Transfer of metformin into human milk

Objectives: Our objectives were to determine the milk-to-plasma ratio of metformin in lactating mothers and to estimate infant exposure.

Methods: Two studies were performed. In study 1, 3 nursing mothers taking metformin were studied throughout a dosing interval at steady state. Blood samples were obtained from 2 suckling infants. In study 2, 5 healthy lactating women who volunteered to express milk after weaning were given metformin, 500 mg, at weaning and were studied for up to 72 hours. In both studies, areas under the plasma and milk concentration-time curves were estimated, and the milk-to-plasma concentration ratio based on area under the concentration-time curve analysis was derived. The infant dose was calculated by standard methods.

Results: In study 1 the milk-to-plasma concentration ratios based on area under the concentration-time curve analysis were 0.37, 0.50, and 0.71. The estimated "doses" of metformin that would be ingested by the breast-fed infants were 0.18%, 0.20%, and 0.21% of the maternal doses, adjusted for weight. In the breast-fed infants, no metformin was detected (n = 2) or adverse effects noted (n = 3). In study 2, the milk-to-plasma concentration ratio based on area under the concentration-time curve analysis was unable to be calculated for 3 subjects because of the unexpected persistence of metformin in milk beyond the study period. For the 2 subjects studied for 72 hours, the milk-to-plasma concentration ratios based on area under the concentration-time curve analysis were 0.27 and 0.47 and the infant doses were 0.11% and 0.25%. The concentration-time profile for metformin in milk in all subjects was unexpectedly flat.

Conclusions: Metformin appears to be "safe" during lactation because of low infant exposure. The unusual concentration-time profile for metformin in milk suggests that the transfer of metformin into milk is not solely dependent on passive diffusion. (Clin Pharmacol Ther 2003;73:71-7.)

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Metformin is an oral biguanide antihyperglycemic agent that is in wide use for the treatment of type 2 diabetes mellitus. It is also finding a niche in the management of polycystic ovary syndrome, a heterogeneous endocrine disorder characterized by hyperandrogenism and chronic anovulation that affects 5% to 10% of premenopausal women.[1] The increasing prevalence of type 2 diabetes mellitus worldwide,[2] coupled with the relatively new role for metformin in polycystic ovary syndrome, suggests that there may be greater use of this agent among women of reproductive age. There is a need for information to guide the use of metformin in lactating mothers.

There appear to be no published data describing the transfer of metformin or related agents (buformin or phenformin) into human breast milk. Metformin is reported to be excreted into the milk of lactating rats, attaining concentrations similar to those that occur in plasma.[3] Substantial interspecies variation means that it is difficult to translate animal data to humans.[4] Models have been developed that attempt to predict transfer from plasma to milk when data from clinical studies are lacking.[5-9] With the use of the Atkinson and Begg model for basic drugs,[8,10] given the assumptions that metformin has negligible protein binding (approximately 1%),[11-13] that the log of the octanol-to-water partition coefficient is −1.43, and that the relevant negative logarithm of the acid ionization constant (pK_a) at physiologic pH is 11.5,[14,15] a milk-to-plasma (M/P)

concentration ratio of 3.0 can be calculated. The method of Agatonovic-Kustrin et al[9] uses the molecular structure of a drug and a computerized neural network to predict transfer and suggests that an M/P ratio of 2.3 can be expected for metformin (personal communication, 2002). On the basis of the assumption that the M/P ratio is 3.0 and infant milk ingestion occurs at a rate of $0.15 \text{ L} \times \text{kg}^{-1} \times \text{d}^{-1}$,[16] the estimated dose that an infant would ingest via milk would be around 1% of the maternal dose, corrected for respective body weight. This would be considered compatible with breast-feeding because it is lower than the arbitrary cutoff of 10% that has been used to guide drug safety.[16]

The aims of this study were to measure the M/P ratio on the basis of the area under the concentration-time curve analysis (M/P_{AUC}) of metformin in lactating mothers and to assess likely infant exposure by estimating the infant's dose and measuring the concentration of metformin in the infant's plasma. A secondary aim was to compare the experimentally determined M/P ratio with that predicted by the two theoretic models.

METHODS

The Canterbury Ethics Committee provided approval for both studies. Informed written consent was obtained from the mothers for their own participation and the involvement of their infants (where appropriate).

Subjects and sampling

Study 1. Three women taking metformin, 500 mg twice daily, for diabetes (subjects 1.1 and 1.2) or polycystic ovary syndrome (subject 1.3) were recruited into this study. Subjects 1.1 and 1.3 had a good supply of milk and were receiving a stable dose of metformin for least 2 weeks before the study. Subject 1.2 was weaning her infant and had been taking metformin for 10 days, with a stable dose for 3 days before the study.

The subjects were admitted to the Department of Medicine Research Centre, Christchurch Hospital, Christchurch, New Zealand, for the first 4 to 5 hours of the study, with the remainder of the study being undertaken in the subjects' homes. Metformin (Metomin, 500-mg tablets; Pacific Pharmaceuticals, Auckland, New Zealand) was administered after a nonstandardized breakfast at the time the mother would usually take her dose (around 8 to 9:30 AM). The subjects fed their infants before metformin ingestion, and a sample of milk was retained for measurement of metformin concentrations.

Maternal blood samples (5-10 mL) were taken via an indwelling intravenous catheter or by venipuncture throughout a dosing interval at approximately 0 (predose), 1, 2, 4, 6 to 8, and 10 to 12 hours after administration of metformin. The exact time of sampling was recorded. Blood was drawn into Vacutainer tubes (Becton Dickinson & Co, Rutherford, NJ) containing ethylenediaminetetraacetic acid and immediately centrifuged at $3000g$ for 10 minutes. Separated plasma was removed, stored at $-80°C$, and analyzed within a week. Milk was collected from both breasts by a manual or electric breast pump at the time that the infant would normally be fed or at approximately 2, 4, 6 to 8, and 10 to 12 hours after dosing. There were two methods of milk collection. Subject 1.2 emptied her breasts of milk at each expression, the milk was mixed, the volume was recorded, and an aliquot (<10 mL) was taken for analysis. Subjects 1.1 and 1.3 provided samples from the middle of each period of breast-feeding. The samples of milk were stored at $-80°C$ before analysis.

A single sample of blood (<2 mL) was taken from the infants of subjects 1.1 and 1.2 for measurement of metformin concentrations. All 3 mothers were asked about any side effects in their infants that they attributed to metformin administration, with particular reference to signs of gastrointestinal upset such as altered feeding habits or diarrhea.

Study 2. Five healthy lactating female subjects (subjects 2.1, 2.2, 2.3, 2.4, and 2.5) volunteered for the single-dose study on the basis that they were to stop breast-feeding at the time of the study and that breast milk during and after the study would not be fed to their infants. Subjects were excluded if they were taking other medicines that were likely to interact with metformin or if they had known medical conditions that may have compromised the study or the subject's health (eg, kidney disease).

Subjects 2.1, 2.2, and 2.3 spent the first 4 to 5 hours of the study at the Department of Medicine Research Centre and the remainder in their homes. Subjects 2.4 and 2.5 were studied completely at home. All subjects ingested metformin, 500 mg orally (Metomin, 500-mg tablets), after a nonstandardized breakfast at approximately 8:30 AM on the study day. The exact time of the dose was recorded.

Maternal blood samples (5-10 mL) were taken at approximately 0 (predose), 1, 2, 4, 8, and 12 hours after dosing, and the exact time was recorded. Additional blood samples were taken at 24 hours in subjects 2.2, 2.3, 2.4, and 2.5. Milk was collected over a 12-hour period for subject 2.1, over a 24-hour period for subjects 2.2 and 2.3, and over a 72-hour period for subjects 2.4 and 2.5. All subjects emptied both breasts of milk with an electric or manual breast pump before admin-

istration of the drug, and a 10-mL sample was retained for analysis. At approximately 2, 4, 8, and 12 hours after dosing, all subjects emptied both breasts, with the exact time recorded. Subjects 2.2, 2.3, 2.4, and 2.5 provided further samples at 24 hours after dosing. Subjects 2.4 and 2.5 provided 4 further samples per day from 24 to 72 hours after ingestion. At each expression, the milk was mixed, the volume measured, and a sample (10 mL) retained for analysis. In some instances, the volume of milk at the expression was <10 mL and all milk was kept. Any excess milk was discarded.

Analytic methods

An HPLC assay was used for the determination of metformin concentrations in plasma and milk. The method has been described elsewhere.[17] All plasma and milk standard curves were linear ($r^2 > 0.99$) over the range 20 to 4000 μg/L. The intraday and interday coefficients of variation (CVs) of the assay were less than 9% at the concentrations of 62.5, 250, 1000, and 4000 μg/L, and the limit of detection (signal-to-noise ratio, 3:1) was 20 μg/L for both plasma and milk.

A different HPLC machine was used to analyze the plasma and milk samples from subjects 2.4 and 2.5 and the infant samples. A lower limit of detection (≥ 5 μg/L) was observed. For this HPLC machine, the standard curves for milk were linear over the range 5 to 4000 μg/L ($r^2 > 0.99$), and the intraday CV of the assay was 13.6% for 10 μg/L and 17.4% for 5 μg/L. The intraday and interday CVs of the assay at concentrations of 62.5, 250, 1000, and 4000 μg/L were as described except that the interday CV at 62.5 μg/L was 11.2%.

All blood and milk samples were analyzed in triplicate and the mean values used in subsequent analyses.

Data analysis

Study 1. With regard to the pharmacokinetic analysis, the time to peak concentration and the maximum concentration were read directly from the data. The plasma area under the concentration-time curve (AUC) for the dosing interval [AUC(0-τ)] was calculated with the use of the linear trapezoidal rule for the ascending part of the curve and the log-linear trapezoidal rule for the descending part of the curve with the use of TOP-FIT (version 2.0; Gustav Fischer, Stuttgart, Germany). The AUC(0-τ) for milk was calculated with use of rectangular areas (sum of concentrations multiplied by collection times). The M/P$_{AUC}$ was calculated by dividing the AUC(0-τ) for metformin in milk by the AUC(0-τ) for metformin in plasma.

The absolute infant dose (in milligrams per kilogram per day) was calculated as the product of the mean milk concentration [AUC(0-τ)/Dose interval] and the estimated infant milk ingestion of $0.15 \text{ L} \times \text{kg}^{-1} \times \text{d}^{-1}$.[16] The infant's dose was expressed as a percentage of the maternal dose, after adjustment for body weight.

Study 2. With regard to the pharmacokinetic analysis, the plasma AUC(0-∞) was calculated as for study 1, except that an estimation of the terminal elimination rate constant (k_e) was made by linear regression of the visually determined postabsorptive elimination phase. This enabled extrapolation of the AUC from the last measurable point (C_{last}) to infinity (ie, C_{last}/k_e). For subjects 2.4 and 2.5, the AUC(0-∞) for milk was calculated with use of rectangular areas (sum of concentrations multiplied by collection interval in hours).

The absolute infant dose was calculated as the product of the mean milk concentration [AUC(0-∞)/12] and infant milk ingestion of $0.15 \text{ L} \times \text{kg}^{-1} \times \text{d}^{-1}$. The absolute infant dose was expressed as a percentage of the weight-adjusted maternal dose. It was assumed that the AUC(0-∞) after a single 500-mg dose of metformin would be equal to the AUC from 0 to 12 hours for a steady-state dosing schedule of 500 mg twice daily.

RESULTS
Study 1

The demographic details for subjects and their infants are presented in Table I and a summary of the results in Table II. Measured peak plasma concentrations were approximately 0.5 to 0.7 mg/L and occurred 2 to 4 hours after dose ingestion. The plasma half-life ranged from 2.4 to 3.9 hours. Milk concentrations were relatively consistent throughout the entire dosing interval, and mean milk concentrations ranged from 0.13 to 0.27 mg/L. In all 3 subjects, metformin milk concentrations were higher than plasma concentrations at time 0 and at the end of the dosing interval. The AUCs for plasma were 3.51, 3.80, and 4.23 mg/L × h, and those for milk were 1.74, 2.71, and 1.57 mg/L × h, respectively. The M/P$_{AUC}$ ratios were 0.37, 0.50, and 0.71, and the infant doses were 0.18%, 0.20%, and 0.21% of the maternal dose, corrected for respective weights. The plasma and milk concentration-time profile for a typical patient (subject 1.3) is displayed in Fig 1. This figure demonstrates the rise and fall of metformin plasma concentrations and the very flat concentration-time profile of metformin in milk. All subjects displayed similar profiles.

Metformin was not detected in the plasma of the 2 infants for whom blood samples were available (limit of detection, 5 μg/L). For the infant of subject 1.1, the sample was taken 3.5 hours after maternal dose inges-

Table I. Demographic data for all subjects and their infants and duration of study

| Subject No. | Mother | | | Infant | | |
	Age (y)	Weight (kg)	Other drug therapy	Age (mo)	Weight (kg)	Study duration (h)
Steady-state study						
1.1	36	78	—	2	5	12
1.2	41	51	—	14	10	12
1.3	38	91	—	5	7	12
Single-dose study						
2.1	32	73	Erythromycin, 400 mg twice daily; ethynodiol diacetate, 0.5 mg/d	4.5	8	12
2.2	32	65	—	7	8	24
2.3	36	63	—	10	11	24
2.4	35	57	Diclofenac, 75 mg/d	14	10	72
2.5	35	63	Folic acid, 0.8 mg/d	14.5	10	72

Table II. Metformin concentrations in maternal plasma and milk, M/P_{AUC} ratio, and infant doses and plasma concentrations

| Subject No. | Maternal dose $(mg \cdot kg^{-1} \cdot d^{-1})$ | M/P_{AUC} | Mean milk concentration (mg/L) | Infant dose | |
				Absolute $(mg \cdot kg^{-1} \cdot d^{-1})$	Relative (%)*
Steady-state study					
1.1	12.8	0.50	0.17	0.026	0.20
1.2	19.6	0.71	0.27	0.041	0.21
1.3	11.0	0.37	0.13	0.020	0.18
Single-dose study					
2.1	13.7†	—	—	—	—
2.2	15.4†	—	—	—	—
2.3	15.9†	—	—	—	—
2.4	17.5†	0.27	0.13	0.020	0.11
2.5	15.9†	0.47	0.27	0.040	0.25
Median		0.47	0.17	0.041	0.20

M/P_{AUC}, Milk-to-plasma concentration ratio based on area under the concentration-time curve analysis.
*Infant dose (in milligrams per kilogram) as a percentage of the maternal dose (in milligrams per kilogram).
†Assuming 500 mg twice daily.

tion, with the most recent breast-feeding having occurred 2.3 hours after dosing. For subject 1.2, the blood sample was taken 1.2 hours after maternal dose ingestion, with the most recent breast-feeding having occurred 2 hours before maternal dose ingestion. None of the infants had evidence of adverse effects that could be attributed to metformin. Subject 1.2 had concerns regarding loose stools and diaper rash in her infant, although these resolved despite ongoing metformin therapy.

Study 2

Demographic data for all subjects and their infants are shown in Table I. Subjects 2.1, 2.4, and 2.5 underwent additional drug therapy in the 2 weeks before the study. Erythromycin was temporarily discontinued for

24 hours before the study in subject 2.1 because of concerns regarding possible gastrointestinal prokinetic effects.

For plasma, the median peak plasma concentration was approximately 0.8 mg/L (range, 0.5-1.0 mg/L) and occurred 2 to 4 hours after dose ingestion. The plasma half-life ranged from 2 to 3 hours. For milk, metformin was detected as early as 2.2 to 2.3 hours after dosing (subjects 2.2 and 2.5). For the remaining subjects, metformin was not quantifiable at the first expression after maternal dose ingestion (around 2 hours) but was detected at the second expression (≥4 hours). The median AUC(0-∞) for the 5 subjects was 4.66 mg/L × h (range, 3.11-6.36 mg/L × h), and in all cases the study period accounted for more than 90% of the AUC(0-∞) for metformin. For milk, a flat concentration-time curve

was observed in all subjects with a median maximum metformin concentration of 0.07 mg/L (range, 0.05-0.11 mg/L) (ie, approximately 10% of the maximum plasma concentrations). Metformin milk concentrations were increasing at the end of the 12-hour milk collection period for subject 2.1, resulting in extension of the study duration to 24 hours for subjects 2.2 and 2.3. Persistence of metformin in milk in these subjects at 24 hours led to extension of milk collection to 72 hours for subjects 2.4 and 2.5 in an attempt to capture the decline in metformin milk concentrations. For these 2 subjects, this was achieved, with metformin detected in milk at 56 hours after dosing (0.007 mg/L) and 72 hours after dosing (0.009 mg/L), respectively. A plasma and milk concentration-time profile for subject 2.5 is shown in Fig 1. The failure to capture the decline in metformin milk concentrations at the end of the study period for subjects 2.1, 2.2, and 2.3 resulted in an inability to determine the AUC(0-∞). For subjects 2.4 and 2.5, the AUC from 0 to 72 hours could be calculated and accounted for >94% of the transfer into milk. In these subjects the half-life values for metformin in milk were 14.1 hours and 15.4 hours, respectively. The M/P_{AUC} ratios for these subjects were 0.27 and 0.47, and the infant doses were 0.11% and 0.25% of the weight-adjusted maternal dose. The results of the AUC and M/P_{AUC} ratio determination for metformin in plasma and milk are displayed in Table II.

Metformin was well tolerated, with none of the women reporting side effects on active questioning. Subjects 2.2 and 2.5 reported that their breasts did not feel as empty of milk as when they were breast-feeding their infants.

DISCUSSION

For the 5 subjects for whom data were available (subjects 1.1, 1.2, 1.3, 2.4, and 2.5), the median M/P_{AUC} ratio for metformin was 0.47 (range, 0.27-0.71), suggesting modest distribution into breast milk. Low metformin concentrations in milk resulted in a median calculated infant dose of 0.20% (range, 0.11%-0.25%) of the weight-adjusted maternal dose. For 3 subjects in the single-dose study (subjects 2.1, 2.2, 2.3), the M/P_{AUC} ratio and infant dose could not be determined because the study duration was insufficient to account for the total transfer of metformin into milk. Lack of detection of metformin in the blood of 2 infants exposed through milk is reassuring, although this was not surprising in one case, because the mother produced very low volumes of milk (<5 mL per expression) and was in the process of weaning her infant. None of the 3 infants exposed to metformin through milk had any side
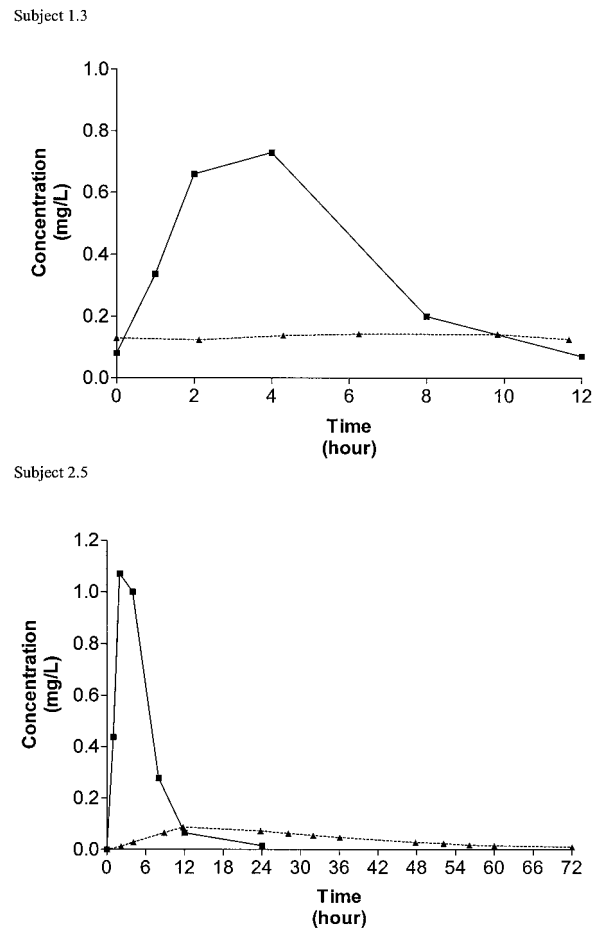

Fig 1. Plasma *(squares)* and milk *(triangles)* metformin concentrations for subject 1.3 at steady state with a dose of metformin of 500 mg twice daily *(top)* and for subject 2.5 after a single 500-mg dose of metformin *(bottom).*

effects that were likely to be attributed to the drug. Infant blood glucose concentrations were not measured because metformin is not usually associated with hypoglycemia, even when large doses are administered.[18]

The M/P_{AUC} ratios of 0.27 to 0.71 obtained in this study are in contrast to the predicted M/P ratios of 3.0 and 2.3.[8-10] These models have been reported to provide useful predictions of the steady-state M/P ratio when compared with clinical studies for drugs that passively diffuse into milk. The unexpected flat concentration-time curve of metformin in milk suggests that the disparity between the observed and predicted M/P ratios may be explained by transfer of metformin into milk by processes other than passive diffusion alone.

Other drugs such as cimetidine and nitrofurantoin also exhibit marked differences between the experimentally determined and predicted M/P ratios.[19,20] However, in contrast to metformin, the observed M/P ratios for these agents are greater than those predicted. These drugs are thought to be actively transported into milk, presumably by an organic cation transporter. Fexofenadine has a flat concentration-time curve in milk[21] that is similar in appearance to that of metformin. Like metformin, fexofenadine does not undergo significant biotransformation. However, its disposition is primarily mediated by the P-glycoprotein efflux pump, whereas metformin is a substrate for an organic cation transporter.[22,23] It is difficult to explain the disposition of metformin in milk on the basis of the precedents of these other drugs. It is possible that there is saturable active transportation of metformin across either the basolateral or the apical membranes, or both, of mammary alveolar cells into milk and ion trapping within these cells. Metformin has been reported to accumulate in tissues such as the small intestine, kidney, and liver, and because most intracellular metformin exists in the cytosol,[24,25] delayed release from this site because of complete ionization may provide a reason for its ongoing presence in milk (ie, a depot may be formed). Another reason for the disparity between the predicted and experimentally derived M/P ratios may be that metformin has physicochemical properties that are different from those of the drugs used in development of the models. Metformin is an unusual drug with a low molecular weight (129 d), negligible protein binding, and essentially complete ionization at physiologic pH. Further investigation is required to determine the mechanism that limits the excretion of metformin into milk.

The results of this study indicate that metformin can be considered compatible with breast-feeding, according to conventional criteria. However, the effect of continued exposure to very small amounts of metformin on the developing infant remains unknown. As always, careful consideration of the risks and benefits is recommended before any drug is initiated in a breast-feeding woman. If metformin is to be used in lactating women, we recommend monitoring the infant for evidence of gastrointestinal toxicity such as altered feeding habits, diarrhea, or failure to thrive.

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