it has recently been recommended that breastfeeding should be withheld for 24–36 h after use [4]. However, there are no published data on the concentrations of amphetamines that occur in breast milk following recreational use, or on adverse effects in the breastfed infant. Although harm minimization was adopted as the basis of Australia's National Drug Strategy in 1985, strategies specifically targeted at breastfeeding amphetamine-using mothers have not been developed.

The aims of this study were to quantify the concentration of amphetamines in breast milk of lactating recreational users and estimate the extent of drug exposure for the breastfed infant. A secondary aim was to better define an appropriate withholding period for breastfeeding.

Methods

The study was approved by the Ethics Committee of Princess Margaret and King Edward Memorial Hospitals, and written informed consent was obtained from the subjects.

Subjects

Two breastfeeding mothers able to express milk readily and to bottle feed their infant for 24 h following the use of amphetamines were recruited from the intervention arm of a Healthways funded randomized controlled trial (HIT) study of illicit drug-using mothers and their infants that tested the impact of a 6-month postnatal home visiting (HV) intervention on breastfeeding and immunization rates. The HV group had eight home visits; the control group (CG) had telephone contact at 2 months and a HV at 6 months [5]. The outcomes of the HV group were not superior to those of the CG. The women were not encouraged to take amphetamines and were recruited opportunistically following self-report of drug use to the research midwives. Both women had normal deliveries and were discharged home with their infants. As determined by the Severity of Dependence Scale [6], both were assessed as being dependent on amphetamines at the time of recruitment (36 weeks' gestation) to the HIT study. Following the birth of their infants the mothers reduced their use of amphetamines to a recreational level of approximately once a fortnight. Both had partners who were also amphetamine users.

Study protocol

The mothers were issued with a sample collection kit consisting of labelled sample jars, a breast pump, a data collection/diary sheet and information forms for the study. They were also educated on sample collection and labelling procedures by a research midwife. Each mother used a single dose (a 'point') of amphetamines procured from their customary source. The purity and amount of drug in the dose was unknown. The women collected a urine sample approximately 4 h after the dose, and stored it in the freezer compartment of the home refrigerator. The sample was subsequently used to identify the amphetamine that had been taken. The women collected milk samples (5–10 ml each) by manual expression or electric breast pump, just before drug use and at 2–6-h intervals for 24 h following the dose. These samples were stored in the freezer compartment of the home refrigerator. The mothers kept a diary record of the dates and time(s) of the amphetamine dose, and of the urine and milk samples. The women were advised to withhold breastfeeding for 24 h following the drug dose, and to bottle feed their infants. The research midwife visited the women at home on the day after the study to check on their infant's well-being, quality control sample collection and documentation, and transport samples to the laboratory.

Materials

d-Amphetamine sulphate and *d*-methylamphetamine hydrochloride were obtained from Sigma-Aldrich Australia (Castle Hill, Australia), and phentermine hydrochloride was a gift from Riker Laboratories Australia Pty Ltd (Sydney, Australia). All other chemicals and solvents were of analytical grade.

Estimation of methylamphetamine and amphetamine in milk by high-performance liquid chromatography

Milk samples were analysed by the method of addition [7]. Briefly, four separate 1-ml aliquots of each milk sample were spiked with either blank diluent, or one of three increasing concentrations of methylamphetamine and amphetamine. Following addition of phentermine (90 ng) as internal stan-

dard, the samples were alkalinized with 0.1 mol l^{-1} NaOH, extracted into 10 ml of hexane by shaking vigorously for 5 min. After centrifugation (1800 *g* for 5 min), 9 ml of the hexane phase was back-extracted into 0.2 ml of 0.05 mol l^{-1} HCl by shaking for 1 min. After further centrifugation, 0.05–0.1-ml aliquots of the acid phase were injected onto the high-performance liquid chromatography (HPLC). The HPLC system consisted of a Phenomenex Aqua 5 µ C_{18} column (250 × 4.6 mm), a mobile phase of 12% v/v acetonitrile in 45 mmol l^{-1} phosphate buffer (pH 3; 1.2 ml min^{-1}), with ultraviolet detection at 200 nm. A standard curve of peak height ratio analyte (phentermine *vs.* added analyte) was constructed and unknown drug concentrations were determined from the negative abscissa intercept. Assay variability was measured as the relative standard deviation (RSD, $n = 5$). For amphetamine at 10 µg l^{-1} and 350 µg l^{-1}, RSDs were 11 and 5.8% intraday, and 11.5 and 7.6% interday, respectively. For methamphetamine at 44 µg l^{-1} and 880 µg l^{-1}, RSDs were 0.9 and 0.5% intraday, and 2.9 and 1.3% interday, respectively. The limit of quantification for both analytes was 3 µg l^{-1}.

Identification of amphetamines in urine Amphetamines were extracted from alkalinized urine with chloroform [8], and an aliquot of the organic phase was analysed by gas chromatography/mass spectrometry. Separation was carried out on a J&W DB5 capillary column, 30 m × 0.25 mm, and eluting compounds were detected using an Agilent 5973 mass spectrometer (Agilent, Forest Hill, Australia). The total ion chromatogram at known retention times for methylamphetamine (4.8 min) and amphetamine (3.8 min) was compared with an in-house library of spectra.

Calculation of pharmacokinetic parameters and absolute infant dose

The half-life ($t_{1/2}$) for each drug concentration–time dataset was calculated by log linear regression of the last four to six data pairs, and area under the milk drug concentration–time curves from zero to the time (t_{last}) of last sample ($AUC_{0-tlast}$) was estimated by the log linear trapezoidal rule [9]. The $AUC_{0-24\,h}$ was calculated from knowledge of the measured $AUC_{0-tlast}$ and the elimination rate constant ($= 0.693/t_{1/2}$). The average concentration of drug in milk (C_{avg}) was calculated as AUC/24. The daily absolute infant dose was estimated as C_{avg} multiplied by an average milk intake of 0.15 l kg^{1} day^{-1} [10].

Results

In case 1, the mother was 29 years old and weighed 64 kg. Her infant was male, aged 4 months and weighed 6 kg. In case 2 the mother was 27 years old and weighed 68 kg. Her infant was female, aged 2 months and weighed 3.6 kg. Both infants were breastfed and, as reported by the mother and as assessed the research midwife on the day after the dose was taken, were healthy and achieving expected development milestones.

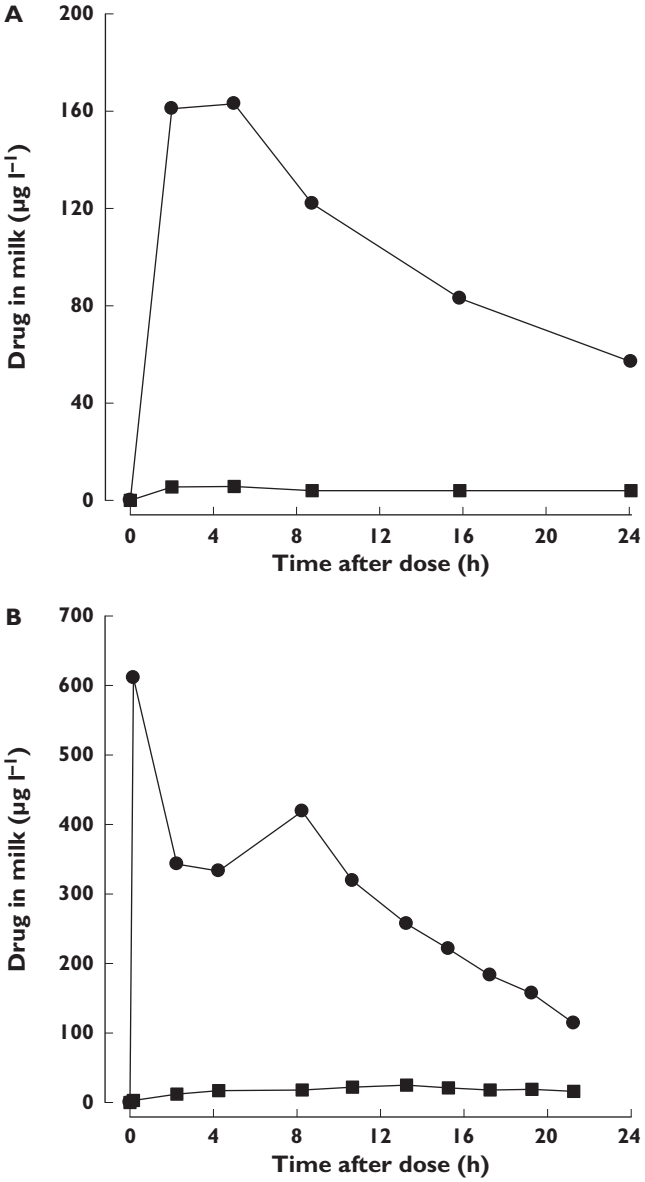

Figure 1

Drug concentration in milk *vs.* time for case 1 (a) and case 2 (b) following self-administration of one 'point' of methylamphetamine at zero time. methylamphetamine (●); amphetamine (■)

Both women injected the 'amphetamine point' intravenously. Urinalysis indicated that the predominant compound present in both cases was methylamphetamine, with a small amount of amphetamine presumed to be of metabolic origin (data not shown). The milk drug concentration–time profiles for the two women are shown in Figure 1a and b, respectively. In both, methylamphetamine was the predominant drug in milk, but there were also very much lower concentrations of amphetamine. The approximate half-lives of methylamphetamine and amphetamine in milk were 13.6 and 43 h (subject 1) and

Table 1

Average milk concentrations (first 24 h after dose) and calculated absolute infant doses for methylamphetamine and its metabolite amphetamine

	Methylamphetamine		Amphetamine	
Case	C_{avg} (μg l^{-1})	Absolute infant dose (μg kg^{-1} day^{-1})	C_{avg} (μg l^{-1})	Absolute infant dose (μg kg^{-1} day^{-1})*
1	111	16.7	4	0.8
2	281	42.2	15	2.5

*As methamphetamine equivalents.

7.4 and 14 h (subject 2), respectively. The milk C_{avg} data and the calculated absolute infant doses for the first 24 h after the dose was self-administered are summarized in Table 1. Total absolute infant dose (methylamphetamine plus amphetamine as methamphetamine equivalents) in the latter time period was 17.5 (case 1) and 44.6 μg kg^{-1} day^{-1} (case 2). Using $t_{1/2}$ estimates for methylamphetamine and amphetamine in milk, we estimated that combined absolute infant doses for methylamphetamine plus amphetamine (as methamphetamine equivalents) in the 24 h after dose would be an additional 6.1 μg kg^{-1} day^{-1} (case 1) and 8.9 μg kg^{-1} day^{-1} (case 2).

Discussion

Methylamphetamine undergoes *N*-demethylation to amphetamine, with this active metabolite accounting for around 4–7% of a dose in a 24-h urine [11]. The demethylation reaction is catalysed by human hepatic cytochrome P4502D6 (CYP2D6) with higher rates of reaction seen for the d-isomer [12]. However, the role of CYP2D6 genetic polymorphism in the N-demethylation of methylamphetamine in humans is unclear from the available published literature. Methylamphetamine was the predominant analyte identified in the urine from both women, but smaller amounts of amphetamine were also present. We conclude that the 'point' they administered was methylamphetamine and that the amphetamine in the urine was most likely to be of metabolic origin.

Although there are no previous reports of the transfer of methylamphetamine into milk, there is one report of the death of a breastfed infant whose mother used methylamphetamine [13]. The prosecution presented evidence that the infant's blood contained 39 μg l^{-1} of the drug and argued that the death was attributable to cardiopulmonary failure caused by exposure to the drug via breast milk. Nevertheless, it was pointed out that the reported blood concentration was 10–1000-fold lower than blood methylamphetamine concentrations found in adult amphetamine-related deaths and that alternative causes such as sudden infant death syndrome should have been investigated [13].

The usual way of assessing infant dose exposure to drugs in breast milk is to calculate both absolute and relative (to mother's weight-adjusted dose) infant doses [10]. Since the maternal dose is unknown in our two cases, we could only calculate the absolute infant dose as the primary measure of infant exposure. Milk transfer of *rac*-amphetamine (15-mg dose) has previously been shown in one case report with milk concentrations of 55–138 μg l^{-1} [3], equating to an absolute infant dose range of 8–21 μg kg^{-1} day^{-1}. In addition, we have reported milk concentrations ranging from 66 to 313 μg l^{-1} and a corresponding range of absolute infant doses from 10 to 47 μg kg^{-1} day^{-1} in four lactating women taking *d*-amphetamine (median daily dose 18 mg) for attention deficit hyperactivity disorder [14]. Our findings for absolute infant dose of methylamphetamine plus amphetamine in the first 24 h after dose are in the same general ranges seen with therapeutic amphetamine use. Estimated infant exposure in the second 24 h after dose was considerably lower. Nevertheless, methylamphetamine crosses the blood–brain barrier more easily than amphetamine, and the effects of infant exposure to the drug in milk could be greater than for amphetamine. In the present study, the exposed infants were achieving expected developmental milestones. Our study presents data from only two subjects and more observations are needed to evaluate fully intersubject variability. Interpretation of infant exposure to methylamphetamine and its metabolite in the broader context of recreational use should also be qualified by the fact that the size of the maternal dose and the identity/purity of the active dose content are not known. We do not condone the use of methylamphetamine while breastfeeding. Nevertheless, breastfeeding mothers who have been habitual methylamphetamine users will, contrary to advice, often continue their drug use while breastfeeding. Therefore, we suggest from our limited data that where mothers choose to use methylamphetamine, withholding breastfeeding for 48 h after is a practical strategy that should minimize infant exposure and the potential for acute adverse effects. Mothers should also be encouraged to have support mechanisms/persons available to protect their infants while they are using.

Competing interests

None declared.

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