Concentration of fentanyl in colostrum after an analgesic dose

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The purpose of this study was to measure the concentration of fentanyl in human colostrum after intravenous administration of an analgesic dose. Thirteen healthy women were given fentanyl 2 $\mu g \cdot kg^{-1}$ for analgesic supplementation during either Caesarean section or postpartum tubal ligation. Serum and colostrum were collected for 45 min, two, four, six, eight, and ten hours following administration of the drug. Radioimmunoassay showed that colostrum fentanyl concentrations were greatest at 45 min, the initial sampling time, reaching 0.40 ± 0.059 ng · ml^{-1}, but were virtually undetectable ten hours later. Fentanyl concentrations were always higher in colostrum than in serum. This concluded that with these small concentrations and fentanyl's low oral bioavailability, intravenous fentanyl analgesia may be used safely in breast-feeding women.

Le but de cette étude était de mesurer la concentration de fentanyl dans le colostrum humain après l'administration intraveineuse d'une dose analgésique. Treize femmes saines ont reçu 2 $\mu g \cdot kg^{-1}$ de fentanyl comme supplément à l'analgésie durant une césarienne ou une ligature tubaire en post-partum. Des échantillons sériques et de colostrum ont été recueillis 45 min, deux, quatre, six, huit et dix heures après l'adminstration du médicament. Le dosage radioimmunologique a montré que les concentrations de fentanyl dans le colostrum étaient les plus élevées à 45 min, le moment initial d'échantillonnage, atteignant 0,40 ± 0,059 ng · ml^{-1} mais elles étaient virtuellement indéterminables dix heures plus tard. Les concentrations de fentanyl étaient toujours plus élevées dans le colostrum que dans le sérum. En conclusion, avec ces faibles concentrations et étant donnée la faible biodisponibilité du fentanyl administré par voie orale, l'analgésie intraveineuse au moyen de fentanyl peut être utilisée de façon sécuritaire chez les femmes qui allaitent.

Key words
ANAESTHESIA: obstetric;
ANAESTHETICS, INTRAVENOUS: fentanyl.

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Funded by the School of Allied Health, University of Kansas and Janssen Pharmaceutica.

Accepted for publication 25th November, 1991.

Fentanyl is frequently used to provide analgesia or anaesthesia to women during the postpartum period. Although mammary excretion of other anaesthetics and analgesics has recently been studied, the excretion of fentanyl into breast milk has not been examined.[1-6] Fentanyl is a potent synthetic phenylpiperidine with an extremely high lipid solubility and high pKa. Thus, it should have a propensity for accumulation in breast milk. Postpartum women who have had anaesthesia often inquire about the amount of drugs transferred to their newborns through their breast milk. In particular, many women receive fentanyl as part of the anaesthetic/analgesic regimen for common procedures such as Caesarean section or postpartum tubal ligation. Since this is such a common concern, the primary aim of this preliminary study was to measure the concentrations of fentanyl present in serum and colostrum after administration of a typical intravenous analgesic dose of fentanyl.

Methods

Institutional approval was granted by the Human Subjects Committee of the University of Kansas Medical Center. Further approval was granted by the administrative board of Poudre Valley Hospital, Fort Collins, Colorado, where the research was conducted. Following informed consent, 2 $\mu g \cdot kg^{-1}$ intravenous fentanyl was administered to 13 healthy women undergoing either an elective Caesarean section or a postpartum tubal ligation.

Women (n = 8) undergoing Caesarean section were prepared for surgery in the usual manner. After a 1500 ml fluid bolus, a spinal anaesthetic of bupivacaine 0.75% was administered. Ephedrine was given intravenously as needed to keep the systolic blood pressure greater than 100 mmHg. The patient was positioned with a left lateral tilt

TABLE I Serum fentanyl concentration ($ng \cdot ml^{-1}$)

	Time of collection (hours)					
Patient	*3/4*	*2*	*4*	*6*	*8*	*10*
1[a]	0.16	NC	0.00	NC	0.00	NC
2[b]	0.35	NC	0.01	NC	0.00	NC
3[b]	0.15	NC	0.02	NC	0.00	NC
4[b]	0.16	0.01	NC	0.00	NC	0.00
5[b]	0.19	0.02	NC	0.00	NC	0.00
6[b]	0.16	0.01	NC	0.00	NC	0.00
7[a]	0.18	0.04	0.01	0.01	NC	NC
8[a]	0.14	NC	0.00	NC	0.00	NC
9[b]	0.27	NC	0.00	NC	0.00	NC
10[b]	0.08	0.02	NC	0.00	NC	0.00
11[a]	0.19	0.01	0.01	0.00	NC	NC
12[a]	0.19	0.01	0.00	0.00	NC	NC
13[b]	0.26	0.03	0.00	0.00	NC	NC
Mean	0.19	0.02	0.01	0.00	0.00	0.00
± SEM	0.019	0.0004	0.002	0.001	0.00	0.00

NC – no collection.
[a]Postpartum tubal ligation.
[b]Caesarean section.
SEM – standard error of the mean.

TABLE II Colostrom fentanyl concentrations ($ng \cdot ml^{-1}$)

	Time of collection (hours)					
Patient	*3/4*	*2*	*4*	*6*	*8*	*10*
1[a]	0.45	NC	0.13	NC	0.00	NC
2[b]	0.20	NC	0.16	NC	0.09	NC
3[b]	0.38	NC	0.13	NC	0.09	NC
4[b]	0.49	0.11	NC	0.09	NC	0.03
5[b]	0.35	0.18	NC	0.04	NC	0.08
6[b]	0.49	0.11	NC	0.09	NC	0.08
7[a]	0.24	NC	0.25	0.08	NC	NC
8[a]	0.97	NC	0.16	NC	0.07	NC
9[b]	0.39	NC	0.19	NC	0.10	NC
10[b]	0.08	0.23	NC	0.00	NC	0.01
11[a]	0.31	0.20	0.11	0.03	NC	NC
12[a]	0.56	0.42	0.13	0.05	NC	NC
13[b]	0.34	0.28	0.12	0.03	NC	NC
Mean	0.40	0.22	0.15	0.05	0.07	0.05
± SEM	0.059	0.041	0.015	0.012	0.018	0.018

NC – no collection.
[a]Postpartum tubal ligation.
[b]Caesarean section.
SEM – standard error of the mean.

and monitored with an automated non-invasive blood pressure cuff, electrocardiogram and pulse oximeter during the Caesarean section. After delivery and cord clamping, an analgesic dose of fentanyl, 2 $\mu g \cdot kg^{-1}$, was administered *iv*. Any need for additional analgesia was met with either morphine or meperidine.

For women (n = 5) undergoing postpartum tubal ligation, an analgesic dose of fentanyl, 2 $\mu g \cdot kg^{-1}$, was administered over 15 min prior to the induction of general anaesthesia. Following preoxygenation for four minutes, anaesthesia was induced with thiopentone, using a rapid-sequence technique. Tracheal intubation was facilitated by succinylcholine. Anaesthesia was maintained with isoflurane 0.5–1.5% with 30% oxygen in nitrous oxide.

Blood and colostrum samples were taken from each woman at 45 min, two, four, six, eight, and ten hours after the fentanyl was given. Sampling was done for all patients at 45 min, then samples were collected by one of three different sampling time protocols, as illustrated in Tables I and II. These patterns were designed to obtain a comprehensive view of fentanyl's concentrations over time, without excessively or repetitively sampling from each woman every two hours. In most women, colostrum was not available in amounts sufficient to collect samples every two hours over a period of ten hours.

To facilitate the collection of blood samples, a three-way stopcock was incorporated into the intravenous line. Five milliliters of blood were withdrawn from the pre-existing *iv* catheter into glass test tubes. After clotting, the blood was centrifuged for five minutes. The serum was extracted and frozen at −20° C until analysis could be accomplished.

TABLE III Patient demographic data and surgical procedure

Pt	*Age*	*Weight (kg)*	*Height (cm)*	*Fentanyl (μg)*
1	33	64.3	170.0	130
2	29	84.5	162.5	169
3	31	80.0	152.5	160
4	30	63.8	172.5	126
5	29	65.9	150.0	131
6	26	77.5	155.0	155
7	29	65.9	155.0	131
8	26	80.0	162.5	160
9	30	81.8	172.5	163
10	29	74.5	172.5	149
11	27	94.5	162.5	189
12	33	68.1	160.5	136
13	25	86.3	160.5	172

Colostrum was simultaneously collected using an electric breast pump, facilitated by gentle manual expression. Two ml of colostrum were collected from the same breast at each sample time and frozen at −20° C until analysis. For samples collected from breast-feeding mothers, the colostrum was taken after the newborn nursed.

Serum and colostrum samples were analysed for fentanyl by Rocky Mountain Instrumental Laboratories of Fort Collins, Colorado. Analysis was by solid phase radioimmunoassay, validated by gas chromatography/mass spectrometry.

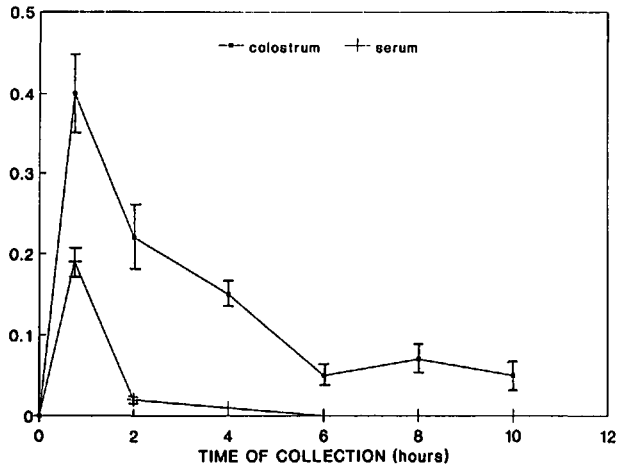

FIGURE Fentanyl concentration in colostrum and serum (ng · ml^{-1}) ± standard error of the mean.

Results

Radioimmunoassay showed that fentanyl appeared in colostrum. The highest concentration, at the times measured, was 0.40 ± 0.059 mg · ml^{-1} 45 min after intravenous administration. At this initial sampling time serum concentrations were also maximal, reaching 0.19 ± 0.019 ng · ml^{-1}. Fentanyl concentrations were greater in colostrum than in serum during all times measured. Fentanyl became undetectable in the blood by two hours after administration. It was virtually undetectable in colostrum by the tenth hour after the analgesic dose was administered (Tables I and II). The decay of fentanyl in serum and colostrum over time is shown in the Figure.

Demographic patient data are illustrated in Table III.

Discussion

Radioimmunoassay (RIA) has been used to evaluate fentanyl concentrations in serum, cerebrospinal fluid and urine.[7,8] Gas chromatography also has been advocated as a sensitive method of serum fentanyl measurements.[9–11] Laboratory analyses for serum fentanyl were performed by solid phase radioimmunoassay and validated by gas chromatography/mass spectrometry.

Fentanyl has not been previously quantified in colostrum. Laboratory analyses for colostrum fentanyl concentration in this study were performed using solid phase radioimmunoassay (RIA) and validated by gas chromatography/mass spectometry. A pilot test, using multiple samples of human urine and goat's colostrum, and one sample of human colostrum, each containing known quantities of fentanyl, examined the recovery of fentanyl. Goat's colostrum was chosen because its content is physiochemically close to that of human colostrum.[12] The recovery of fentanyl from human colostrum and goat colostrum was 100%. Precision for the RIA was 5.1% RSD at the 1 ng · ml^{-1} level. The correlation coefficient for the log-logit plot was 0.9942, and the limit of detection was 0.05 ng · ml^{-1}. All control sample results were within the target ranges specified by the manufacturer. Standards prepared in urine resulted in log-logit plots identical to those prepared on goat colostrum. The detection limit for the gas chromatography/mass spectometry was 0.05 ng · ml^{-1}, and the precision for the assay at 1 ng · ml^{-1} was 12.9%. No cross-reactivity was detected at any concentration for norfentanyl or despropionyl fentanyl, the two major metabolites of fentanyl.

An inherent limitation in this study was the previously untested laboratory technique chosen for analysis of fentanyl in colostrum. The amount of fentanyl could have been below the limits of detection. However, if fentanyl concentrations were below the detection limits, this information supports the safety of breast feeding after the administration of analgesic doses of fentanyl.

Although the study was limited to 13 patients, the results agree closely with the published results of morphine in colostrum.[6] Fentanyl, like morphine, has an alkaline pKa, in contrast to the more acidic breast milk. Based on this and its extreme lipophilicity, one would expect it to accumulate in colostrum. Fentanyl is one of the most lipophilic narcotics, as measured by its octanol:water coefficient. This characteristic should confer a passive transfer across biologic membranes, such as the mammary epithelium. Once inside the milk compartment, fentanyl is thought to ionize and become trapped in the acidic colostrum. This is a likely reason for a milk-to-plasma concentration ratio (M/P ratio) greater than one.

The use of three different sampling time protocols to avoid excessive or repetitive sampling from each woman was a limitation of the study. However, an overview of serum and colostrum fentanyl concentrations over time was attained. The rapid decline in serum and colostrum over time could be explained primarily in terms of fentanyl's large volume of distribution and, also, short beta elimination half-life. The absorption, distribution, metabolism and elimination of fentanyl have been described in detail by Hug,[13] who found that the pharmacokinetic behavior of fentanyl was independent of dose. An intravenous dose rapidly distributes to the central compartment, consisting of the vessel-rich organs such as the heart, brain, lung and liver. Following this, it redistributes to the more peripheral compartments, such as muscle and fat. This sequestration to a large volume of distribution limits further fentanyl delivery to the breast. The elimination via metabolic processes gives fentanyl a beta elimination half-life of approximately 219 min which also limits the amount of drug available for continued transport to the

breast. This hepatic biotransformation and redistribution to the peripheral body stores explains the decline in serum and colostrum with time. Unfortunately, peak serum and colostrum fentanyl levels may have been missed due to the first and second samples being taken 45 and 120 min after fentanyl administration. In most cases, few mothers were able to nurse within 45 min of the induction anaesthesia. In addition, these sampling times were chosen to allow for mother-baby bonding.

Although breast feeding often occurs after the mother has had an anaesthetic, the effects of many drugs on the neonate have not been elucidated. Koehntop *et al.*[14] determined that neonates younger than 14 days succumb to respiratory depression at lower serum levels of fentanyl than infants, children and adults. The oral bioavailability of fentanyl lies between 0–49%, and the transmucosal-bioavailability is 49%.[15–17] Several physiological factors combine to make the neonate more vulnerable to drug toxicities. Metabolic and elimination pathways at birth are functioning at only a fraction of adult capacities. Protein binding of drugs is diminished quantitatively and qualitatively in the neonate, which permits more drug to be free for action at its receptor site. The respiratory chemoreceptors have a decreased sensitivity to carbon dioxide and hypoxia at birth. Considering these factors, if any doubt exists concerning the safety of breast feeding, the mother should be advised to pump her breasts to maintain lactation and resume nursing at a later time. Principal factors which determine neonatal effects from drug exposure through breast milk include the maternal dose, the volume of milk consumed and the child's post-conceptual age.

This study showed that fentanyl does appear in colostrum after an analgesic dose. However, considering the small and fleeting amount of fentanyl detected in colostrum, full-term infants should not be restricted from breast feeding. Neonates consume very little colostrum in the first few days of life, but gradually increase their intake to an average 150 $ml \cdot kg^{-1} \cdot day^{-1}$.[18] Taking the worst example, the amount of fentanyl a neonate is likely to receive is extremely small. If one assumes a concentration of fentanyl as high as 1 $ng \cdot ml^{-1}$ in colostrum and if the baby ingests as much as 100 ml, the neonate could receive 100 ng of fentanyl *po*. Assuming 49% bioavailability, and a three kilogram infant, this represents a dose of 0.016 $\mu g \cdot kg^{-1}$. It would be surprising if such a low dose would produce any deleterious effects.

Considering the large number of women receiving pharmacological care, the investigation of drugs in breast milk remains unexplored. Future studies should be conducted to validate the fentanyl analysis in colostrum and full neonatal neurobehavioural responses following exposure to fentanyl via breast milk. However, this study has shown that fentanyl appears in colostrum after an analgesic dose but the transfer of fentanyl to the neonate via colostrum is very low.

References

1 *Anderson LW, Qvist T, Hertz J, Mogensen F.* Concentrations of thiopentone in mature breast milk and colostrum following an induction dose. Acta Anaesthesiol Scand 1987; 31: 30–2.

2 *Baker PA, Schroeder D.* Interpleural bupivacaine for postoperative pain during lactation. Anesth Analg 1989; 69: 400–2.

3 *Bernstein J, Patel N, Moszczynski BS, Parker F, Ramananthan S, Turndorf H.* Colostrum morphine concentrations following epidural administration. Anesth Analg 1989; 68: S23.

4 *Dailland P, Cockshott ID, Lirzin JD, et al.* Intravenous propofol during cesarean section: placental transfer, concentrations in breast milk, and neonatal effects. A preliminary study. Anesthesiology 1989; 71: 827–34.

5 *Feilberg VL, Rosenborg D, Christensen CB, Mogensen JV.* Excretion of morphine in human breast milk. Acta Anaesthsiol Scand 1989; 33: 426–8.

6 *Giesecke AH, Rice LJ, Lipton JH.* Alfentanil in colostrum. Anesthesiology 1985; 63: A284.

7 *Schleimer BA, Benjamini E, Eisele J, Henderson G.* Pharmacokinetics of fentanyl as determined by radioimmunoassay. Clin Pharmacol Ther 1978; 23: 188–94.

8 *Singleton HA, Rosen JI, Fisher DM.* Plasma concentration of fentanyl in infants, children and adults. Can J Anaesth 1987: 34: 152–5.

9 *Gillespie TJ, Gandolfi AJ, Maiorino RM, Vaughn RW.* Gas chromatographic determination of fentanyl and its analogue in human plasma. J Anal Toxicol 1981; 5: 133–7.

10 *Gourlay GK, Kowalski SR, Plummer JL, et al.* Fentanyl blood concentration-analgesic response relationship in the treatment of postoperative pain. Anesth Analg 1988; 67: 329–37.

11 *Wilson TD, Maloney T, Amsden WB.* High-performance liquid chromatography determination of fentanyl citrate in a parenteral dosage form. J Chromatogr 1988; 445: 229–304.

12 *Wilson JT, Brown RD, Cherek DR, et al.* Drug excretion in human breast milk: principal pharmacokinetics and projected consequences. Clin Pharmacol 1980; 15: 1–66.

13 *Prys-Roberts C, Hug CC* (Eds.). Pharmacokinetics and dynamics of narcotic analgesics. *In*: The Pharmacokinetics of Anaesthesia. Oxford: Blackwell Scientific Publication 1984; 187–234.

14 *Koentop DE, Rodman JH, Brundage DM, Hegland MC, Buckley JJ.* Pharmacokinetics of fentanyl in neonates. Anesth Analg 1986; 65: 227–32.

15 *Mather LE.* Clinical pharmacokinetics of fentanyl and its newer derivatives. Clin Pharmacol 1983; 8: 422–46.
16 *Lehmann KA, Freier J, Daub D.* Fentanyl-pharmacokinetics and postoperative atemdepression. Anaesthesia 1982; 31: 111–8.
17 *Tarver SD, Stanley TH.* Alternative routes of drug administration and new drug delivery systems. *In*: Stoelting RK, Barash PG, Gallagher TJ (Eds.). Advances in Anesthesia. Chicago: Year Book Medical Publishers, 1990; 337–67.
18 *Atkinson HC, Begg GJ, Darlow BA.* Drugs in human milk. Clinical pharmacokinetic considerations. Clin Pharmacol 1988: 14: 217–40.