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Pharmacokinetics in lactating women: prediction of alprazolam transfer into milk

C. Y. OO[1], R. J. KUHN[2], N. DESAI[3], C. E. WRIGHT[4] & P. J. McNAMARA[1]
Division of [1]Pharmacology and Experimental Therapeutics, Division of [2]Pharmacy Practice and Science, College of Pharmacy, Department of [3]Pediatrics, College of Medicine, University of Kentucky, Lexington, Ky 40536 and [4]Clinical Pharmacokinetics Unit, The Upjohn Company, Kalamazoo, MI, USA

1 Alprazolam, a triazolobenzodiazepine, is extensively prescribed for the treatment of anxiety disorders, which predominantly affect women of child-bearing age. The purpose of the present study was to assess the pharmacokinetics of alprazolam and its two hydroxylated metabolites: 4-hydroxy-alprazolam and α-hydroxy-alprazolam in lactating human volunteers and to test the predictability of four recently reported models for drug transfer into milk based on physicochemical properties.

2 Multiple milk and serum samples in eight lactating subjects were collected up to 36 h following single oral doses of 0.5 mg alprazolam; suckling of the infant was discontinued after drug administration. 4-Hydroxy-alprazolam was the predominant metabolite in serum samples while α-hydroxy-alprazolam was not detected.

3 The mean oral clearance of alprazolam was 1.15 ± 0.32 ml min^{-1} kg^{-1}. The time course of alprazolam in milk roughly paralleled the respective plasma time profile (mean serum residence time = 16.42 ± 4.69 h; mean milk residence time = 18.93 ± 7.03 h). The mean terminal half-life in serum was 12.52 ± 3.53 h.

4 Observed milk/serum concentration ratios were determined *in vivo* as AUC_{milk}/AUC_{serum} (mean M/S_{obs} = 0.36 ± 0.11). Predicted M/S ratios were calculated from the *in vitro* measures of the unbound fractions of alprazolam in serum and skim milk (mean f_s = 0.18 ± 0.02, mean f_m = 0.74 ± 0.05 respectively); the unionized fractions in serum and whole milk (both values approached unity); the skim to whole milk drug concentration ratio (mean S/W = 0.86 ± 0.09); crematocrit (mean Cr = 0.06 ± 0.02), and assuming the milk lipid:ultrafiltrate partition coefficient, P_m = 5.48. The diffusion based models using *in vitro* measurements adequately predicted M/S_{obs}.

5 In conclusion, the neonatal dose of alprazolam in breast milk is low [between 0.3–5 μg kg^{-1} day^{-1}; or 3% (body weight adjusted) of the maternal dose] and its transfer into milk was consistent with a passive diffusion mechanism.

Keywords alprazolam pharmacokinetics blood-milk transfer prediction model breast feeding

Introduction

Benzodiazepines as a class, are the most commonly prescribed anxiolytics in the United States. Alprazolam (Xanax®) a triazolo-benzodiazepine introduced in 1980, has replaced diazepam as the most widely prescribed benzodiazepine; partly due to its shorter half-life resulting in less cumulative drowsiness [1, 2]. It is commonly prescribed for the treatment of generalized anxiety disorder and panic disorder which are twice as frequently manifested among women than among men [3, 4]. The age of onset is usually 18–45 years old which coincides with age of child bearing. The incidence of psychiatric illness is higher in the first 12 weeks of postpartum than at any other time in a women's life [5]. Breast feeding has its inherent

Correspondence: Dr P. J. McNamara, Division of Pharmacology and Experimental Therapeutics, University of Kentucky, Lexington, Ky 40536

advantages in terms of milk composition, immunoprotection, and bonding [6]. Benzodiazepines such as diazepam, oxazepam, lorazepam, lormetazepam, quazepam, midazolam, nitrazepam, flunitrazepam, metaclazepam and lormetazepam have been found in breast milk to varying degrees, with milk:serum (M/S) ratios ranging from 0.1–3 [7–16]. These reports show that neonatal levels were generally low and not associated with obvious adverse effects, with the exception of sedation [16]. However, the impaired ability of the neonate to oxidize and conjugate benzodiazepines prior to their renal elimination continues to be a clinical concern [17]. Faced with limited treatment option, clinicians have a propensity to advise lactating mothers suffering from anxiety or panic disorders to refrain from breast feeding.

Very little is known about the blood-milk transfer of alprazolam, or its two major metabolites: α-hydroxy-alprazolam and 4-hydroxy-alprazolam. In a cohort study, mild drowsiness in an infant which resolved spontaneously despite continued therapy was reported in one of the five cases in which alprazolam was being consumed by the breast feeding mothers [18]. However, an estimate of the infant's dose could not be made as no plasma or milk concentrations were assayed. A more rigorous study design is needed to address the potential exposure of alprazolam in view of its prevalent use in women of child bearing age.

Previously, we have proposed a diffusion model to predict the transfer of drug into milk based on physicochemical properties of the drug [19–21]. The model incorporates pH partition theory, binding to serum and milk proteins, and partitioning into milk fat to make prediction of M/S ratio. A direct comparison of the model predictions with *in vivo* measurements for a number of model compounds were made using lactating New Zealand White rabbits [20, 21]. Three other diffusional models have been proposed by Atkinson & Begg [22], Begg & Atkinson [23], and by Stebler & Guentert [24]. To date, none of these models has been prospectively tested in humans. The availability of a good model is appealing because of its potential to make useful clinical prediction from the physicochemical data.

The purpose of the study was to study the blood-milk transfer of alprazolam in lactating women and to validate model prediction of M/S ratio from the *in vitro* determinations.

Methods

Subjects and study design

The study population consisted of eight healthy, non-obese, lactating human volunteers 6–28 weeks postpartum who had decided to stop nursing or suspend nursing for the duration of the study. All subjects signed the informed consent forms according to the University Institutional Review Board prior to their participation in the study. The subjects did not receive any known enzyme inducing or inhibiting agents for a period of 30 days, or any other medication for a period of 7 days, or alcohol 2 days preceding their participation in this study. An electronic breast pump (Egnell LACT-E, Cary IL) was used for the collection of milk samples. Each subject received a single oral dose of alprazolam (two 0.25 mg Xanax® Tablets). Multiple blood (7 ml) and milk (15–60 ml) samples were obtained at 0.0, 0.25, 0.50, 1.0 2.0, 4.0 6.0, 8.0, 12.0, 24.0 and 36 h. Prior to dosing, blank serum and milk samples were obtained for *in vitro* determinations of pH, skim to whole milk concentration ratio, protein binding and crematocrit. Following collection, milk samples and serum samples were harvested and immediately stored at −20° C until drug analysis.

In vitro *determinations*

Measurements of milk pH were performed anaerobically at 37° C within 1 h of collection using a clinical blood gas analyzer. Fresh whole milk (spiked with [^{14}C]-alprazolam) was vortexed gently for 1 min. An aliquot of 100 μl of whole milk was removed (in triplicate) for analysis. The remaining whole milk was centrifuged at 15,000 rev min^{-1} for 5 min. Aliquots of the skim milk (100 μl, triplicates) were analyzed. Subsequently, skim to whole milk concentration ratio (S/W) was calculated. Skim milk samples (300 μl), in triplicates (spiked with [^{14}C]-alprazolam) were dialyzed in plexiglass cells (separated by Spectorpor-2- dialysis membrane with M.W. cutoff of 12,000–14,000) for 6 h against pH 7.1 phosphate buffer at 37° C. At the end of dialysis, 5 ml of scintillation fluid was added to each of the 200 μl aliquots of buffer and skim milk, which were then counted in a scintillation counter. Volume shift in each chamber, as well as pH of the buffer were measured. The ratio of the buffer to milk is the free fraction in skim milk (f_m). Similarly, the free fraction in serum (f_s) was determined with serum dialyzed against pH 7.2 phosphate buffer; which increased to approximately 7.4 after 6 h dialysis. Fresh, well mixed milk sample was drawn into a sealed haematocrit tube and centrifuged for 10 min. The length of the creamy layer was measured with a magnifying glass with imprinted micro-scale. The percentage of the length of the creamy layer to the whole length was defined as the crematocrit.

Analytical assay

To 2 ml of whole milk, 50 μl of standard solution (15.6 to 250 ng ml^{-1} of alprazolam, 4-hydroxy-alprazolam and α-hydroxy-alprazolam) and 25 μl of internal standard (206 ng ml^{-1} diazepam) was added. Acetonitrile (5 ml) was added dropwise while vortexing gently to precipitate the milk proteins. After standing for 5 min in a −20° C freezer, the supernatants were transferred and evaporated under nitrogen gas until about 0.5 ml remained. Water (1 ml) was added to the remaining supernatant and then loaded into a Bond Elut CN solid-phase extraction

cartridge (Varian®, Harbour City, CA), which had been preactivated with 2 ml methanol followed by 2 ml Milli-Q water. The cartridge was rinsed with 1 ml Milli-Q water and centrifuged for 1 min to remove any residual water. The cartridge was then reset on the Vac Elut manifold and eluted with two 1 ml volumes of acetonitrile. After blow-drying, 135 µl acetonitrile was added. The reconstituted sample (100 µl) was injected into a h.p.l.c. system (Shimadzu Scientific Instruments Inc., Columbia, MD). The mobile phase consisted of acetonitrile:isopropanol:Milli-Q water (336:32:20). The flow rate was 1 ml min^{-1} and the effluent was detected at 223 nm u.v. Separations were carried out on a Zorbax Silica column (250 mm × 4.6 mm i.d.) with a Zorbax Silica guard column (12.5 mm × 4.0 mm i.d.). The retention times were 5.6, 8.8, 10.2 and 14.0 min for diazepam, α-hydroxy-alprazolam, 4-hydroxy-alprazolam and alprazolam respectively. The serum procedure was similar to the milk procedure with the following exceptions. The sample size used was 1 ml serum. The internal standard used was 4-hydroxy-triazolam (517.5 ng ml^{-1}). The mobile phase consisted of acetonitrile:isopropanol:Milli-Q water (336:40:26). The retention times were 6.4, 7.0, 8.1 and 11.0 min for 4-hydroxy-triazolam, α-hydroxy-alprazolam, 4-hydroxy-alprazolam and alprazolam respectively.

Data analysis

Serum and milk drug concentration *vs* time data were analyzed by fitting a triexponential equation to these profiles using nonlinear regression analysis (RSTRIP, MicroMath, Salt Lake City, UT). Area under the drug concentration-time curve (AUC) and area under the first moment curve (AUMC) were determined from the coefficients and exponents of these fitted relationships. The subscripts s and m refer to serum and milk, respectively. Peak alprazolam concentrations (C_{max}) and the corresponding times (t_{max}) were noted directly from the data.

$$M/S_{obs} = \frac{AUC_m}{AUC_s} \qquad \text{Equation 1}$$

Oral clearance (CL_{po}) was calculated from

$$CL_{po} = \frac{Dose}{AUC_s} \qquad \text{Equation 2}$$

Mean residence time was determined as

$$MRT = \frac{AUMC}{AUC} \qquad \text{Equation 3}$$

Four recently published models have been proposed to predict the distribution of drugs between milk and plasma. Predicted M/S value (M/S_{pred}) can be calculated from the *in vitro* physicochemical properties of the drug, assuming a passive simple diffusion.

Predicted M/S values of Model 1 (Fleishaker *et al.*, 1987) [19] were derived by assuming only the free, unionized xenobiotic will be able to cross the blood-milk barrier:

$$M/S_{pred1} = \frac{f_s^{un} f_s}{f_m^{un} f_m (S/W)} \qquad \text{Equation 4}$$

where f^{un} and f values refer to fractions unionized and unbound in the respective fluids of milk or serum and S/W is the skim to whole milk partition ratio.

Predicted M/S values of Model 2 (Atkinson & Begg, 1990) [22] were calculated from the summation of the contribution of the skim milk portion and the milk fat portion:

$$M/S_{pred2} = \frac{f_s^{un}}{f_m^{un}} f_s K \qquad \text{Equation 5}$$

where K is defined by

$$K = \left[\frac{(1\text{-}Cr)}{f_m} + Cr\, P_m \right] \qquad \text{Equation 6}$$

and Cr is the crematocrit; P_m is the milk lipid:ultrafiltrate partition coefficient which is estimated from the derived relationship with octanol: water partition coefficient: $\log P_m = -0.88 + 1.29 \log (O/W)$ [25]. The O/W value of alprazolam is 18 [26].

Predicted M/S values of Model 3 as modified via ln transformation and regression analysis for basic drugs (Begg & Atkinson, 1993) [23] yields

$$\ln M/S_{pred3} = 0.025 + 2.28 \ln \left(\frac{f_s^{un}}{f_m^{un}} \right) + 0.886 \ln f_s + 0.505 \ln K \qquad \text{Equation 7}$$

Predicted M/S values of Model 4 (Stebler & Guentert, 1992) [24] used extended Model 2 by incorporating measured S/W ratio:

$$M/S_{pred4} = \frac{f_s^{un} f_s}{f_m^{un}} \left[\frac{(1\text{-}Cr)}{f_m} S/W + CrP_m (1\text{-}S/W) \right] \qquad \text{Equation 8}$$

The regression coefficients (r^2) of the four models were used in testing significant difference from one another (Z-test) at $P < 0.05$ [27]. In addition, the model with the lowest absolute mean error (ME), mean square error (MSE) and root mean square error (RMSE) would be deemed superior [28].

Results

The mean weight of the eight subjects was 62.7 ± 8.0 kg. The mean postpartum period was 11.8 ± 2.3 weeks. The mean pH of milk prior to drug administration was 7.13 ± 0.12. 4-Hydroxy-alprazolam was found in serum, but not milk, at the detection limit of 0.5–1 ng ml^{-1} or less; α-hydroxy-alprazolam was not detected in any of the samples. The serum and milk concentration-time profile of alprazolam for a representative subject following the oral administration of alprazolam is presented in Figure 1. Alprazolam concentrations in serum and milk peaked and declined in

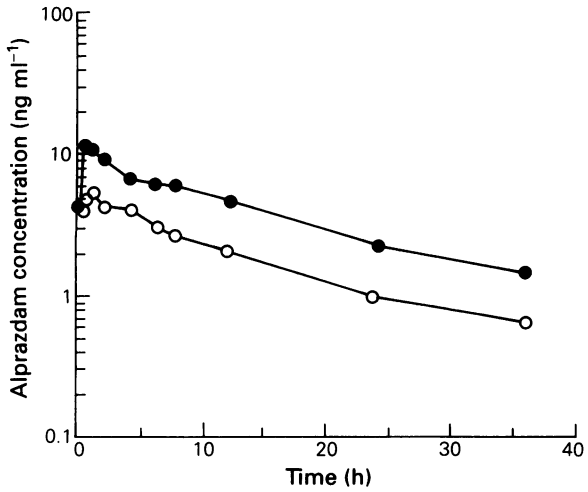

Figure 1 Concentration-time profile for alprazolam in serum (●) and milk (○) following an oral dose of 0.5 mg alprazolam in a representative lactating human volunteer.

Table 1 Mean (± s.d.) values (t_{max} is median and range) for pharmacokinetic parameters for alprazolam after an oral dose of 0.5 mg alprazolan in eight lactating human volunteers

Parameter	*Serum*	*Milk*
C_{max} (ng ml^{-1})	8.88 ± 2.69	3.70 ± 1.59
t_{max} (h)	0.60	1.10
	(0.45–2.65)	(0.47–3.83)
MRT (h)	16.42 ± 4.69	18.93 ± 7.03
$t_{1/2,z}$ (h)	12.52 ± 3.53	14.46 ± 6.27
CLpo (ml min^{-1} kg^{-1})	1.15 ± 0.32	

Table 2 Values for f_s, f_m, S/W and Cr obtained from *in vitro* studies for eight lactating human volunteers

Patient	f_s	f_m	*S/W*	*Cr*
1	0.181	0.665	0.855	0.078
2	0.184	0.785	0.644	0.081
3	0.209	0.809	0.898	0.097
4	0.160	0.689	0.886	0.047
5	0.176	0.701	0.864	0.048
6	0.214	0.701	0.905	0.042
7	0.188	0.760	0.898	0.065
8	0.170	0.784	0.924	0.036
Mean	0.185	0.737	0.859	0.062
s.d.	0.018	0.054	0.090	0.022

Table 3 Values for predicted M/S for four models obtained from *in vitro* studies and M/S_{obs} from *in vivo* studies for eight lactating human volunteers

Patient	*Model 1*	*Model 2*	*Model 3*	*Model 4*	*M/Sobs*
1	0.318	0.328	0.304	0.226	0.438
2	0.364	0.297	0.291	0.168	0.488
3	0.288	0.345	0.330	0.221	0.188
4	0.263	0.263	0.260	0.201	0.283
5	0.290	0.285	0.281	0.213	0.446
6	0.337	0.341	0.331	0.269	0.457
7	0.276	0.299	0.295	0.215	0.332
8	0.235	0.242	0.255	0.196	0.245
Mean	0.296	0.300	0.293	0.213	0.360
s.d.	0.042	0.037	0.025	0.029	0.113
MSE	0.014	0.019	0.020	0.044	—
RMSE	0.117	0.138	0.143	0.209	—
ME	−0.063	−0.060	−0.066	−0.146	—

ME, Mean error (bias indicator).
MSE, Mean Square Error.
RMSE, Root Mean Square Error (precision indicator).

roughly a parallel fashion. The pharmacokinetic analysis of the data is given in Table 1. As reflective of the time profile depicted in Figure 1, the time of peak concentration and the mean residence time in milk were equivalent to their respective values in serum. Milk concentrations were lower than the serum concentrations as shown by the lower values for peak concentrations and AUC values.

The *in vitro* parameters used to estimate the predicted M/S values are presented in Table 2. Fractions unionized for both serum and milk are unity as the pKa of alprazolam is 2.8. The predicted M/S values of the four models and the observed M/S values are presented in Table 3. From the mean M/S predicted value, Model 1 (0.296 ± 0.042), Model 2 (0.300 ± 0.037) and Model 3 (0.293 ± 0.025) were found to be closer to the mean M/S observed (0.360 ± 0.113) than Model 4 (0.213 ± 0.029). Although not statistically significantly different from one another ($P > 0.05$), Model 1 has the highest regression coefficient (r^2 = 0.604, 0.049, 0.029, 0.009, respectively), the lowest sum of square error (MSE = 0.014, 0.019, 0.020, 0.044, respectively), and the lowest root mean square error compared with Model 2, Model 3 and Model 4 (0.117, 0.138, 0.143, 0.209, respectively) (Table 3). Model 4 has a higher mean error (−0.146) than Model 1, Model 2 and Model 3 which have similar mean error (−0.063, −0.060, −0.066, respectively) (Table 3).

Discussion

Lactation did not change the serum pharmacokinetic parameters of alprazolam except the free serum fraction (f_s = 18%; literature reported f_s = 24–31% [2]). The reason for a lower free serum fraction for the study is unclear. Low concentrations of 4-hydroxyalprazolam were detected in serum while α-hydroxyalprazolam was not detected at all following an oral dose of 0.5 mg alprazolam. This finding is consistent with the literature in that less than 10% of the dose is detected as metabolites in serum, with 4-hydroxyalprazolam as the major metabolite [29–32].

As with other benzodiazepines [7–16], alprazolam is rapidly absorbed and distributed into milk, with the time of peak concentration of both serum and milk around 60 min. The parallel blood and milk concentration-time profile suggests that alprazolam can readily diffuse across the blood-milk barrier in a

bidirectional fashion. Peak concentration in milk is 60% lower than serum peak concentration, in line with the M/S_{obs} value of 0.36. The lower peak concentration in milk and the M/S_{obs} value when compared with other benzodiazepines, such as diazepam may be caused by the lower partitioning into milk fat or S/W (ln octanol:water partition coefficient 468 *vs* 18 for diazepam and alprazolam, respectively) and a lower serum protein binding of alprazolam compared with diazepam.

The linear and dose-independent nature of alprazolam pharmacokinetics over a wide range of doses have been shown [33, 34]. Hence, extrapolation from the present single dose study to the steady-state situation appears justified. Steady state serum concentration of 20–40 ng ml^{-1} of alprazolam is needed for treating anxiety disorders, while concentrations above 40 ng ml^{-1} may be required for optimal suppression of panic attacks [29]. By using the mean oral clearance (1.15 ml min^{-1} kg^{-1}) and the mean observed M/S ratio (0.36) obtained from the present study, the approved range of daily doses of alprazolam of 10–140 μg kg^{-1} day^{-1} [29], and an ingested milk volume of 150 ml kg^{-1} day^{-1} [35] the average dose ingested by the neonate can range from 0.5–5 μg kg^{-1} day^{-1} or around 3% of the maternal dose (body weight adjusted).

In order to utilize the infant dose as an indication of neonatal risk during alprazolam exposure via lactation, two assumptions are required. First, the assumption that the clearance of alprazolam (on a body weight basis) is comparable in the infant, hence a similar dose would give rise to comparable serum concentrations. Some evidence would suggest that drug metabolic activity is not fully expressed in the newborn, with reports of the impaired ability of the neonate to oxidize and conjugate benzodiazepines [17]. The second assumption is that the resulting serum concentration of alprazolam would evoke the same pharmacodynamic response in the infant. Pharmacokinetic and pharmacodynamic relationships, in general, have not been well-characterized in the newborn. In this regard, no pharmacokinetic/pharmacodynamic studies of alprazolam have been conducted in the human newborn. Despite these caveats, the present analysis would suggest that alprazolam breast milk concentrations would be low and unlikely to result in any pharmacological effect on the nursing infant. However, good clinical judgement should be exercised in weighing the benefits of breastfeeding versus any potential risk to the infant.

In terms of the predictive models, Model 1, 2 and 3 estimated well the observed M/S; while Model 4 seemed to be inadequate. It should be noted that both Model 1 and 2 use the same three physicochemical characteristics (ionization fraction; protein binding and lipid solubility). The difference being that Model 2 utilized octanol:water partitioning ratio to predict milk fat partitioning while Model 1 incorporated a direct measurement of skim:whole milk concentration ratio. These two models can be regarded as essentially equivalent as they can be derived from each other. Model 3 is derived from regression analysis of Model 2 for a series of weak bases [23]. It should be noted that Model 2 and 3 were derived from a series of drugs and were not intended to be predictive of variation for one drug within a group of subjects [22, 23].

Comparisons of predictive models should be approached with a specific goal. The original objective of Model 1 was to test the hypothesis that most drugs distribute into milk by passive processes. When substantial deviations from model predictions are observed (i.e., cimetidine in rats [36]), a mechanism other than passive diffusion, such as active transport, is proposed. To explore mechanisms of drug transfer into milk, Model 1 appears most appropriate given sufficient *in vitro* data. Model 3 would appear to offer advantages as an *a priori* prediction based on established physiochemical characteristics of the drug and limited experimental data. Model 4 was used to predict M/S ratio for diazepam when Model 1 and 2 appeared to systematically underpredict the *in vivo* value in rabbits [24]. The derivation of the Model 4 relationship was not presented [24] and its value to aid in the prediction of mechanism of transfer (passive *vs* active) or its widespread application to other drugs has not been evaluated.

In conclusion, the neonatal dose of ingested alprazolam is low when alprazolam is administered to the breast-feeding mother. Human M/S ratio for alprazolam was readily predicted from *in vitro* determinations and the overall results support using diffusional models for predicting transfer of alprazolam into breast milk.

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References

1 Garzone PD, Kroboth PD. Pharmacokinetics of the Newer Benzodiazepines. *Clin Pharmacokin* 1989; **16**: 337–364.

2 Greenblatt DJ, Wright CE. Clinical pharmacokinetics of alprazolam: Therapeutic Implications. *Clin Pharmacokin* 1993; **24**: 453–471.

3 Shader RI, Greenblatt DJ. Use of benzodiazepines in anxiety disorders. *N Engl J Med* 1993; **328**: 1399–1409.

4 Michels R, Marzuk PM. Progress in psychiatry. *N Engl J Med* 1993; **329**: 628–638.

5 Buist A, Norman TR, Dennerstein L. Breastfeeding and the use of psychotropic medication: a review. *J Affect Disorders* 1990; **19**: 197–206.

6 Lawrence RA. Breastfeeding and medical disease. *Med Clin North Am* 1989; **73**: 583–603.

7 Erkkola R, Kanto J. Diazepam and breastfeeding. *Lancet* 1972; i: 1235–1236.

8 Brandt R. Passage of diazepam and desmethyldiazepam into breast milk. *Arzneim-Forsch/Drug Res* 1976; **26**: 454–457.

9 Wretlind M. Excretion of oxazepam in breast milk. *Eur J Clin Pharmacol* 1987; **33**: 209–210.
10 Whitelaw AG, Cumminngs AJ, McFadyen IR. Effect of maternal lorazepam on the neonate. *Br Med J* 1981; **282**: 1106–1108.
11 Hilbert JM, Gural RP, Symchowicz S. Excretion of quazepam into breast milk. *J Clin Pharmacol* 1984; **24**: 457–462.
12 Kanto J, Aaltonen L, Kangas L, Erkkola R, Pitkanen Y. Placental transfer and breast milk levels of flunitrazepam *Curr Ther Res* 1979; **26**: 539–546.
13 Matheson I, Lunde PKM, Bredesen JE. Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. *Br J Clin Pharmacol* 1990; **30**: 787–793.
14 Muller AS, Gunther C, Hausleiter HJ, Achtert G. Transfer of metaclazepam and its metabolites into breast milk. *Arzneim Forsch/Drug Res* 1989; **39**: 1468–1470.
15 Humpel M, Stoppelli I, Milia S, Rainer E. Pharmacokinetics and Biotransformation of the New Benzodiazepine, Lormetazepam, in Man; III. Repeated administration and transfer to neonates via breast milk. *Eur J Clin Pharmacol* 1982; **21**: 421–425.
16 Patrick MJ, Tilstone WJ, Reavey P. Diazepam and breastfeeding. *Lancet* 1972; **i**: 542–543.
17 Szefler SJ. Drug excretion in human breast milk: potential effect on infant development. *J Pediatr Gastroenterol Nutr* 1983; **2**: S120–S126.
18 Ito S, Blajchman A, Stephenson M, Eliopoulos C, Koren G. Prospective follow-up of adverse reactions in breastfed infants exposed to maternal medication. *Am J Obstet Gynecol* 1993; **168**: 1393–1399.
19 Fleishaker JC, Desai N, McNamara PJ. Factors affecting the milk to plasma drug concentration ratio in lactating women: Physical interactions with protein and fat. *J Pharm Sci* 1987; **76**: 189–193.
20 Fleishaker JC. McNamara PJ. *In vivo* evaluation in the lactating rabbit of a model for xenobiotic distribution into breast milk. *J Pharmacol Exp Ther* 1988; **244**: 919–924.
21 Fleichaker JC, McNamara PJ. Effect of altered serum protein binding on propranolol distribution into milk in the lactating rabbit. *J Pharmacol Exp Ther* 1988; **244**: 925–928.
22 Atkinson HC, Begg EJ. Prediction of drug distribution into human milk from physicochemical characteristics. *Clin Pharmacokin* 1990; **18**: 151–167.
23 Begg EJ, Atkinson HC. Modelling of the passage of drugs into milk. *Pharmac Ther* 1993; **59**: 301–310.
24 Stebler T, Guentert TW. Studies on the excretion of diazepam and nordiazepam into milk for the prediction of milk-to plasma drug concentration ratios. *Pharm Res* 1992; **9**: 1299–1304.
25 Atkinson HC, Begg EJ. Relationship between human milk lipid:ultrafiltrate and octanol:water partition coefficients. *J Pharm Sci* 1988; **77**: 796–798.
26 Greenblatt DJ, Arendt RM, Abernethy DR, *et al.* In vivo quantitation of benzodiazepine lipophilicity in relation to *in vivo* distribution. *Br J Anaesth* 1983; **55**: 985–989.
27 Kleinbaum DG, Kupper LL, Muller KE. *Applied regression analysis and other multivariable methods*, second edition. 1988; 92–93. PWS-KENT Publishing Co. Boston.
28 Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. *J Pharmacokinet Biopharm* 1981; **9**: 503–512.
29 Ciraulo DA, Antal EJ, Smith RB, *et al.* The relationship of alprazolam dose to steady-state plasma concentrations. *J Clin Psychopharmacol* 1990; **10**: 27–32.
30 Smith RB, Kroboth PD. Influence of dosing regimen on alprazolam and metabolite serum concentrations and tolerance to sedative and psychomotor effects. *Psychopharmacol* 1987; **93**: 105–112.
31 Dehlin O, Kullingsjo H, Liden A, *et al.* Pharmacokinetics of alprazolam in geriatric patients with neurotic depression. *Pharm Toxicol* 1991; **68**: 121–124.
32 Kroboth PD, McAuley JW, Smith RB. Alprazolam in the elderly: pharmacokinetics and pharmacodynamics during multiple dosing. *Psychopharmacol* 1990; **100**: 477–484.
33 Fleishaker JC, Phillips JP, Eller MG, Smith RB. Pharmacokinetics and pharmacodynamics of alprazolam following single and multiple oral doses of a sustained-release formulation. *J Clin Pharmacol* 1989; **29**: 543–549.
34 Wright CE, Chambers JH. Influence of alprazolam input rate and steady-state pharmacokinetics on psychomotor performance in healthy subjects. *Pharm Res* 1991; **8**: 250.
35 Wilson JT, Brown RD, Hinson JL, Dailey JW, Pharmacokinetic pitfalls in the estimation of the breast milk/plasma ratio for drugs. *Ann Rev Pharmacol Toxicol* 1985; **25**: 667–689.
36 McNamara PJ, Burgio D and Yoo SD, Pharmacokinetics of cimetidine during lactation: species difference in cimetidine transport into rat and rabbit milk. *J Pharmacol Exp Ther* 1992; **261**: 918–923.

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