

Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk

Background and objectives: Lactating women undergoing operations requiring general anesthesia are advised to pump and discard their milk for 24 hours after the procedure. Data on anesthetic drug transfer into breast milk are limited. This study determined the pharmacokinetics of midazolam, propofol, and fentanyl transfer into milk to provide caregivers with data regarding the safety of breast milk after administration of these drugs.

Methods: Five lactating women participated in this study after providing institutionally approved written informed consent. Patients underwent premedication with midazolam before induction of anesthesia with propofol and fentanyl. Anesthesia was maintained with a potent volatile anesthetic. Milk and blood were collected before drug administration. Milk was collected 5, 7, 9, 11, and 24 hours after drug administration. Venous blood was collected at intervals up to 7 hours. Plasma and milk midazolam, propofol, and fentanyl concentrations were measured by HPLC with tandem mass spectrometric or fluorescence detection. The pharmacokinetics of drug transfer into milk was modeled with plasma pharmacokinetics.

Results: Plasma midazolam, propofol, and fentanyl pharmacokinetics were consistent with reports of others. In 24 hours of milk collection, averages of 0.005% (range, 0.002%-0.013%) of the maternal midazolam dose, 0.027% (0.004%-0.082%) of the propofol dose, and 0.033% (0.006%-0.073%) of the fentanyl dose were collected in milk, representing averages of 0.009%, 0.025%, and 0.039% of the respective elimination clearances.

Conclusion: The amount of midazolam, propofol, and fentanyl excreted into milk within 24 hours of induction of anesthesia provides insufficient justification for interrupting breast-feeding. (Clin Pharmacol Ther 2006;79:549-57.)

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Despite the recognized social and medical benefits of breast-feeding, the safety of breast milk after the administration of most drugs remains poorly understood. Although there are numerous drugs for which careful risk assessment is recognized as necessary,¹ there are seldom adequate data to provide the basis of a recom-

mendation regarding the safety of breast milk after maternal drug administration. Too often, safety recommendations are made on the basis of theoretical risks, case reports, or case studies.² Because dangerous amounts of many drugs are assumed to be transferred into breast milk, breast-feeding mothers either avoid medication or do not breast-feed their infants while taking medications for fear of harming them through unnecessary drug exposure, often on the overly cautious recommendation of their health caregiver.² Despite the numerous obstacles to studying drug disposition in breast-feeding women, such studies must be conducted to provide health care providers with data on the safety of breast milk after drug administration so they can provide their patients with informed advice on breast-feeding after drug exposure.³

Drugs used commonly for outpatient anesthesia or conscious sedation include benzodiazepines, hypnotics, and opioids. Breast-feeding women must sometimes undergo surgery requiring anesthesia or conscious se-

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dation with these drugs and want to know when they may resume breast-feeding safely. Although the transfer of diazepam, methohexital, and meperidine into breast milk has been estimated,⁴ there are few data regarding how much of their modern equivalents midazolam, propofol, and fentanyl is transferred to milk, and the information that is available is from studies in the immediate postpartum period when colostrum is produced rather than mature milk,⁵⁻⁷ which differs from colostrum in both volume and composition.⁸ Therefore, physicians err on the side of caution and advise mothers to pump and discard their breast milk for 24 hours after an operative procedure rather than risk giving their infant an unsafe amount of drug by way of their breast milk. We studied midazolam, propofol, and fentanyl transfer into mature human breast milk to provide surgical and anesthesia caregivers with data regarding the safety of breast milk after administration of these drugs.

METHODS

Subjects and study design. Five lactating women with a preoperative hemoglobin level of more than 10 g/dL who had scheduled operative procedures necessitating general anesthesia participated in this study after providing institutionally approved, written informed consent. Exclusion criteria include patients with American Society of Anesthesiologists Physical Status score greater than II, gastroesophageal reflux disease, peptic ulcer disease, hiatal hernia, body mass index greater than 28 kg/m², and allergies to midazolam, fentanyl, or propofol. Each patient was instructed not to ingest anything by mouth after midnight the night before the planned procedure. Intravenous access was established for drug administration. After local anesthesia, a 16- or 18-gauge catheter, attached to a stopcock, was placed in a vein to facilitate blood sampling in the arm opposite that in which intravenous drugs were being administered. The patient was then brought to the operating room where monitors were applied according to the American Society of Anesthesiologists Standards for Basic Intraoperative Monitoring. A standard dose of midazolam, 2 mg over 30 seconds, was administered intravenously to provide preoperative anxiolysis. The patient was given oxygen for 5 minutes before induction of anesthesia with standard doses of fentanyl, 100 µg over 30 seconds, and propofol, 2.5 mg/kg over 30 seconds. When ease of mask ventilation was confirmed, a standard dose of a neuromuscular blocking agent was administered to facilitate tracheal intubation. Anesthesia was maintained with an inhaled potent volatile anesthetic agent. At the conclusion of the procedure, neuromuscular blockade was antagonized with stan-

dard reversal agents, the trachea was extubated when usual criteria were met, and the patient was brought to the postanesthesia care unit. The patient was discharged to the hospital room from the postanesthesia care unit after the usual discharge criteria had been met.

Ten milliliters of blood to provide plasma for drug concentration measurement was withdrawn through the large-bore intravenous catheter before drug administration and at 2, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 300, and 420 minutes after drug administration. Blood sampling after propofol and fentanyl administration was timed to coincide with blood sampling after midazolam whenever possible. All samples obtained were centrifuged, and the plasma was collected and frozen until assayed for propofol, midazolam, and fentanyl concentrations.

Patients were asked to pump breast milk before drug administration to be used as a blank and to empty the breasts before operation. All milk produced within 24 hours of drug administration was collected from both breasts and used solely for purposes of the study, as recommended for optimal study design⁹; none was returned to the mother for administration to her infant. Five hours after drug administration and again at 7, 9, 11, and 24 hours after drug administration, the patient pumped the breasts with a standard electric breast pump, the most efficacious method of milk expression.¹⁰ The milk expressed from both breasts at each collection time was combined into 1 sample, the volume was measured and recorded, and the entire volume was frozen until assayed for propofol, midazolam, and fentanyl concentrations.

Analytic methods. Plasma and milk midazolam concentrations were determined by liquid chromatography–tandem mass spectrometry after sample preparation by solid-phase extraction. In brief, 10 µL of 0.1-µg/mL flurazepam dihydrochloride (internal standard) solution and 0.2 mL of a plasma or milk sample were added to a 1.5-mL polypropylene tube and acidified by the addition of 20 µL of 85% phosphoric acid. The sorbent of each well of the Oasis MCX 30 mg Extraction Plate (Waters Chromatography, Milford, Mass) was conditioned with 1 mL methanol and 1 mL water, the prepared sample was applied to the conditioned sorbent, and the sorbent was washed with 1 mL of 0.1-mol/L hydrochloric acid and 1 mL methanol. Samples were eluted into a 96-well plate with 500 µL of 2% ammonium hydroxide in methanol, dried under vacuum, and reconstituted with 200 µL of mobile phase (described later). Twenty microliters of the reconstituted eluant was analyzed by an API 3000 liquid chromatography–tandem mass spectrometry system (Ap-

plied Biosystems, Foster City, Calif) equipped with an Agilent 1100 series HPLC system (Agilent Technologies, Wilmington, Del). Samples were eluted isocratically from a Synergi 4- μ m Hydro-RP 80A column (50×2.0 mm; Phenomenex, Torrance, Calif) with a mobile phase consisting of water and methanol (47.5:52.5 [vol/vol]) containing 0.1% formic acid at a flow rate of 0.15 mL/min. The tandem mass spectrometer was operated with its electrospray source in the positive ionization mode. The mass-to-charge ratios of the precursor-to-product ion reactions monitored were 326 \rightarrow 291 for midazolam and 388 \rightarrow 315 for flurazepam. The retention time of midazolam was 2.8 minutes, and that of flurazepam was 2.6 minutes. Both the plasma and the milk midazolam standard curves were linear from 0.018 to 36.9 ng base/mL with coefficients of variation of less than 7.5% throughout the entire concentration range.

Plasma and milk propofol concentrations were determined by modification of the method of Plummer,¹¹ with liquid chromatography–fluorescence spectroscopy as described by Knibbe et al¹² after sample preparation by liquid-liquid extraction as described by Ibrahim et al.¹³ In brief, 10 μ L of 150- μ g/mL thymol (internal standard) solution, 0.5 mL of a plasma or milk sample, and 0.125 mL of 1.0N sodium hydroxide were added to a conical glass centrifuge tube and the contents were mixed. One and one half milliliters of ethyl acetate/heptane (1:1 [vol/vol]) was added to each tube, and the contents were mixed thoroughly on a vortex mixer for 30 seconds and centrifuged for 3 minutes at 1400g. The supernatant was transferred to a polypropylene tube, evaporated to dryness at ambient temperature under a stream of nitrogen, and reconstituted with 200 μ L of mobile phase. One hundred microliters of the reconstituted eluant was analyzed by an HPLC system consisting of a Waters 510 pump (Waters Chromatography), a Waters 717 autosampler (Waters Chromatography), and a Varian 2070 spectrofluorometric detector (Varian, Palo Alto, Calif). Samples were eluted isocratically from a LiChrospher 5- μ m 100 RP-18 column (125×4.0 mm; Merck KGaA, Darmstadt, Germany) with a LiChrospher 5- μ m (4 \times 4 mm; Merck KGaA) guard column with a mobile phase consisting of acetonitrile and water (60:40 [vol/vol]) containing 0.1% trifluoroacetic acid at a flow rate of 1.5 mL/min. Fluorescence detection was accomplished with excitation at 276 nm and emission at 310 nm. Both the plasma and the milk propofol standard curves were linear from 0.01 to 10 ng/mL with coefficients of variation of 12% or less throughout the entire concentration range.

Plasma and milk fentanyl concentrations were determined by liquid chromatography–tandem mass spectrometry after sample preparation by solid-phase extraction. In brief, 10 μ L of 0.1- μ g/mL alfentanil hydrochloride monohydrate (internal standard) solution and 0.2 mL of a plasma or milk sample were added to a 1.5 mL polypropylene tube. The sorbent of each well of the Oasis HLB 30 mg Extraction Plate (Waters Chromatography) was conditioned with 1 mL methanol and 1 mL water, the prepared sample was applied to the conditioned sorbent, and the sorbent was washed with 1 mL of 5% methanol in water. Samples were eluted into a 96-well plate with 500 μ L of 2% acetic acid in methanol, dried under vacuum, and reconstituted with 200 μ L of mobile phase (described later). Twenty microliters of the reconstituted eluant was analyzed by an API 3000 liquid chromatography–tandem mass spectrometry system (Applied Biosystems) equipped with an Agilent 1100 series HPLC system (Agilent Technologies). Samples were eluted isocratically from a Synergi 4- μ m Max-RP 80A column (50×2.0 mm; Phenomenex) with a mobile phase consisting of water and methanol (62.5:37.5 [vol/vol]) containing 0.1% formic acid at a flow rate of 0.25 mL/min. The tandem mass spectrometer was operated with its electrospray source in the positive ionization mode. The mass-to-charge ratios of the precursor-to-product ion reactions monitored were 337 \rightarrow 188 for fentanyl and 417 \rightarrow 197 for alfentanil. The retention time of fentanyl was 2.1 minutes and that of alfentanil was 2.6 minutes. Both the plasma and the milk fentanyl standard curves were linear from 0.0064 to 31.8 ng/mL with coefficients of variation of 8% or less throughout the entire concentration range.

The pharmacokinetic model. Venous plasma drug concentration-versus-time data were fit with 3-compartment pharmacokinetic models by the SAAM II software system (SAAM Institute, Seattle, Wash) implemented on a Pentium-based (Intel, Santa Clara, Calif) personal computer. Drug transfer into breast milk was modeled both as excretion in the series of individual milk samples and as the cumulative excretion simultaneously with the plasma data (Fig 1). The fraction of drug elimination clearance by transfer into milk was defined as $f_e \cdot Cl_E$, and drug elimination by all other routes was $(1 - f_e) \cdot Cl_E$. The SAAM II objective function was the extended least-squares maximum likelihood function using data weighted with the inverse of the model-based variance of the data at the various times.¹⁴ To model the transfer of drug into breast milk, it was necessary to incorporate a delay element between central volume (V_C) and the interval milk amounts and

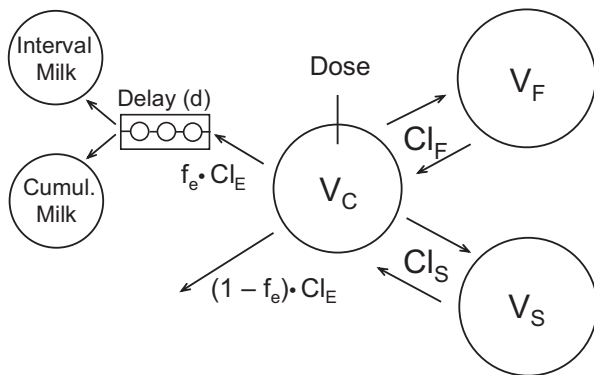


Fig 1. General model for analysis of pharmacokinetics of drug distribution and elimination by transfer into milk ($f_e \cdot Cl_E$), as well as by all other routes ($[1 - f_e] \cdot Cl_E$). For the sake of simplicity, the amount of drug collected in each of the timed milk collections (Interval Milk) and the cumulative amount in collected milk (Cumul. Milk) are represented as being modeled with the same fractional elimination clearance ($f_e \cdot Cl_E$) and delay element (d) when, in fact, they were modeled simultaneously with separate fractional clearances and delays constrained to be equal. The delay element is represented generically by a *rectangle* surrounding 3 compartments, although the number of compartments needed in a delay was typically 5.

the cumulative milk amounts. The delay element is represented generically by a rectangle surrounding 3 compartments although the number of compartments needed in the delay was typically 5. A time delay accounts for the noninstantaneous appearance of drugs in milk after being transferred from V_C , a common observation in studies of drug transfer to breast milk.¹⁵ Possible systematic deviations of the observed data from the calculated values were sought by use of the 1-tailed 1-sample runs test, with $P < .05$, corrected for multiple applications of the runs test, as the criterion for rejection of the null hypothesis. Possible model misspecification was sought by visual inspection of the measured and predicted marker concentrations versus time relationships.

Statistical analysis. Data are expressed as mean \pm SD or median and range.

RESULTS

The 5 women participating in this study underwent tubal ligation ($n = 3$) or laparoscopic cholecystectomy ($n = 2$) while they were under general anesthesia at a median of 12 weeks (range, 6-15 weeks) after they were delivered of a healthy term infant. Patient characteristics are summarized in Table I.

Table I. Subject characteristics

No. of patients	5
Age (y)	30.2 \pm 5.6
Weight (kg)	75.8 \pm 5.0
Weeks post partum	11 \pm 4
Volume of milk (mL/24 h)	324 \pm 159
Operative procedures	
Tubal ligations	3
Laparoscopic cholecystectomy	2

Data are mean \pm SD.

The median volume of milk collected within 24 hours was 250 mL (range, 125-490 mL) (Table I). The median amount of midazolam recovered within 24 hours was 0.08 μ g, which is 0.004% of the maternal dose of 2 mg. The median propofol recovery within 24 hours was 26 μ g, which is 0.015% of the median maternal dose of 180 mg. The median amount of fentanyl recovered within 24 hours was 0.024 μ g, which was 0.024% of the maternal dose of 100 μ g. These data are summarized in Table II.

The pharmacokinetic models characterized not only the venous plasma drug concentration history but also the amount of drug collected in each of the timed milk collections as well as the cumulative amount of drug collected for all 3 drugs accurately (Figs 2-4). The plasma pharmacokinetics was well characterized with a 3-compartment model, and the fractional elimination clearance and pharmacokinetic delay fully described drug transfer to breast milk as it was collected over a 24-hour period (Table III). The average fractional midazolam elimination clearance by transfer to milk was 0.009%, that for propofol was 0.025%, and that for fentanyl was 0.039%. The pharmacokinetic delays for drug transfer to breast milk were rather long, with average pharmacokinetic delays of 9.0 hours for midazolam, 5.3 hours for propofol, and 6.3 hours for fentanyl.

Although not a focus of this study, it was noted that drug concentrations in milk tended to parallel the drug concentrations in the central, rapidly equilibrating, and slowly equilibrating compartments of the 3-compartment pharmacokinetic model, which had equilibrated by the time the first milk sample was obtained. This finding is illustrated for the drug fentanyl in Fig 5 but is similar for propofol and midazolam.

DISCUSSION

This study is significant for several reasons. The most important is that it has demonstrated that the

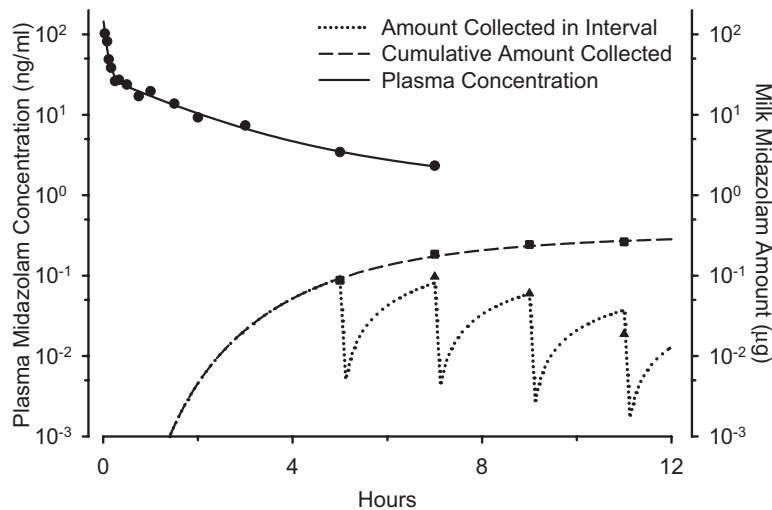


Fig 2. Plasma midazolam concentration history for first 7 hours and amount of midazolam collected in each timed milk collection, as well as cumulative amount of midazolam collected in milk for first 11 hours after intravenous administration to one of the 5 subjects. *Symbols* represent observed values, and *lines* represent values predicted by the model.

Table II. Drug transfer to milk within 24 hours of administration

Drug	Dose administered (mg)	Amount recovered in milk (mg)	Fraction of maternal dose transferred to milk	Weight-normalized infant dose* (mg/kg)
Midazolam	2.0	0.00008 (0.00003-0.00026)	0.00004 (0.00002-0.00013)	0.000016 (0.000006-0.000053)
Propofol	180 (180-200)	0.026 (0.008-0.148)	0.00015 (0.00004-0.00082)	0.0052 (0.0015-0.0296)
Fentanyl	0.10	0.000024 (0.000006-0.000073)	0.00024 (0.00006-0.00073)	0.000005 (0.000001-0.000015)

Data are presented as median and range (N = 5).

*Calculated with assumption that infants weighed 5 kg and that they consumed the entire volume of milk collected by pumping over a 24-hour period.

Table III. Pharmacokinetic parameters

Drug	Volumes (L/kg)*				Clearances (mL/min/kg)†			$t_{1/2\beta}$ (min)	d_{\ddagger} (min)	$f_e\S$ ($\times 10^{-3}$)
	V_C	V_F	V_S	V_{SS}	CL_F	CL_S	CL_E			
Midazolam	0.14 ± 0.07	0.29 ± 0.13	0.72 ± 0.18	1.15 ± 0.29	31 ± 12	6 ± 4	5 ± 1	213 ± 33	537 ± 220	0.09 ± 0.05
Propofol	0.23 ± 0.11	0.57 ± 0.42	1.77 ± 0.26	2.57 ± 0.49	42 ± 20	21 ± 9	22 ± 6	146 ± 54	321 ± 56	0.25 ± 0.30
Fentanyl	0.27 ± 0.07	0.46 ± 0.16	2.02 ± 0.45	2.75 ± 0.49	50 ± 34	40 ± 15	14 ± 4	185 ± 67	379 ± 121	0.39 ± 0.41

Data are presented as mean ± SD (N = 5).

*The volumes (V) of the central (C), rapidly (fast) equilibrating (F), and slowly equilibrating (S) compartments and the volume of distribution at steady state (V_{SS}), which is the sum of all volumes.

†The clearances (CL) of the rapidly (fast) equilibrating (F) and slowly equilibrating (S) compartments and elimination clearance (CL_E).

‡Delay time for transfer into breast milk.

§That portion of the elimination clearance represented by transfer to breast milk.

maximum exposure of the nursing infant to the commonly used intravenous anesthetics midazolam, propofol, and fentanyl within 24 hours after their administration was less than 0.1 % of the maternal dose (Table

II). The comprehensive study design that includes a full description of both maternal drug disposition and 24-hour breast milk drug excretion demonstrates the feasibility of conducting such studies in breast-feeding

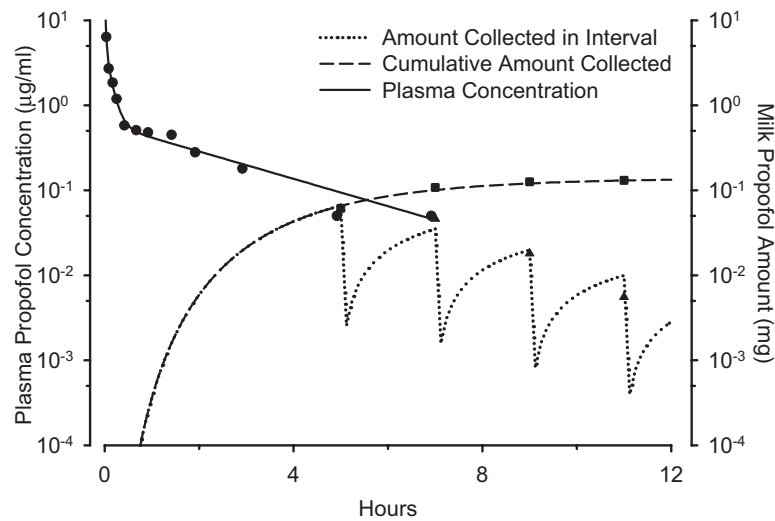


Fig 3. Plasma propofol concentration history for first 7 hours and amount of propofol collected in each timed milk collection, as well as cumulative amount of propofol collected in milk for first 11 hours after intravenous administration to one of the 5 subjects. *Symbols* represent observed values, and *lines* represent values predicted by the model.

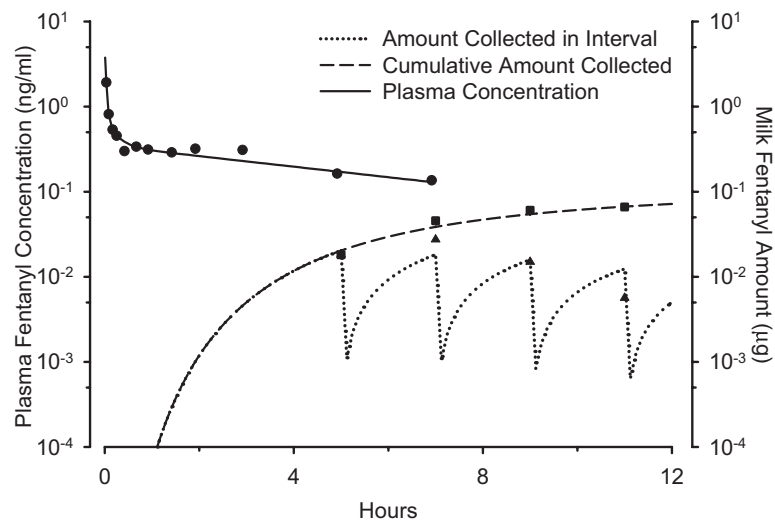


Fig 4. Plasma fentanyl concentration history for first 7 hours and amount of fentanyl collected in each timed milk collection, as well as cumulative amount of fentanyl collected in milk for first 11 hours after intravenous administration to one of the 5 subjects. *Symbols* represent observed values, and *lines* represent values predicted by the model.

women despite numerous obstacles. Finally, the pharmacokinetic model used in our study should be generally applicable to describing the maternal disposition and excretion in milk of other drugs.

Although it is desirable to avoid unnecessary drug exposure, it has been suggested that a clinically insignificant exposure of a healthy term infant to

drug by way of breast milk is less than 10% of the weight-normalized adult dose.^{1,16} The most important finding of the current study is that the maximum exposure of the nursing infant to the commonly used intravenous anesthetics midazolam, propofol, and fentanyl within 24 hours after their administration was less than 1.25% of the weight-normalized ma-

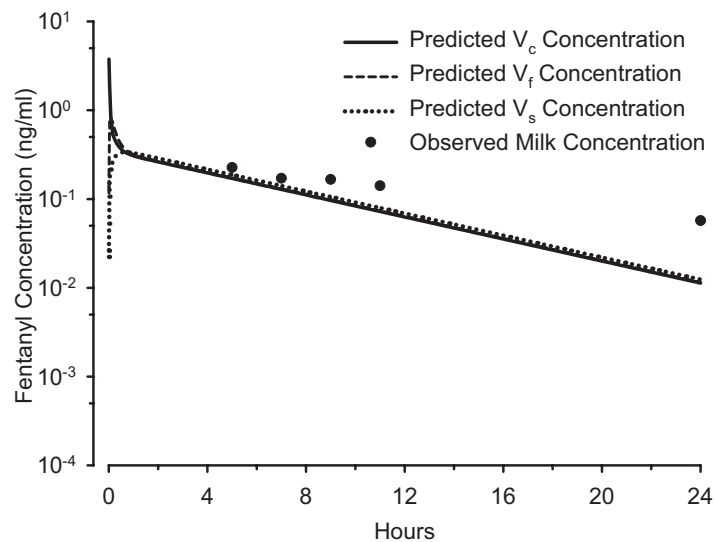


Fig 5. Model-predicted compartmental fentanyl concentration history for 24 hours after drug administration to one of the 5 subjects and measured milk fentanyl concentrations graphed at end of collection periods.

ternal dose. This calculation was made with the assumption that the infants weighed 5 kg and that they consumed the entire volume of milk collected by pumping over a 24-hour period. Infant exposure by breast-feeding to the benzodiazepine, hypnotic, and opioid commonly used in contemporary outpatient anesthesia and surgery, namely, midazolam, propofol, and fentanyl, would therefore be less than the estimated exposure to an earlier generation of the same class of drug, namely, diazepam, methohexital, and meperidine (INN, pethidine), as predicted by Borgatta et al.⁴ Thus our data are supportive of the current opinion that breast-feeding may be resumed as soon after surgery and anesthesia with these 3 drugs as the mother is physically and mentally able.¹⁷

To estimate exposure of the breast-feeding infant to maternal medications, it is frequently necessary to depend on reported milk-to-maternal plasma drug concentration ratios, maternal plasma drug concentration estimates, and an estimate of the volume of milk consumed over a given time.¹⁵ For example, the milk-to-maternal plasma drug concentration ratio method was used to estimate infant exposure to methohexital, meperidine, and diazepam in breast milk.⁴ The optimal way to estimate infant exposure to drug by way of breast milk is to collect the entire volume of milk from both breasts over 24 hours and measure both the volume of milk and the drug concentration in each of the samples collected

over that time.⁹ Although such complete collections may be impractical and techniques used to measure drug concentrations may not have sufficient sensitivity to measure drug concentrations over such an extended time, useful information is certainly gained when such studies are done. For example, when breast milk was collected over approximately a 48-hour period after oral administration of 5 mg of tritiated prednisolone, it was found that only 0.14% of the radioactivity was recovered per liter of milk.¹⁸ Our study has demonstrated, on the basis of the collection of the entire volume of milk from both breasts for 24 hours after anesthetic administration, that exposure of the breast-feeding infants of all 5 of the subjects studied to the commonly used intravenous anesthetics midazolam, propofol, and fentanyl would have been less than 0.1% of the absolute (ie, not weight-normalized) administered maternal dose of each of these agents (Table II). This low estimate of infant exposure actually represents an upper limit of exposure because it is based on the assumption that the entire volume of milk produced by the mother would be consumed by the infant and that all drug ingested would be 100% bioavailable, which is unlikely. In addition, this dose administered to the infant via breast milk would not be administered in the short term but would be spread out over 24 hours.

The pharmacokinetic model used in this study should be generally applicable to describing the maternal disposition and excretion in milk of other drugs. Pharma-

cokinetic models of drug transport to breast milk that have been proposed or used by others are either impractical or not generalizable. Wilson et al,¹⁵ for example, proposed a 3-compartment catenary model with a rate constant for milk excretion in the distal compartment that is zero order during feeding and off when the infant is not feeding, leading to the accumulation of milk and drug in the third compartment. Although they cited the delay between the time to peak plasma drug concentrations and the time to peak milk concentration as supporting their model, in our study it was found that the time course of drug concentrations in milk approximately paralleled model-predicted concentrations in all 3 compartments of the open mammary model by the time milk was collected (Fig 5). Stec et al¹⁹ described theophylline transfer into breast milk with a multicompartmental model that included cumulative drug elimination as part of overall drug elimination clearance. Thus our model is similar to that of Stec et al except that ours includes a delay because we observed a delay in drug elimination, whereas that of Stec et al did not because they observed no such delay. In our study drug elimination clearance by transfer of midazolam, propofol, and fentanyl into breast milk (ie, $f_e \cdot Cl_E$, Fig 1) was never more than 0.1% of the overall drug elimination clearance (ie, Cl_E) for each of these drugs in all 5 of the subjects studied (Table III). The model-estimated elimination clearance in breast milk is consistent with the fraction of the dose recovered in milk collected over a 24-hour period expressed as a percentage of the administered maternal dose (Table II), as discussed earlier.

The pharmacokinetic model used in this study (Fig 1) characterized both the plasma drug concentration and drug transfer into breast milk well (Figs 2-4). The plasma pharmacokinetic parameters (Table III) were consistent with those reported by others. The pharmacokinetics of midazolam in the current study is virtually identical to that reported for young adults by Smith et al,²⁰ as well as those we reported in young women.²¹ The propofol pharmacokinetics in this study is consistent with that in the large series of Shafer et al²² and that used to design a validated target-controlled drug infusion by Tackley et al.²³ The current fentanyl kinetics is nearly identical to that reported in volunteers by McClain and Hug²⁴ and in surgical patients by Koska et al.²⁵ The pharmacokinetic results suggest that the small amount of these drugs that appears in breast milk is due, at least in part, to the extensive distribution of a dose throughout the tissues of the body, as well as the relatively efficient elimination of the drugs from the body by hepatic metabolism.

Delays in the time of peak milk drug concentrations relative to the time to peak maternal plasma drug concentrations have been reported for a number of drugs.¹⁵ To model the transfer of drug into breast milk, it was necessary to incorporate a delay element in the pharmacokinetic model (Fig 1). The average delays observed for the drugs in our study (Table III), 9.0 hours for midazolam, 5.3 hours for propofol, and 6.3 hours for fentanyl, are longer than were expected from the delays reported for other drugs. The prolonged delays in this study may reflect in part the timing of the collection of the first milk sample, which was 5 hours after drug administration to allow for the duration of anesthesia and surgery and the time to recover from the effects of anesthesia. Another factor contributing to the prolonged delay may have been reduced milk production seen after surgery because of perioperative fluid restriction and volume losses, as well as stress-induced inhibition of milk production.²⁶ The reduced postoperative milk production may be especially reflected in the first (ie, 5-hour) sample, the median volume of which was 10 mL (range, 3-80 mL), and, to a lesser extent, in the total volume collected in 24 hours, the median volume of which was 270 mL (range, 125-490 mL), which is less than half of the typical mature milk production by well-nourished women in the first 6 months post partum.²⁷

A potential limitation of this study is our failure to measure the metabolites of midazolam, propofol, and fentanyl. However, the metabolites were not measured because they are either pharmacologically inactive or contribute minimally to the pharmacologic activity of the parent drug because they are present in such low concentrations after intravenous administration.²⁸⁻³⁰

The amount of midazolam, propofol, and fentanyl appearing in breast milk over a 24-hour period after a single dose of each of these agents is administered as part of a general anesthetic is very small and therefore unlikely to affect a healthy term infant. This study therefore provides data to support the recommendation that breast-feeding not be interrupted after postoperative recovery from anesthesia.

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