Anesthesiology
73:864–869, 1990

# *Exogenous Opioids in Human Breast Milk and Acute Neonatal Neurobehavior: A Preliminary Study*

*Bernard Wittels, M.D., Ph.D.,* David T. Scott, Ph.D.,† Raymond S. Sinatra, M.D., Ph.D.‡*

**Opioid analgesia requirements, distribution into breast milk, and influence on neonatal neurobehavior were evaluated in ten parturient–neonate pairs nursing after elective cesarean section during epidural anesthesia. Five patients received first a loading dose of intravenous meperidine after umbilical cord clamping, then patient-controlled analgesia (PCA) with intravenous meperidine, and finally meperidine tablets as needed. Five patients received morphine in the same manner. Treatment groups showed no differences with respect to neonatal Apgar scores or visual analog scale (VAS) pain or satisfaction scores at 24 and 48 h postpartum. Breast milk specimens, obtained at 12, 24, 36, 48, 72, and 96 h postpartum and analyzed for opioids and metabolites, showed persistently elevated normeperidine concentrations in the meperidine group. A blinded psychologist evaluated each infant once on the 3rd day of life with the Brazelton Neonatal Behavioral Assessment Scale (NBAS). *A priori*, the "alertness" and three "human orientation" outcomes of the NBAS were chosen for analysis as best measures of opioid-induced effects. On all four outcomes, neonates in the morphine group scored significantly higher ($P < 0.05$) than neonates in the meperidine group. We conclude that post-cesarean delivery PCA with morphine provides equivalent maternal analgesia and overall satisfaction as that provided by PCA with meperidine, but with significantly less neurobehavioral depression among breast-fed neonates on the 3rd day of life. (Key words: Anesthesia: obstetric. Pain: patient-controlled analgesia. Analgesics, opioid: morphine, meperidine, distribution into breast milk. Neonatology: neurobehavioral assessment.)**

THE CLINICAL EFFICACY of intravenous patient-controlled analgesia (PCA) has been well documented with a variety of opioid analgesics in post-cesarean delivery patients.[1–4] Although morphine is the standard analgesic used in this setting, a recent blinded comparison noted a more rapid onset of pain relief and less sedation with meperidine.[4]

Morphine and meperidine, as well as their major metabolites morphine-3-glucuronide and normeperidine, are secreted into colostrum and breast milk.[5,6] However, previous studies of PCA have not considered breast milk uptake and its possible consequences in nursing neonates.

Morphine and meperidine have very similar pharmacokinetics,[7,8] although they differ in onset, duration of action, and metabolism. As a result, concentrations of parent opioids, measured alone, in tissue compartments show inconsistent correlation with concurrent clinical effects. Notably, meperidine is metabolized *via* hepatic n-demethylation to normeperidine, which is approximately one half as potent as meperidine with respect to analgesia, but more potent as a central nervous system (CNS) stimulant and convulsant. In contrast, morphine undergoes hepatic conjugation to form, predominantly, inactive morphine-3-glucuronide. (Approximately 10% of morphine conjugates are recovered as the active, morphine-6-glucuronide.)[9,10]

Previous analyses of colostrum have documented opioid secretion after administration of single doses by oral, intramuscular, and epidural routes.[5,6,11] By these routes, meperidine and normeperidine appear to accrue in equal concentrations in breast milk, whereas morphine accumulates to a lesser degree than does morphine-3-glucuronide. Overall, this implies that maternal opioid detoxification is greater with morphine than meperidine; however, the pattern of distribution of these opioids and their metabolites into breast milk during PCA is more complex than that suggested by single-dose pharmacokinetics in plasma and urine. In addition, evidence that morphine, meperidine, and normeperidine all have prolonged plasma elimination half-lives in neonates, compared to adults,[12,13] does suggest that neonates are at increased risk for opioid toxicity. Consequently, in a prospective, single-blinded manner, we examined post-cesarean delivery patients using PCA and also examined their nursing infants. This preliminary evaluation assessed: 1) the distribution of morphine, meperidine, and their metabolites into colostrum and breast milk, and 2) the neurobehavioral effects of breast milk opioids on neonates during their 3rd day of life.

## Materials and Methods

After the Human Investigation Committee of Yale University School of Medicine had approved the current protocol, written informed consent was obtained from 12 multigravida parturients scheduled for elective cesarean section and opting to breast-feed. Patients were free of any co-existing disease (ASA physical status 1 or 2) and had no history of alcohol or drug abuse. Epidural anesthesia, 2% lidocaine with epinephrine 1:200,000, was administered *via* catheter in a volume sufficient to achieve a T4 sensory level bilaterally.

Patients were assigned into one of two groups (mor-

* Clinical Fellow in Anesthesiology.
† Associate Professor of Pediatrics.
‡ Associate Professor of Anesthesiology.

Received from the Departments of Anesthesiology and Pediatrics, Yale University School of Medicine, Yale–New Haven Hospital, New Haven, Connecticut. Accepted for publication June 12, 1990.

Address reprint requests to Dr. Sinatra: Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510.

phine or meperidine) in a nonrandom manner, based on clinical judgment (*e.g.*, history of adverse reactions to meperidine or morphine) and evenness of distribution. After umbilical cord clamping, patients were given a loading dose of opioid intravenously, in titrated increments to a total of 1.0 mg/kg for meperidine or 0.1 mg/kg for morphine. Upon transfer to the postanesthesia recovery area, patients received the study drug *via* intravenous PCA with an Abbott pump (meperidine in a 12.5-mg incremental dose and with 6-min lockout; morphine in a 1.0–1.5-mg incremental dose and with 6-min lockout). Intravenous catheters were discontinued between 20 and 43 h postpartum, after which the study drug was administered orally in tablet form (meperidine 50–300 mg every 2–3 h as needed; morphine 5–30 mg every 2–3 h as needed).

Each patient was followed continually throughout her hospitalization until discharge. Visual analog scales (VAS) for analgesia and overall satisfaction were administered at 24 and 48 h postpartum with 10-cm unmarked lines. The pain scale was anchored at 0 cm representing no pain and 10 cm representing the worst imaginable pain; on the satisfaction scale, 0 cm indicated least satisfaction and 10 cm indicated greatest satisfaction.

Colostrum and breast milk specimens (minimum of 3 ml) were obtained either by manual expression or by assistance from an electronic suction pump under obstetric nursing supervision at 12, 24, 36, 48, 72, and 96 h postpartum, with a 3-h interval of acceptability (*i.e.*, 10.5–13.5 h, 22.5–25.5 h postpartum, *etc.*). Specimens were immediately placed on ice at 0° C and then frozen at −20° C within 6 h for later analysis.

Analysis of colostrum and breast milk specimens for meperidine and normeperidine was performed in a single-blinded manner using organic solvent extraction, gas chromatography, mass spectrometry, and selected ion monitoring, as previously described.[6] This assay had a coefficient of variation (CV) of 3.4% (n = 5) when measuring meperidine at 200 ng/ml and a CV of 8.9% (n = 5) when measuring normeperidine at 100 ng/ml. Analysis of colostrum and breast milk specimens for morphine and morphine-3-glucuronide was performed in duplicate with a radioimmunoassay specific for morphine (Coat-a-Count Morphine, Diagnostic Products Corp.), with or without prior digestion for 24 h at 37° C with 250 U β-glucuronidase (type VII A, Sigma Chemical Company). This assay did not require the extraction of opioids from breast milk and had a CV of 5.4% (n = 20) when measuring morphine at 52 ng/ml. In addition, this assay had cross-reactivities to morphine-3-glucuronide (0.03%), codeine (0.06%), and morphine-6-glucuronide (0.15%), but these were low enough to be considered negligible. Furthermore, recognizing that morphine-6-glucuronide comprises less than 10% of all endogenous morphine conjugates,[10] we simplified our analysis by assuming that morphine-3-glucuronide is the only metabolite of morphine.

Neonatal outcome was assessed on the 3rd day of life with Brazelton's Neonatal Behavioral Assessment Scale (NBAS).[14] The NBAS was chosen because it is a widely used behavioral assessment for the neonatal period, and because its psychometric advantages and limitations have been extensively investigated.[15,16] The NBAS was administered in the standard manner by a pediatric psychologist previously certified in the use of this test. The psychologist was blinded with respect to each infant's treatment-group assignment and perinatal history.

In order to control type I error, a limited number of *a priori* outcomes were selected from the NBAS. The NBAS "alertness" item was selected as the primary outcome to measure neonatal depression, which is typically the principle concern attendant on the use of opioids in patients who are breastfeeding. In addition, three secondary outcomes were selected: these were 1) "orientation—animate visual," 2) "orientation—animate auditory," and 3) orientation—animate visual and auditory." These animate-orientation items were selected as secondary outcomes because of their presumed relevance for early mother–infant interaction, which may be perturbed by neonatal depression.

One patient dropped out of the study because of anxiety regarding lactation, and a second patient was excluded from the study because the neonatal examination could not be performed on schedule. Thus, ten patients, five in each group, completed the study.

Statistical analysis included four two-tailed tests to compare outcomes between groups. $P$ values less than 0.05 were considered significant. Student's $t$ tests were used to evaluate treatment groups with respect to maternal age, height, pregnant weight, gravidity and parity, neonatal gestational age and birth weight, time elapsed from last nursing to neonatal exam, cumulative opioid doses, and milk opioid potencies. Neonatal sex ratios and the success rate for scheduled production of milk specimens were analyzed with Fisher's exact test. Spearman correlation coefficients were used to assess cumulative opioid dose with respect to patient weight. Finally, Wilcoxon rank sum tests were used to evaluate Apgar scores and to compare VAS and NBAS scores between groups.

## Results

There were no significant differences between parturient groups with regard to maternal or neonatal characteristics (tables 1 and 2, respectively). No intraoperative hypotension occurred, and every neonate achieved an Apgar score of 9 at 5 min of age. All patients used PCA appropriately to control postoperative pain. Analysis of VAS scores showed that there were no significant differ-

ences between groups with regard to analgesia or overall satisfaction at either 24 or 48 h postpartum (table 3), although a type II error cannot be excluded. Complications of PCA (nausea, pruritus, or involuntary muscle spasms) were infrequent and mild, and resolved with adjuvant medications (droperidol, diphenhydramine, and naloxone).

Cumulative opioid doses (mean ± standard deviation) are presented in the lower panels of figures 1 and 2 for meperidine and morphine, respectively. Since intravenous PCA therapy was converted to oral therapy between 20 and 43 h postpartum, mean cumulative doses at 12, 24, and 36 h postpartum best represent true PCA usage, whereas increases in mean values after 48 h represent oral opioid therapy with relatively decreased bioavailability. At all time points, regardless of patient group, there was no statistical correlation between cumulative opioid dose and patient weight—a result common to previous studies of postoperative PCA.[4,17,18] Assuming that morphine is ten times as potent as meperidine (milligram for milligram, a mass potency ratio of 10:1), patients in the morphine group received more opioid at all measured time points than did patients in the meperidine group. From 12 to 96 h postpartum, the percentage difference in cumulative equipotent opioid dose between groups progressively increased from 30 to 100%; however, none of these differences achieved statistical significance ($P = 0.0506$ at 96 h).

The collection of breast milk specimens was attempted on six occasions during the first four postoperative days; however, previous trials with two primigravida parturients were unsuccessful. So the current protocol was restricted to multigravida parturients in order to maximize milk-sampling efficiency. Within each group of five patients, there were 30 scheduled occasions (each lasting 3 h) to produce milk specimens. Unexpectedly, the success rate for scheduled milk production in the morphine group (26/30 = 87%) was significantly greater than was the success rate for the meperidine group (18/30 = 60%) with $P = 0.039$.

Concentrations (mean ± standard deviation) of opioids and their metabolites in breast milk is presented in the upper panels of figures 1 and 2, for the meperidine and morphine groups, respectively. Assuming a mass potency ratio of 10:1:0.5:0 for morphine:meperidine:normeperidine:morphine-3-glucuronide, opioid potencies of milk specimens were compared between groups at each of the six postpartum times. The only statistically significant difference occurred at 12 h postpartum, with greater opioid potency in milk from patients in the meperidine group ($P = 0.02$). At all other times, milk opioid potency was equivalent between groups. At the time of neonatal examination (72 h postpartum), the ratio normeperidine: meperidine in milk approximated 3:1 (469:156 ng/ml), in contrast to the observed ratio of approximately 1:1 for morphine:morphine-3-glucuronide (23:19 ng/ml).

Results of the NBAS, summarized in table 4, show that among the four outcomes chosen *a priori* for analysis, *all* were statistically significant ($P < 0.05$). Neonates in the morphine group were more alert and better oriented than were neonates in the meperidine group on their 3rd day of life.

TABLE 1. Maternal Characteristics

| Characteristic | Meperidine Group | Morphine Group | P |
|---|---|---|---|
| Age (yr) | 35.4 ± 3.58 | 33.0 ± 4.69 | NS |
| Height (cm) | 160.0 ± 5.8 | 160.0 ± 5.5 | NS |
| Pregnant weight (kg) | 73.2 ± 7.69 | 75.2 ± 9.88 | NS |
| Gravidity | 2.8 ± 1.30 | 3.0 ± 1.22 | NS |
| Parity | 2.4 ± 0.89 | 2.4 ± 0.55 | NS |

Values are means ± SD.

TABLE 2. Neonatal Characteristics

| Characteristic | Meperidine Group | Morphine Group | P |
|---|---|---|---|
| Sex ratio (M/F) | 3/2 | 2/3 | NS |
| Gestational age (weeks) | 38.60 ± 0.89 | 39.20 ± 0.84 | NS |
| Birth weight (kg) | 3.66 ± 0.30 | 3.41 ± 0.46 | NS |
| Apgar (1 min) | 9 (8–9) | 9 (8–9) | NS |
| Apgar (5 min) | 9 (9–9) | 9 (9–9) | NS |
| Time elapsed from last nursing to neonatal exam (h) | 1.60 ± 0.90 | 0.87 ± 0.79 | NS |

Values are means ± SD except for Apgar scores, which are medians with range shown in parentheses.

## Discussion

This pilot investigation, although limited by its population size and omission of invasive quantitation of plasma opioid concentrations, held advantages over previous clinical studies: post-cesarean delivery analgesia was both flexible and patient-controlled to provide optimal pain relief and overall satisfaction, and breast milk specimen collections and neonatal behavioral examinations were performed in a noninvasive manner. Opioid pharmaco-

TABLE 3. VAS Scores

| Maternal Outcome | Time (h) | Meperidine Group | Morphine Group | P |
|---|---|---|---|---|
| Pain | 24 | 2.0 (0.8–7.6) | 2.0 (1.4–2.8) | NS |
| | 48 | 1.7 (0.8–8.7) | 1.3 (0.9–1.8)* | NS |
| Satisfaction | 24 | 9.2 (7.3–9.6) | 9.0 (6.9–9.5) | NS |
| | 48 | 8.25 (6.2–9.6) | 9.75 (8.0–9.8)* | NS |

Values are median with range in parentheses.
* n = 4.

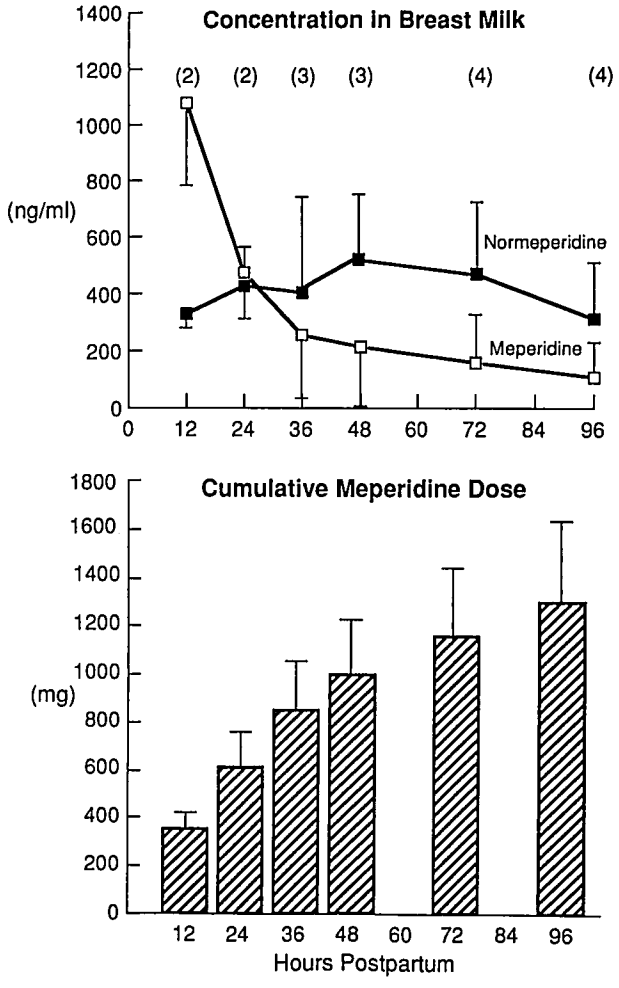


FIG. 1. Cumulative meperidine doses and concentrations of meperidine and normeperidine in breast milk from patients receiving meperidine. Data represent mean values ± 1 SD. Numbers in parentheses represent number of patients from whom breast milk was obtained, at each given time.

kinetics in plasma have been studied in the setting of PCA,[17,18] but the kinetics of breast milk opioid concentrations have not been determined previously. Opioid distribution kinetics from the vascular compartment into breast milk were not assessed; however, any neurobehavioral depression among nursing infants relates more directly to opioid concentrations in breast milk than in maternal plasma.

Although the assignment of patients to either the morphine or meperidine group was not random, selection bias was limited, because 1) individual pain tolerance was not predictable; 2) opioid usage did not correlate with patient weight; and 3) initial maternal characteristics were equivalent between groups.

Elective cesarean deliveries were performed with epidural anesthesia using 2% lidocaine with epinephrine 1: 200,000, a method previously shown to be free of adverse neonatal effects.[19] In fact, with the use of epidural anesthesia with lidocaine, cesarean delivery produced neonates with better NBAS scores and better regulation of state than neonates born *via* vaginal delivery.[20] Opioid analgesics were administered only after umbilical cord clamping, in order to prevent placental transfer of opioids to the fetus.

Generally, one would predict that breast milk containing opioids in high concentrations and with increased potency and lipid solubility and decreased enterohepatic de-

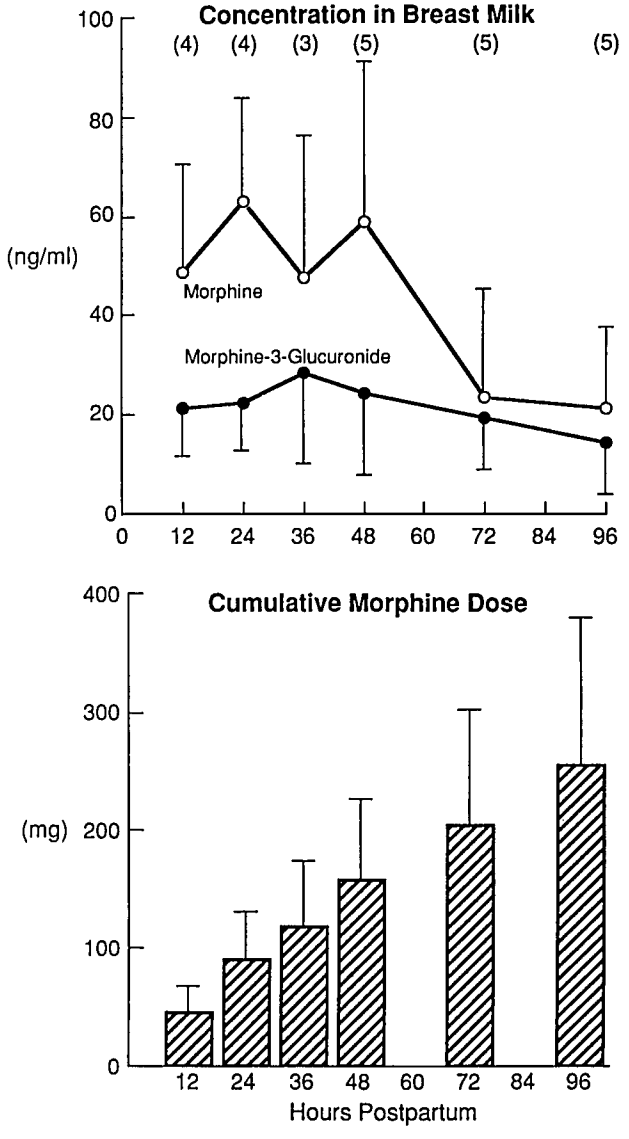


FIG. 2. Cumulative morphine doses and concentrations of morphine and morphine-3-glucuronide in breast milk from patients receiving morphine. Data represent mean values ± 1 SD. Numbers in parentheses represent number of patients from whom breast milk was obtained, at each given time.

TABLE 4. NBAS Scores

| Neonatal Outcome | Meperidine Group | Morphine Group | P |
|---|---|---|---|
| Alertness | 2 (2–3) | 6 (4–8) | 0.010 |
| Orientation to human face | 2 (1–5) | 6 (3–7) | 0.045 |
| Orientation to human voice | 3 (2–5) | 5 (4–6) | 0.043 |
| Orientation to both human face and voice | 2 (1–5) | 6 (4–7) | 0.035 |

Values are medians with range shown in parentheses.

Alertness scores ranged from 1 (inattentive; rarely or never responds to direct stimulation) to 9 (always alert in best periods; stimulation always elicits alerting and orienting; reliably uses stimulation to quiet self or maintain quiet state).

toxification would produce the greatest degree of neurobehavioral depression in nursing neonates. Beyond 12 h postpartum, there was no significant difference between groups with respect to opioid potency of milk. But meperidine and normeperidine are much more lipid-soluble than either morphine or morphine-3-glucuronide; only morphine undergoes a deactivating hepatic glucuronidation (first-pass effect), whereas meperidine undergoes hepatic N-demethylation to form normeperidine, even in the neonate.[21–23] These factors suggest that breast-milk meperidine and normeperidine have greater potential for producing neonatal CNS depression because of increased enteral bioavailability. Accumulation of normeperidine in maternal plasma has been documented after multiple meperidine doses,[24] so it is not surprising that, even though breast milk concentrations of meperidine decrease dramatically after only 12 h, normeperidine concentrations in milk remain persistently elevated; normeperidine: meperidine ratios are 3:1 after 48 h postpartum. Furthermore, neonatal elimination half-lives for meperidine ($t_{1/2}$ = 13 h) and normeperidine ($t_{1/2}$ = 63 h) are markedly prolonged,[13] so that regular nursing not only leads to progressive increases in neonatal plasma opioid concentrations with increased risk for normeperidine toxicity, but also may prolong any adverse opioid effects for days and perhaps weeks. This phenomenon is similar to that of meperidine–normeperidine toxicity seen in adults with renal insufficiency.[25]

As a result, post-cesarean PCA with meperidine leads to accumulation of normeperidine in breast milk, which is associated with neonatal neurobehavioral depression on the 3rd day of life. By contrast, after cesarean delivery and maternal PCA with morphine, nursing neonates achieve NBAS scores similar to those of normal, full-term neonates after spontaneous vaginal delivery.[26]

The difference in neonatal behavior between the two treatment groups was consistent across all four outcomes. On the primary outcome, alertness, there was no overlap in the scores for the two treatment groups. In the meperidine group, there was uniform evidence for neurobehavioral depression: in all cases, the child's responses to stimulation had delayed onset and brief duration. No child exposed to meperidine was brought to a fully alert state during the course of the standard maneuvers entailed by the examination. In contrast, the range of behaviors in the morphine group was not unlike that observed in normal, full-term infants who lack exposure to psychoactive agents.[26] Infants in the morphine group typically used the stimulation of the standard maneuvers to achieve an alert state.

For the population of nursing, post-cesarean delivery patients, the approaches used in this study—including continuity of patient care, accurate determination of opioids in breast milk, and sensitive evaluation of neonatal behavior—should form the basis for assessing maternal efficacy and neonatal safety of opioids in future trials of PCA. Further investigations to assess the duration, severity, and differential etiology of the depressant effects should also consider serial neonatal neurobehavioral exams, regular documentation of neonatal respiratory rates, and quantitation of plasma glucose and opioid concentrations in depressed infants.

The authors appreciate the assistance of Ferne B. Sevarino, M.D., Theresa Z. O'Connor, M.P.H., Wayne T. Brashear, and Jacki Fitzpatrick.

## References

1. Graves DA, Foster TS, Batenhorst RL, Bennett RL, Baumann T: Patient-controlled analgesia. Ann Intern Med 99:360–366, 1983
2. Harrison DM, Sinatra RS, Morgese L, Chung JH: Epidural narcotics and PCA for post-cesarean section pain relief. ANESTHESIOLOGY 68:454–457, 1988
3. Sinatra RS, Chung KS, Silverman DG, Brull SJ, Chung JH, Harrison DM, Donielson DM, Weinstock A: An evaluation of morphine and oxymorphone administered *via* patient-controlled analgesia (PCA) or PCA plus basal infusion in post-cesarean delivery patients. ANESTHESIOLOGY 71:502–507, 1989
4. Sinatra RS, Lodge K, Sibert K, Chung KS, Chung JH, Parker A, Harrison DM: A comparison of morphine, meperidine and oxymorphone as utilized in PCA following cesarean delivery. ANESTHESIOLOGY 70:585–590, 1989
5. Findlay JWA, DeAngelis RL, Kearney MF, Welch RM, Findlay JM: Analgesic drugs in breast milk and plasma. Clin Pharmacol Ther 29:625–633, 1981
6. Quinn PG, Kuhnert BR, Kaine CJ, Syracuse CD: Measurement of meperidine and normeperidine in human breast milk by selected ion monitoring. Biomed Environ Mass Spectrom 13:133–135, 1986
7. Stanski DR, Greenblatt DJ, Lowenstein E: Kinetics of intravenous and intramuscular morphine. Clin Pharmacol Ther 24:52–59, 1978
8. Mather LE, Tucker GT, Pflug ARE, Lindop MJ, Wilkerson C: Meperidine kinetics in man. Clin Pharmacol Ther 17:21–30, 1975
9. Brunk SF, Delle M: Morphine metabolism in man. Clin Pharmacol Ther 16:51–57, 1974
10. Hand CW, Moore RA, McQuay HJ, Allen MC, Sear JW: Analysis

of morphine and its major metabolites by differential radioimmunoassay. Ann Clin Biochem 24:153–160, 1987

11. Bernstein J, Patel N, Moszczynski RS, Parker F, Ramanathan S, Turndorf H: Colostrum morphine concentrations following epidural administration (abstract). Anesth Analg 68:S23, 1989
12. Koren G, Butt W, Chinyanga H, Soldin S, Yok-Kwang T, Pape K: Postoperative morphine infusion in newborn infants: Assessment of disposition characteristics and safety. J Pediatr 107: 963–967, 1985
13. Kuhnert BR, Kuhnert PA, Philipson EH, Syracuse CD: Disposition of meperidine and normeperidine following multiple doses in labor. Am J Obstet Gynecol 151:410–415, 1985
14. Brazelton TB: Neonatal Behavioral Assessment Scale. Philadelphia, J. B. Lippincott Co., 1973, pp 1–66
15. Brooks-Gunn J, Weinraub M: Origins of infant intelligence testing, Origins of Intelligence: Infancy and Early Childhood. Edited by Lewis M. New York, Plenum Press, 1983, pp 25–66
16. Sameroff AJ: Summary and conclusions: The future of newborn assessment, Organization and Stability of Newborn Behavior: A Commentary on the Brazelton Neonatal Behavior Assessment Scale (monograph). Edited by Sameroff AJ. The Society for Research in Child Development, vol. 43 (nos. 5–6, serial no. 177), 1978, pp 102–117
17. Dahlstrom B, Tamsen A, Paalzow L, Hartvig JE: PCA therapy IV: Pharmacokinetics and analgesic plasma concentrations of morphine. Clin Pharmacokinet 7:266–279, 1982
18. Hull CJ: Pharmacokinetics of opioid analgesics, Patient-Controlled Anesthesia. Edited by Harmar M, Rosen M, Vickers MD. London, Blackwell, 1984, pp 7–17
19. Abboud TK, Kim NC, Noueihed R, Kuhnert BR, DerMardirossian N, Moumdjian J, Sarkis F, Nagappala S: Epidural bupivacaine, chloroprocaine or lidocaine for cesarean section: Maternal and neonatal effects. Anesth Analg 62:914–919, 1983
20. Kuhnert BR, Harrison MJ, Linn PL, Kuhnert PM: Effects of maternal epidural anesthesia on neonatal behavior. Anesth Analg 63:301–308, 1984
21. O'Donoghue SEF: Distribution of pethidine and chlorpromazine in maternal, fetal and neonatal biological fluids. Nature 229: 124–125, 1971
22. Hogg MIJ, Wiener PC, Rosen M, Mapleson WW: Urinary excretion and metabolism of pethidine and norpethidine in the newborn. Br J Anaesth 49:891–899, 1977
23. Kuhnert BR, Kuhnert PM, Tu ASL, Lin DCK: Meperidine and normeperidine levels following meperidine administration during labor. Am J Obstet Gynecol 133:909–914, 1979
24. Kuhnert BR, Philipson EH, Kuhnert PM, Syracuse CD: Disposition of meperidine and normeperidine following multiple doses during labor. Am J Obstet Gynecol 151:406–409, 1985
25. Szeto HH, Inturris CE, Houde R, Sall S, Cheigh J, Reidenberg MM: Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure or cancer. Ann Intern Med 86:738–741, 1977
26. Horowitz FD: Stability and instability in the newborn infant: The quest for elusive threads, Organization and Stability of Newborn Behavior: A Commentary on the Brazelton Neonatal Behavior Assessment Scale (monograph). Edited by Sameroff AJ. The Society for Research in Child Development, vol. 43 (nos. 5–6, serial no. 177), 1978, pp 29–45