Anesthesiology
66:136–139, 1987

Morphine Pharmacokinetics in Early Infancy

Anne M. Lynn, M.D., John T. Slattery, Ph.D.†*

The pharmacokinetics of morphine in ten infants ≤ 10 weeks of age who were receiving morphine infusions were determined. Infants 1–4 days of age (newborns) showed longer elimination half-lives than the older infants (6.8 *vs.* 3.9 h). Clearance in the newborns is less than one-half that found in older infants (6.3 *vs.* 23.8 $ml \cdot min^{-1} \cdot kg^{-1}$). The combination of lower clearance and longer elimination half-life in newborns (0–7 days) may well explain a prolonged duration of action for morphine in very young infants, but other etiologies are needed to explain the respiratory sensitivity believed to persist in older infants. (Key words: Anesthesia: pediatric. Anesthetics, intravenous: morphine. Pharmacokinetics: morphine.)

OPIATE NARCOTICS ARE used frequently for anesthesia in infants, but the intraoperative and postoperative use of narcotics is restricted by a concern that infants are more susceptible to the respiratory depressant effects of narcotics than are adults.[1,2] It has been shown that newborns, in the first 3 days of life, are more susceptible than adults to the respiratory-depressant effects of morphine administered on a mg/kg basis.[3] Older infants have not been evaluated. A prolonged or greater respiratory depression following morphine in newborns could be due to greater brain penetration of the drug, opiate receptor differences, and/or slower elimination of the drug from the body.

Two studies of morphine pharmacokinetics in children have included data from infants, two of whom were less than 1 month old.[4,5] A recent report determined the elimination half-life of morphine in eight infants less than 1 month of age and clearance in seven infants whose ages and gestations were not reported.[6] In order to evaluate the role of drug disposition factors in the sensitivity of infants to the respiratory-depressant effects of morphine and to obtain some insight into the time course of maturation of morphine clearance, we have determined the pharmacokinetics of the drug in infants under 10 weeks of age.

Methods

Infants between 1 day and 10 weeks of age, being cared for in the intensive care unit, who had cardiovascular stability and normal renal function, and whose birth weight was more than 1,500 g were eligible for study. The protocol was approved by the hospital Human Subjects Committee, and informed consent was obtained from parents. All infants studied were receiving intermittent intravenous injections of morphine (as the sulfate salt) and all were being mechanically ventilated for pulmonary disease or had undergone surgery prior to enrollment. Upon enrollment, infants received morphine by intravenous infusion at a constant rate equivalent to the average hourly dose rate of morphine administration prior to enrollment in the study. Rates of infusion varied among infants from 20 to 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Arterial blood samples, 0.5 ml, were obtained at 12-h intervals during the infusion and serially ten times over the 48 h following discontinuation of the infusion. During the period of blood sampling after the infusion was discontinued, meperidine or fentanyl was administered if needed for analgesia.

Morphine concentration in plasma was determined by high-pressure liquid chromatography, as previously reported.[7] The method is specific for unchanged drug and is sensitive to 2 ng/ml. Clearance was calculated from the ratio of infusion rate to steady-state concentration, half-life from the terminal slope of a plot of log concentration *versus* time (by linear regression), and volume of distribution as the product of half-life and clearance divided by ln 2. Steady-state was confirmed when two or more consecutive plasma levels during the infusion were within 10% of one another or when the infusion rate had remained constant for five half-lives. Pharmacokinetic parameters for newborn infants (0–7 days of age) were compared with older infants by Student's t test with $P < 0.05$ considered significant.

Results

Ten patients (six male, four female) were studied. One patient was studied at 2 and 17 days of age. Table 1 lists patient age, weight, morphine infusion rate, and indication for mechanical ventilation and morphine administration. All infants were born after 36–41 week gestation and were hemodynamically stable on no vasopressors. Three infants (numbers 1, 4, and 5) required phototherapy for physiologic hyperbilirubinemia. No infant required exchange transfusion. Urine output was greater than 1 $ml \cdot kg^{-1} \cdot h^{-1}$, and serum creatinine and BUN were within normal limits in all infants studied. Morphine infusion rates ranged from 20 to 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (mean 38 $\mu g \cdot kg^{-1} \cdot h^{-1}$), and the duration of infusion varied from 14 h to 15 days (mean 2.8 days). Morphine levels of patient 5 are displayed in Figure 1.

* Assistant Professor Anesthesiology and Pediatrics (Adjunct).

† Associate Professor Pharmaceutics and Anesthesiology (Adjunct).

Received from the Departments of Anesthesiology, Pediatrics, and Pharmaceutics, University of Washington School of Medicine and Children's Orthopedic Hospital and Medical Center, Seattle, Washington. Accepted for publication August 25, 1986. Supported by NIH Biomedical Research Grant PHS RR05655.

Address reprint requests to Dr. Lynn: Department of Anesthesiology, Children's Orthopedic Hospital and Medical Center, Seattle, Washington 98105.

TABLE 1. Illnesses Requiring Mechanical Ventilation and Morphine Infusions

Patient No.	Weight (kg)	Age (day)	Morphine Infusion ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	Diagnosis
1	2.96	4	25	IRDS
2	3.06	2	50	IRDS
3	2.74	2	55	Resection lung malformation
4	3.64	2	100	Meconium aspiration
5	4.24	2	24	IRDS
6	3.04	1	20	Diaphragmatic hernia
7	3.60	2	24	Meconium aspiration
	6.00	17	15	
8	3.84	29	25	VSD repair
9	3.38	58	47	RSV pneumonia
10	5.39	65	23	Viral pneumonia

IRDS = infant respiratory distress syndrome; VSD = ventricular septal defect; RSV = respiratory syncytial virus.

Complete data could be obtained in eight of the ten infants. Only clearance could be calculated for one infant, who died suddenly following a tension pneumoperitoneum. Infant 6 had a short infusion, which allowed a calculation of half-life only. (Insufficient data were obtained for a calculation of clearance by area under the curve).

Pharmacokinetic parameter values are given in table 2. The newborn group (0–7 days of age) differed significantly from the group of older infants in clearance (values one-third that of older infants) and in elimination half-life (approximately 1.7 times that of older infants). The volume of distribution tended to be somewhat larger in the older infants, but the difference was not statistically significant. Infant 7 received morphine by constant infusion for 15 days. Clearance was calculated on day 2; the appearance of significant edema by day 17 when morphine was discontinued made his volume of distribution and clearance difficult to interpret, so only his elimination half-life is included in table 2.

Discussion

We determined clearance in seven newborns and in three infants of approximately 1–2 months of age. We found clearance to be significantly less in newborns than in older infants. The clearance of morphine has been reported twice previously for infants between 1 and 10 months of age,[4,5] but the results of the previous reports do not agree. In one case, clearance was determined following single bolus administration of morphine,[4] and in the second from steady-state concentration during a constant rate of infusion.[5] The mean value of clearance for infants was 11.4 $ml \cdot min^{-1} \cdot kg^{-1}$ (n = 3) as determined following bolus dose,[4] and 19.4 $ml \cdot min^{-1} \cdot kg^{-1}$ (n = 3) as determined from steady-state concentration.[5]

There is reason to doubt the values determined in the bolus dose study. Both studies also determined clearance in children older than 1 yr of age. Following bolus, the value calculated was 6.17 $ml \cdot min^{-1} \cdot kg^{-1}$ (n = 8)[4] and following infusion was 19.4 $ml \cdot min^{-1} \cdot kg^{-1}$ (n = 5).[5] A value of 23.4 ± 8 $ml \cdot min^{-1} \cdot kg^{-1}$ was calculated from 31 children 1–17 yr old in a previous study of ours,[7] also using a steady-state morphine infusion approach.

The clearance values obtained for children aged 1–17 years in the two infusion studies[5,7] are in close agreement. A reason for the extremely low value of clearance determined following single bolus dose[4] might be that the area under the concentration-time curve (AUC) was calculated from the coefficients and exponents describing the triexponential curve fit to the data. Close inspection of the results suggests that the procedure may have introduced artifactual error. Comparison of the mean extrapolated 0 time intercept (approximately 4 μg/ml) to the mean plasma level data (approximately 1.5–2 μg/ml) suggests that AUC was considerably overestimated by the data fitting procedure.[4] An overestimate of AUC would cause an underestimate of clearance.

The value of clearance determined in our seven newborns, 6.29 $ml \cdot min^{-1} \cdot kg^{-1}$ is approximately one-third

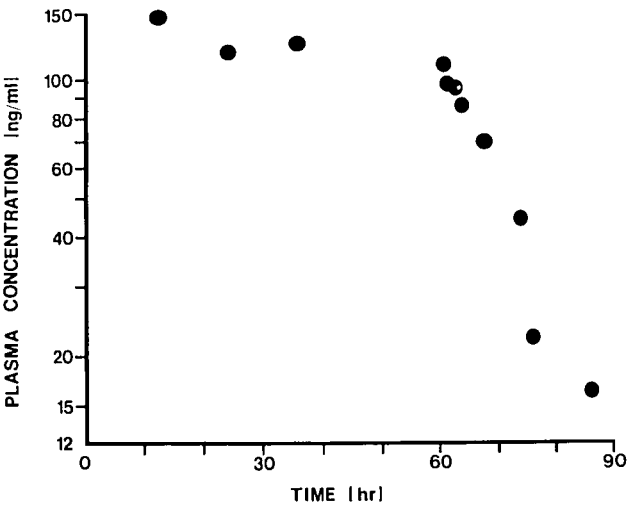

FIG. 1. Serial morphine levels in infant 5.

TABLE 2. Pharmacokinetic Parameters of Morphine in Newborns and Infants

Patient No.	Weight (kg)	Age (day)	Clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	Volume of Distribution (l/kg)	Elimination Half-life (h)
Newborn					
1	2.96	4	5.63	2.22	4.56
2	3.06	2	6.13	4.25	7.99
3	2.74	2	4.98	3.15	7.31
4	3.64	2	9.87	4.55	5.33
5	4.24	2	3.57	2.75	8.92
6	3.04	1	ND	ND	6.73
7	3.60	2	7.58	ND	ND
Mean	3.33	2.14	6.29†	3.38	6.81†
SD	0.52	0.90	2.19	0.99	1.63
Infant					
7*	6.00	17			4.74
8	3.84	29	13.3	3.29	2.86
9	3.38	58	39.0	ND	ND
10	5.39	65	19.2	7.01	4.22
Mean	4.65	42	23.8	5.15	3.91
SD	1.26	23	13.5	2.63	1.0

ND = not determined.
* Patient 7 was studied at 2 and 17 days of age.
† Significantly different from older infants, $P < 0.05$.

that found in the three infants aged 29 to 65 days (23.8 $ml \cdot min^{-1} \cdot kg^{-1}$) and in the three infants previously reported in whom clearance has previously been determined by steady-state infusion methodology (19.4 $ml \cdot min^{-1} \cdot kg^{-1}$).[5] Clearance in full-term infants older than 1 month of age is comparable to that of children 1–17 yr old. Clearance of morphine in unanesthetized adults is 11.5 $ml \cdot min^{-1} \cdot kg^{-1}$.[8] The early maturation of morphine clearance superficially suggests that processes of elimination have approached or surpassed those of the adult at a very early age. However, this may not be true.

Morphine is eliminated primarily by glucuronidation in adults, but also by sulfation. In the adult, approximately four times as much morphine is recovered in urine in the form of the glucuronide conjugate as the sulfate conjugate.[9,‡] Acetaminophen, another phenolic compound eliminated by sulfation and glucuronidation, has also been studied in children. Miller *et al.*[10] have found that the rate constant values for acetaminophen sulfate formation in infants (<3 days of age) can be as much as twice those of adults, while the infants are correspondingly deficient in glucuronidation of acetaminophen. Children aged 3–9 yr in the study of Miller *et al.*[10] had half-lives of acetaminophen similar to those found in adults. The similar half-lives were due to the greater ability of the children to sulfate the drug, while the adults eliminated more of the drug as its glucuronide. We have carried out preliminary studies that suggest that infants show both a pronounced capability to form the sulfate conjugate of morphine and a deficiency to form its glucuronide at 1 month of age, in agreement with the observations with acetaminophen. Thus, the routes of elimination of morphine are not mature in our older infants. Sulfation in the older infants is probably more efficient than that of the adult. This issue can be resolved by measuring formation clearances of the conjugates in infants as a function of age.

Koren *et al.*[6] determined the elimination half-life of morphine in five infants less than 4 days of age. The mean value from four of the five infants was 7.93 h (range 5.2–12 h); the fifth infant was 2 days old, had a 35-week gestation, and had a half-life of 28 h, which corresponded to the value of a late phase of morphine elimination detected in other children in the study of Koren *et al.* The authors felt this late phase did not reflect a clearance process, but more likely represented a tissue binding or distributional phenomenon. Alternatively, premature birth could affect postnatal morphine clearance. The elimination half-life values we observed in full-term infants younger than 4 days of age in our study agree well with those reported by Koren *et al.*[6]

The half-life of morphine is approximately 2 h in adults, and the steady-state volume of distribution is 2.4 l/kg.[8] Half-life in our newborns was 6.8 h, considerably longer than the adult value. The longer half-life in the infant is apparently due to its lower clearance. Our data suggest that half-life of morphine begins to approach the adult value after an age of 1 month. However, we have data from only three infants, and the literature does not address this issue.

‡ Yeh SY: Isolation and identification of morphine ethereal sulfate, normorphine and normorphine conjugate as morphine metabolites in man. Fed Proc 32:763, 1973.

In summary, we have shown that the clearance of morphine reaches or surpasses adult level by 1 month of age. Infants older than 1 month of age have not been shown to be more sensitive to the respiratory-depressant effects of morphine than are adults, although infants are believed to be at increased risk for respiratory depression following morphine administration.[1,2] Our findings agree with those of Vandenberghe *et al.*[5] The data suggest that the suspected greater respiratory sensitivity of infants to morphine should be reexamined and other mechanisms investigated. Kupferberg and Way[11] suggested an incomplete blood–brain barrier allows greater penetration of morphine to CNS sites of action based on results obtained in newborn rats. However, the newborn rat brain is relatively immature compared with the newborn human infant,[12] and the blood–brain barrier of the newborn rat is quite permeable relative to that of other mammals. The results obtained in rats may not be applicable to humans.

Because the steady-state concentration achieved during continuous infusion is a function of clearance, infants in the first week of life will achieve a higher serum concentration at steady-state than older infants, given the same infusion rate. When the drug is then discontinued, concentration will decline more slowly in the newborn infants because of their longer elimination half-life. The combination of higher steady-state morphine concentrations when infusions are discontinued and the slower rate of fall because of the slower clearance may well be the explanation for the prolonged duration of action of morphine in very young infants. In older children, serum levels in the 10–25 ng/ml range at steady-state are associated with a Pa_{CO_2} of less than 45 mmHg.[7] Newborns would achieve such levels on morphine infusions of 5–10 $\mu g \cdot kg^{-1} \cdot h^{-1}$; older infants with morphine infusions of 10–30 $\mu g \cdot kg^{-1} \cdot h^{-1}$. However, the relationship between serum morphine levels and ventilatory drive in infancy has not been determined and remains to be studied.

References

1. Gregory GA: Pediatric Anesthesia. New York, Churchill Livingstone, 1983, p 331
2. Steward DJ: Manual of Pediatric Anesthesia, 2nd edition. New York, Churchill Livingstone, 1985, p 42
3. Way WL, Costley EC, Way EL: Respiratory sensitivity of the newborn infant to meperidine and morphine. Clin Pharmacol Ther 6:454–461, 1965
4. Dahlstrom B, Bolme P, Feychting H, Noack G, Paalzow L: Morphine kinetics in children. Clin Pharmacol Ther 26:354–365, 1979
5. Vandenberghe H, MacLeod S, Chinyanga H, Endrenyi L, Soldin S: Pharmacokinetics of intravenous morphine in balanced anesthesia studies in children. Drug Metab Rev 14:887–903, 1983
6. Koren G, Buh W, Chinyanga H, Soldin S, Tan Y-K, Pape K: Postoperative morphine infusion in newborn infants: Assessment of disposition characteristics and safety. J Pediatr 107:963–967, 1985
7. Lynn AM, Opheim KE, Tyler DT: Morphine infusion after pediatric cardiac surgery. Crit Care Med 12:863–866, 1984
8. Stanski DR, Paalzow L, Edlund PO: Morphine pharmacokinetics: GLC assay *versus* radioimmunoassay. J Pharmacol Sci 71:314–317, 1982
9. Yeh SY: Urinary excretion of morphine and its metabolites in morphine-dependent subjects. J Pharmacol Exp Ther 192:201–210, 1975
10. Miller RP, Roberts RJ, Fischer LJ: Acetaminophen elimination kinetics in neonates, children and adults. Clin Pharmacol Exp Ther 19:284–294, 1975
11. Kupferberg HJ, Way EL: Pharmacologic basis for the increased sensitivity of the newborn rat to morphine. J Pharmacol Exp Ther 141:105–112, 1963
12. Bradbury M: The blood–brain barrier during the development of the individual and the evolution of the phylum, The Concept of a Blood–Brain Barrier. Edited by Bradbury M. New York, Wiley and Sons, 1979, pp 289–322