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Excretion of diazepam and its metabolites in human milk during withdrawal from combination high dose diazepam and oxazepam

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The excretion of diazepam, *N*-desmethyldiazepam, temazepam and oxazepam in breast milk was studied during withdrawal of a 22-year-old patient from combined high dose diazepam and oxazepam therapy. Concentrations of these benzodiazepines in plasma from both the woman and her nursing infant (1 year old) were also documented. Diazepam, *N*-desmethyldiazepam, temazepam and oxazepam were found in the maternal plasma and milk with mean milk : plasma ratios of 0.2, 0.13, 0.14 and 0.10 respectively. It was calculated on a mg kg^{-1} basis that the infant received some 4.7% of the maternal dose. Diazepam could not be detected in the infant's plasma, but low levels of *N*-desmethyldiazepam (20 and 21 $\mu g\ l^{-1}$), temazepam (7 $\mu g\ l^{-1}$) and oxazepam (7.5 and 9.6 $\mu g\ l^{-1}$) were present. The infant showed no overt physical or mental symptoms of benzodiazepine intoxication.

Keywords diazepam *N*-desmethyldiazepam oxazepam temazepam neonate human milk

Introduction

Diazepam and some of its major metabolites are lipophilic compounds (Harvey, 1985) with intermediate to long half-lives (Greenblatt *et al.*, 1981) and are therefore likely on theoretical grounds to be excreted significantly in breast milk (Atkinson *et al.*, 1988). However, the high degree of plasma protein binding of the benzodiazepines (Harvey, 1985) would limit the extent of their penetration into the milk compartment. Actual case reports of such excretion for diazepam are sparse (Erkkola & Kanto, 1972; Wesson *et al.*, 1985) but suggest that the milk:plasma (M:P) ratio is around 0.1 at a dose of 10 mg daily. Despite this relatively small extent of excretion, both diazepam and *N*-desmethyldiazepam have been detected in the blood of nursing infants (Brant, 1976; Cole & Hailey, 1975; Erkkola & Kanto, 1972) and there has been one report of lethargy and weight loss with EEG evidence of sedation in a breast-fed infant of a mother taking 30 mg diazepam daily (Patrick *et al.*, 1972). To our knowledge, there is only one previous report of oxazepam excretion in human milk (Wretlind, 1987). In one patient, the mean M:P ratio at steady state was 0.13 and it was calculated that the suckling infant could have received less than 0.1% of the maternal dose (30 mg day^{-1}). In the present study, we have documented the excretion of diazepam and its metabolites *N*-desmethyldiazepam, oxazepam and temazepam in plasma and breast milk from a lactating mother taking high dose diazepam and oxazepam. Benzodiazepine concentrations in her nursing infant's plasma were also measured.

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Methods

Patients and sample collection

The patient was a 22-year-old female (47 kg) polydrug abuser who presented to the Central Drug Unit at the Western Australian Alcohol and Drug Authority for detoxification from a cocktail of benzodiazepines. Over a period of some 21 months, she had been consuming large amounts of diazepam, flunitrazepam and oxazepam and at the time of presentation was taking 80 mg diazepam and 30 mg oxazepam daily. She had a 12-month-old male infant (11.5 kg) who was being breast-fed. Over the 39 days of the study, the infant was weaned from 6 to 3–4 feeds per day.

Milk samples (20 ml) were obtained by expression. Pre-feed samples were obtained 1.1–1.7 h and immediate post-feed samples 1.6–2.6 h respectively after the morning dose of diazepam on days 14, 15, 23, 25 and 30 of the withdrawal schedule, and on day 39 when the patient had been drug free for 9 days. A venous blood sample (10 ml) was also obtained from the mother 0.8–1.3 h after the morning dose of diazepam on each of the above days.

Venous blood (2 ml) was obtained from the infant 2.2 and 3.7 h after the mother's morning dose of diazepam on days 14 and 28 during the withdrawal procedure and again after the mother had been drug free for 8 days. These blood samples were obtained opportunistically at times when blood was taken for diagnostic tests (HIV; days 13 and 28) and prior to minor surgery (day 38).

Measurement of benzodiazepines in milk and plasma

Concentration of diazepam, oxazepam and their metabolites in milk and plasma were measured by high performance liquid chromatography (h.p.l.c.) as previously described (Dusci & Hackett, 1987) with the following modifications. A Waters μ Bondapak Phenyl column (30 cm × 4 mm i.d.) was used with a mobile phase of 35% v/v acetonitrile in 45 mM KH_2PO_4 buffer adjusted to pH 3 with H_3PO_4 and pumped at a flow rate of 1.6 ml min^{-1}. Ultra-violet absorbing peaks were detected at 310 nm. Under these conditions, oxazepam, *N*-desmethyldiazepam, temazepam, flunitrazepam and diazepam chromatographed at approximate retention times of 7.2, 9.2, 10.6, 12.8 and 15 min, respectively.

Plasma (0.5 ml) was made alkaline with 0.5 ml of 50 mM sodium borate buffer (pH 9) following the addition of 200 ng flunitazepam as internal standard. Samples were then extracted by shaking with 7 ml diethylether, and after centrifugation, 6 ml of the organic phase was transferred to a clean tube and evaporated to dryness under a stream of dry nitrogen at 45° C. The residue was redissolved in 2 ml hexane and 1 ml of acetonitrile, vortexed for 1 min, centrifuged and the lower acetonitrile layer was recovered and evaporated to dryness as above.

This residue was reconstituted in 200 μl of h.p.l.c. mobile phase and aliquots (50 μl) were injected onto the h.p.l.c. column. Standard curves were prepared by spiking known amounts of diazepam, *N*-desmethyldiazepam, oxazepam and temazepam into plasma and extracting as outlined above. Linearity of the plot of peak height ratio (drug:internal standard) *vs* drug concentration was shown over the range 20–1500 μg l^{-1} with correlation coefficients greater than or equal to 0.99. Within-day coefficients of variation (n = 5) ranged from 1.5–4.0% for oxazepam (1000–16 μg l^{-1}), 1.7–4.2% for *N*-desmethyldiazepam (1000–14 μg l^{-1}), 1.9–10.5% for temazepam (1000–30 μg l^{-1}) and 1.5–3.3% for diazepam (1000–33 μg l^{-1}).

Benzodiazepines in milk (1 ml samples) were assayed by the addition of known amounts of diazepam, *N*-desmethyldiazepam, oxazepam or temazepam to give final concentrations of 0, 50, 100 and 150 μg l^{-1}. Milk samples were extracted as described above for plasma and 100 μl aliquots of the final reconstituted extract were injected onto the h.p.l.c. column. A plot of peak height ratio (drug:internal standard) *vs* concentration of added benzodiazepine in milk was constructed and the concentration of unknown drug was obtained from the *y*-axis intercept. Within-day coefficients of variation for the four benzodiazepines ranged from 5.9–11.1 and 5.3–9% at 50 and 100 μg l^{-1}, respectively.

Results

The drug withdrawal schedule for diazepam and oxazepam therapy and the maternal plasma benzodiazepine concentrations are summarised in Figure 1. The patient showed mild withdrawal symptoms at the start of the procedure and was successfully detoxified in 30 days. Total plasma concentration decreased from plateau levels around 2000–2500 μg l^{-1} on days 14–25 to 89 μ l^{-1} on day 39, as the drug dosage was decreased and eventually withdrawn. The increase in plasma diazepam concentrations on days 15, 23 and 25 could not be explained in terms of a decreased interval between sampling time and

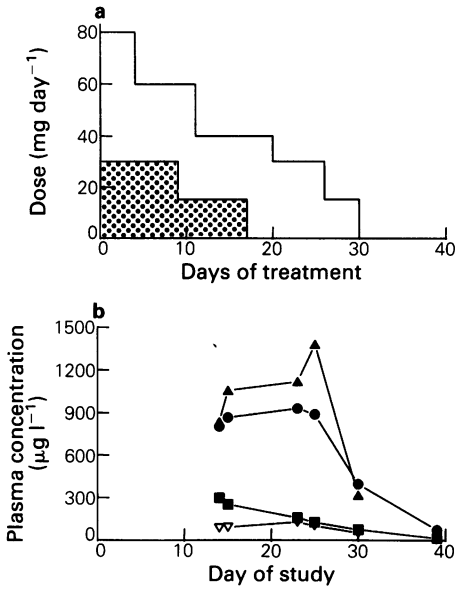

Figure 1 Maternal dosage schedule for a) diazepam (□) and oxazepam (⊡) and b) plasma concentrations of diazepam (▲), *N*-desmethyldiazepam (●), oxazepam (■) and temazepam (▽).

time of last dose. Mean benzodiazepine concentrations in milk were an order of magnitude lower (Table 1) than in plasma and decreased in parallel to the plasma concentrations and drug dosage. For both plasma and milk, the approximate order of concentrations was diazepam > *N*-desmethyldiazepam > oxazepam = temazepam.

The concentration of all four benzodiazepines in the post-feed milk was consistently greater than in the pre-feed milk, with mean ratios varying from 1.11 for oxazepam to 1.9 for temazepam (Table 1). Milk : plasma ratios (M:P) are also summarised in Table 1. Transfer of diazepam was greatest with a mean M:P ratio of 0.2 while that for oxazepam was least with a mean M:P ratio of 0.1.

Diazepam was not detected (limit of detection = 5 μg l^{-1}) in any of these plasma samples from the infant, while low concentrations of *N*-desmethyldiazepam (21 and 20 μg l^{-1}), oxazepam (7.5 and 9.6 μg l^{-1}) and temazepam (7 and 7 μg l^{-1}) were present on days 14 and 25 respectively, while the mother was taking diazepam and oxazepam but were undetectable 8 days after cessation of maternal therapy. Throughout the study, the infant showed no overt physical or mental symptoms of benzodiazepine intoxication.

Discussion

The phase I metabolism of diazepam in man proceeds via parallel pathways of *N*-desmethylation (to *N*-desmethyldiazepam) and 3-hydroxylation (to temazepam). These two compounds are then metabolised by the contralateral pathway to oxazepam (Mandelli *et al.*, 1978). Previously, following administration of diazepam, only diazepam and *N*-desmethyldiazepam have been identified in breast milk (Brandt, 1976; Cole & Hailey, 1975; Erkkola & Kanto 1972). Our study is the first to show that temazepam and oxazepam are also present as metabolites. Admittedly, some of the oxazepam must have been derived from its oral administration to our patient. However since oxazepam has a half-life of 4–15 h (Greenblatt *et al.*, 1981), its presence in the milk, 7, 9 and 14 days respectively after cessation of oral therapy indicates that the oxazepam in milk was also derived from diazepam.

Table 1 Milk concentrations, post-feed: pre-feed milk ratios and milk:plasma ratios for various benzodiazepines

Drug	*Concentrations[1] milk on days 14, 15, 23, 25, 30 and 39 resepectively* (μg l^{-1})	*Post-feed:Pre-feed* (*mean* ± *s.e. mean;* n)	*Milk:Plasma[2]* (*mean* ± *s.e. mean;* n)
Diazepam	185, 307, 200, 158, 67, 6	1.56 ± 0.18(5)	0.20 ± 0.03(5)
N-Desmethyldiazepam	124, 141, 140, 85, 42, 6	1.56 ± 0.22(5)	0.13 ± 0.01(6)
Oxazepam	30, 22, 14, 13, 8, ND	1.11 ± 0.24(5)	0.10 ± 0.004(5)
Temazepam	13, 18, 13, 14, 6, ND	1.90 ± 0.44(4)	0.14 ± 0.02(5)

[1]Calculated as the average of pre- and post-feed milk concentrations
ND = not detectable
[2]Calculated as mean of pre- and post-feed milk concentrations divided by the plasma concentration

The M:P ratios for diazepam, *N*-desmethyldiazepam and oxazepam were in the same range as those from previous studies (Brandt, 1976; Cole & Hailey, 1975; Erkkola & Kanto, 1972; Wretlind, 1978).Temazepam was shown to have a similar M:P ratio to those for oxazepam and *N*-desmethyldiazepam. The overall order of M:P ratios was diazepam > temazepam > *N*-desmethyldiazepam > oxazepam which generally reflects the order of log P octanol/buffer partition coefficients for these drugs (Greenblatt *et al.*, 1983). The concentration of all four benzodiazepines was up to 1.9 times greater in post-feed compared with pre-feed milk samples. This is consistent with the known increase in milk lipid content occurring during feeding (Hall, 1975) and the high lipid solubility of many benzodiazepines.

In the present study, diazepam could not be detected in the infant's plasma, although low concentrations of *N*-desmethyldiazepam, temazepam and oxazepam were present. *N*-desmethyldiazepam concentrations were similar to combined diazepam plus *N*-desmethyldiazepam concentrations reported by Cole & Hailey (1975) and ranged from 2/3 to 1/12 of those reported by Erkkola & Kanto (1972) in a 4–6 day old neonate. Assuming a daily milk intake of one litre per day by the infant and mean values for total milk benzodiazepine concentration, it can be calculated that his benzodiazepine exposure (on a mg kg^{-1} basis as described by Bennett, 1988) was some 4.7% (mean value) of the maternal dose and is similar to that reported for diazepam and *N*-desmethyldiazepam (8%; Erkkola & Kanto, 1972). If maximum post-feed benzodiazepine concentrations are used in the calculation, mean total benzodiazepine exposure increases to 5.4%. The low levels of benzodiazepines in the infant are indicative of active phase I and II hepatic metabolism and are in agreement with the lack of any drug-related side-effects.

In summary, despite a relatively large maternal diazepam and oxazepam dose, the excretion of these drugs and their active metabolites temazepam and oxazepam in breast milk was small. Benzodiazepine concentrations in the nursing infant were also very low. While benzodiazepine-related side effects in the suckling infant may sometimes occur, the benefits of breast feeding during maternal treatment with diazepam or oxazepam should be achievable on many occasions provided that the infant's wellbeing is closely monitored.

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