Opioid-Induced Analgesia in Neonatal Dogs: Pharmacodynamic Differences between Morphine and Fentanyl

ANDREW M. LUKS, MAURICE S. ZWASS, RONALD C. BROWN, MARIE LAU, GOPAL CHARI and DENNIS M. FISHER

Department of Anesthesia, University of California, San Francisco, California (A.M.L., M.S.Z., R.C.B., M.L., D.M.F.), and Department of Pediatrics, University of Illinois, Chicago, Illinois (G.C.)

Accepted for publication September 3, 1997 This paper is available online at http://www.jpet.org

ABSTRACT

Whether the analgesic effects of opioids change as a neonate matures is not well understood. To address this issue, we determined the pharmacokinetics and pharmacodynamics of analgesic effects of morphine and fentanyl in 35 dogs aged 1 to 34 days. Opioids were infused to produce analgesia, response times to a noxious thermal stimulus were measured and plasma opioid concentrations were determined. An effect compartment pharmacodynamic model was fit to the values for time to response to determine the rate constant for equilibration ($k_{eo}$) between plasma and effect-site (Ce) concentrations and analgesic effect (increase in time to response to a noxious stimulus) above baseline per μg/ml of Ce (∆). A time-to-event data analysis (modeled with a Weibull function) was used to account for censored time to response values. For both opioids, values for $k_{eo}$ did not vary with age. Values for ∆ decreased with age (∆, decreasing sensitivity with increasing age), and the magnitude of the change during the first month of life was similar for the two opioids. In the context of our previous study concerning ventilatory depressant effects of these opioids (that sensitivity to morphine, but not to fentanyl, decreased markedly during the first month of life), these results in dogs suggest that fentanyl has greater utility than morphine in neonates during spontaneous ventilation.

Most studies of the effects of opioids in neonates have examined end points such as fatality or ventilatory depression. For example, Kupferberg and Way (1963) reported that the intraperitoneal dose of morphine that killed 50% of rats (LD50) increased markedly during the first month of life. Recently, Bragg et al. (1995) found that the effect-site concentration of morphine required to depress ventilation increased markedly with age, whereas that for fentanyl increased to a much smaller extent. Although toxic end points such as ventilatory depression might limit opioid dosing in neonates, dosing of these drugs probably should be guided by analgesic requirements.

Whether the analgesic effects of opioids change as a neonate matures is not well understood. One study (McLaughlin and Dewey, 1994) concluded that morphine, meperidine and fentanyl (each administered as a single intraperitoneal dose) were more potent in suppressing both the tail-flick and hot-plate response in neonates compared with adult rats. However, McLaughlin and Dewey did not measure plasma concentrations of these opioids and therefore could not determine whether opioid sensitivity in neonates resulted from maturational changes in pharmacokinetics or pharmacodynamics; the present study is designed to address this limitation. Building on a previous study from our laboratory (Bragg et al., 1995) demonstrating marked maturational changes in the ventilatory depressant effects of morphine (and lesser changes for fentanyl), we investigated the analgesic effects of these opioids in neonatal dogs. By measuring analgesia repeatedly during and after opioid administration and by examining the pharmacokinetics, pharmacodynamics and equilibration between plasma opioid concentrations and effect, we determined the etiology of maturational changes in analgesic effects of these drugs.

Methods

After obtaining approval from our institutional review board and while observing the National Institutes of Health Guidelines for the Care and Use of Animals, we studied 35 purebred Beagle dogs, aged 1 to 34 days, obtained from a single vendor. Their weights ranged from 300 to 1570 g; runts were excluded. To minimize the influence

ABBREVIATIONS: Ce, opioid concentration at effect site; $k_{eo}$, rate constant for equilibration between plasma and effect-site opioid concentrations; Cl, total plasma clearance; Clrapid, rapid distributional clearance; Clslow, slow distributional clearance; ∆, analgesic effect (increase in time to response to a noxious stimulus) per μg/ml of Ce; $V_1$, volume of the central compartment; $V_2$, volume of the shallow peripheral compartment; $V_3$, volume of the deep peripheral compartment; $V_{ss}$, volume of distribution at steady state.
of interlitter variability, dogs from each of the six litters were studied with each opioid.

Analgesia was evaluated as the increase in time to response to a supramaximal noxious thermal stimulus applied to the animal’s shaved back (Yaksh et al., 1986). The stimulus was applied using a round probe, 1.0 cm in diameter, that was thermostatically controlled to maintain a constant temperature (<0.5°C variability) during each application and throughout each study (Yaksh et al., 1986). To determine the temperature yielding a supramaximal stimulus, the probe was initially heated to 55°C and applied firmly to the skin. Time to response (termed latency period in many analgesia studies) was defined as the time that elapsed from application of the probe until the animal withdrew from the stimulus. After three applications of the probe (each at different sites), its temperature was increased 2.5°C, and three more stimuli were applied. This incremental process was repeated until we identified a probe temperature that elicited a time to response of <3 sec during each of the three applications; this temperature was designated the target temperature for that animal.

Anesthesia was then induced with isoflurane in nitrous oxide and oxygen, and the trachea was intubated. Catheters were placed by cutdown in the femoral artery (for blood sampling) and femoral vein (for drug and fluid administration). After surgery, 1% lidocaine was infiltrated into the incision to provide analgesia, isoflurane was discontinued and the animal was permitted to awaken. Each animal also received an intramuscular injection of cephalixin (25 mg/kg) and a 2.5 ml/kg intravenous bolus of lactated Ringer’s solution with 5% dextrose. Normothermia was maintained throughout the study using heat lamps and a water mattress.

At 15-min intervals beginning 120 min after surgery, three thermal stimuli of the target temperature were applied at 1.5-min intervals, and times to response were measured. When three consecutive time to response measurements were <3 sec, we assumed the animal had recovered from analgesic effects of isoflurane; the mean of these three time to response measurements was designated as the predrug base-line value. In anticipation of blood loss, the animal was then given a second intravenous bolus of 2.5 ml/kg lactated Ringer’s solution with 5% dextrose.

When the animal was calm and still, fentanyl (n = 17) or morphine (n = 18) was infused. Infusion rates were based on our published data regarding opioid-induced ventilatory depression in neonatal dogs (Bragg et al., 1995) and on preliminary studies (not included in the present report). Fentanyl was infused at a rate of 2.0 μg/kg·min⁻¹; morphine infusion rates increased with age, ranging from 45 to 800 μg/kg·min⁻¹. During the opioid infusion, thermal stimuli were applied at intervals of 1 min and times to response were measured (fig. 1). If the animal did not respond within 12 sec, the probe was removed to avoid skin injury and time to response was designated as 12 sec (cutoff value). When consecutive times to response were at or near the cutoff value, the opioid infusion was discontinued and thermal stimuli were applied at regular intervals. With fentanyl, stimuli were applied at intervals of 1 min for 60 min, 2 min for 30 min and 3 min for the remainder of the study. With morphine, stimuli were applied at intervals of 1 min for 30 min, 2 min for 30 min, 3 min for 30 min and 5 min for the remainder of the study. These intervals were selected to permit adequate sampling, while avoiding overexposure to the stimulus. Stimulation regimens differed between morphine and fentanyl to account for the drugs having different offset times, thereby ensuring that the number of stimuli applied was similar for the two drugs. When time-to-response measurements returned to predrug base-line values, application of the stimuli was discontinued, and the study was concluded.

Arterial blood samples (0.4 ml each) were obtained before the opioid infusion, at 2-min intervals during the infusion, and at intervals of 2 to 40 min after the infusion (fig. 2). The number of samples varied from 12 to 22. Samples were iced immediately; plasma was separated within 2 hr and stored at −70°C. Fentanyl concentrations were determined by radioimmunoassay (Research Diagnostics, Flanders, NJ) sensitive to 0.1 ng/ml with a coefficient of variation of <5% at that concentration. Morphine concentrations were determined by radioimmunoassay (Diagnostic Products, Los Angeles, CA) sensitive to 0.8 ng/ml with a coefficient of variation of <10% at that concentration. In morphine studies, additional arterial plasma samples (1 ml each) were obtained at the end of the infusion and 30 and 60 min after the infusion to determine concentrations of morphine-3-glucuronide and morphine-6-glucuronide by high-pressure liquid chromatography (Bhat et al., 1992) sensitive to 1.0 ng/ml with a coefficient of variation of <8% at a concentration of 10 ng/ml.

The pharmacokinetics and pharmacodynamics of each opioid were determined independently using NONMEM Version V, Level 1.1 (Beal and Sheiner, 1992). The pharmacokinetic analysis was performed using a population approach. Two- and three-compartment pharmacokinetic models were fit to the plasma concentration vs. time data for each animal, and the appropriate model was selected using the likelihood ratio test (Bates and Watts, 1988). The structural parameters for each model were Cl, Clrapid, Clslow, V₁, V₂ and V₃. Random interanimal differences were permitted in each of these parameters. After the “typical” population values were determined, the post hoc step of NONMEM was used to obtain empirical Bayesian estimates of the pharmacokinetic parameters for each animal. Vᵢ was determined as the sum of V₁ and V₂ (and V₃ when appropriate).

To determine the pharmacodynamics of each opioid, we modified a semiparametric approach described previously by Unadkat et al. (1986). We assumed that plasma concentration of the opioid at a given time could be described by linear interpolation of the preceding and subsequent measured values. For example, a measured fentanyl concentration of 2.0 ng/ml at 3 min and 3.0 ng/ml at 5 min would yield a concentration of 2.5 ng/ml at 4 min. The effect of the opioid is
assumed to relate directly to the concentration (Ce) in a theoretical effect compartment having negligible size (i.e., drug entry to the effect compartment does not alter systemic pharmacokinetics). This effect compartment equilibrates with the plasma compartment (given by the linear interpolation function just described) with a first-order rate constant $k_{eo}$ (Shenier et al., 1979).

We assumed that Ce related linearly to time to response: $M = base line + \Delta \cdot Ce$, where M is the median time to response, base line is the median time to response before opioid is administered and after complete recovery and $\Delta$ is the analgesic effect (increase in time to response above base line) per $\mu g/ml$ Ce. We also assumed that the relationship between Ce and time to response follows a Weibull probability density distribution (see Appendix), typically used instead of a normal distribution in time-to-event analyses (Kalbfleisch and Prentice, 1980). The Weibull distribution has two parameters: median time to response (M) and a parameter that defines the “shape” of this probability distribution (Z). The likelihood of an observed time to response is proportional to the density (probability) evaluated at that observed time to response. For example, consider that an infusion regimen results in Ce values for morphine of 50, 100 and 200 ng/ml at three time points after the start of an infusion. Values for time to response at these times after the start of the infusion might be 3.0, 9.5 and 11.0 sec, respectively (fig. 3). For each Ce value, the likelihood of the observed time to response (if no cutoff was applied) can be determined from the values M and Z of the Weibull distribution. However, because the analysis is confounded by censoring observations at the cutoff value (i.e., observed time to response can never exceed 12 sec), the likelihood for an observation of more than the 12-sec cutoff (censored) is calculated as proportional to the area under the Weibull density curve from 12 sec to infinity (Kalbfleisch and Prentice, 1980). In that each animal has numerous observations, the total likelihood of a particular set of parameters (base line, $k_{eo}$, $\Delta$, Z) is the product of the likelihoods for each observation for that animal (Kalbfleisch and Prentice, 1980). The parameters were adjusted iteratively to maximize the total likelihood for that animal.$^2$

The ratio of concentrations of morphine-3-glucuronide and morphine-6-glucuronide to the corresponding values of morphine was determined at each sampling interval. The effect of age on these ratios was determined by analysis of linear regression.

The effect of age on probe temperature, predrug base-line time to response, opioid dose, duration of opioid infusion and pharmacokinetic and pharmacodynamic parameters was determined by analysis of linear regression. Differences between groups were determined with Student’s $t$ test for unpaired data or analysis of covariance. $P < .05$ was considered statistically significant. Except where noted, values are reported as mean ± S.D.

**Results**

The temperature of the probe was 62.7 ± 2.8°C and did not vary with age. Duration of the infusion was 5.5 ± 1.2 min for fentanyl and 7.2 ± 2.1 min for morphine. Fentanyl dose ranged from 7 to 16 $\mu g/kg$, and morphine dose ranged from 300 to 3600 $\mu g/kg$. For fentanyl, there was no relationship between age and either infusion duration or weight-normalized dose. For morphine, duration decreased and weight-normalized dose increased with age.

For fentanyl, weight-normalized $Cl_{rapid}$ and $V_1$ decreased with age (table 1). For morphine, weight-normalized Cl increased with age. None of the other pharmacokinetic parameters changed with age.

Three animals (two, aged 1 and 4 days, given fentanyl, and one, aged 13 days, given morphine) reached cutoff rapidly and did not recover adequately to predrug control values. Because of the preponderance of censored pharmacodynamic data for these animals, we were unable to fit the pharmacodynamic model to the time-to-response data. Consequently, pharmacodynamic values are reported for only 32 animals: 15 with fentanyl and 17 with morphine.

For both fentanyl and morphine, the modeled value for base-line time to response (data not shown) did not vary with age or between drugs. Value for $k_{eo}$ (fig. 4) did not vary with age for either fentanyl ($r^2 = .01, P = .69$) or morphine ($r^2 = .03, P = .63$). However, mean values for $k_{eo}$ were larger with fentanyl ($0.39 \pm 0.04$ min$^{-1}$) than with morphine ($0.086 \pm 0.004$ min$^{-1}$, $P < .0001$) (i.e., fentanyl equilibrates more rapidly). For both opioids (fentanyl: $r^2 = .38, P = .02$; morphine: $r^2 = .33, P = .02$), values for $\Delta$ decreased with age (fig. 5) (i.e., sensitivity decreased with age). The slope of the regression lines was similar for the two drugs (P > .96). Values for $\Delta$ were larger for fentanyl than for morphine (P < .0001) (i.e., fentanyl is more potent).

At the end of the infusion, concentrations of the 3-glucuronide and 6-glucuronide metabolites of morphine were 6.7 ± 3.7% and 1.9 ± 1.1%, respectively, of the corresponding concentrations of morphine (table 2). The ratio of the concentrations of both metabolites of morphine to the concentrations of morphine did not vary with age at any of the three measurement intervals.

**Discussion**

Little is known about the extent to which the analgesic properties of opioids change as a neonate matures. Instead, many studies of opioid-induced effects have focused on outcomes other than analgesia. For example, Schlossmann (1937), Dobeli (1911) and Kupferberg and Way (1963) examined age-related changes in morphine’s lethal dose in various species. Subsequently, Way et al. (1965) and Bragg et al. (1995) used ventilatory depression as their end point. Although both lethality and ventilatory depression are important concerns, opioid administration should be guided pri-
TABLE 1

Values for pharmacokinetic parameters for morphine and fentanyl in dogs aged 1 to 34 days

<table>
<thead>
<tr>
<th></th>
<th>Fentanyl</th>
<th>Morphone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of dogs</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Cl, ml/kg (\text{min}^{-1})</td>
<td>60.3 ± 6.0</td>
<td>43.8 ± 1.8 (\text{age (}\text{ng} \cdot \text{ml}^{-1} \cdot \text{min}^{-1})</td>
</tr>
<tr>
<td>Cl(_{\text{m,app}}), ml/kg (\text{min}^{-1})</td>
<td>920 - 21.2 (\text{age (}\text{ng} \cdot \text{ml}^{-1} \cdot \text{min}^{-1})</td>
<td>228 ± 129</td>
</tr>
<tr>
<td>V(_{1}), ml/kg</td>
<td>24.1 - 0.0067 (\text{age (}\text{ng} \cdot \text{ml}^{-1} \cdot \text{min}^{-1})</td>
<td>91.0 ± 0.1</td>
</tr>
<tr>
<td>V(_{2}), ml/kg</td>
<td>4432 ± 7616</td>
<td>388 ± 405</td>
</tr>
<tr>
<td>V(_{3}), ml/kg</td>
<td>3904 ± 2492</td>
<td>1622 ± 332</td>
</tr>
<tr>
<td>V(_{ss}), ml/kg</td>
<td>8361 ± 6389</td>
<td>2101 ± 283</td>
</tr>
</tbody>
</table>

For parameters for which age-related changes were demonstrated, regression equations are shown; age is given in days. For the remaining parameters, values are expressed as mean ± S.D.

![Graph](image_url)

**Fig. 4.** Values for (log) \(k_{eo}\), with fentanyl (•) and morphine (○) are plotted against (log) age. Lines are determined by analysis of linear regression; neither was statistically significant. Values for \(k_{eo}\) were larger for fentanyl than for morphine (P < .0001 by Student’s t test for unpaired data).

![Graph](image_url)

**Fig. 5.** Values for (log) \(\Delta\) (increase in time to response per \( \mu \text{g/ml} \) concentration of the opioid in the effect compartment) with fentanyl (•) and morphine (○) are plotted against (log) age. Lines are determined by analysis of linear regression. For both fentanyl and morphine, time to response decreased with age; the slope of the regression lines was similar for the two drugs. Values for \(\Delta\) were larger for morphine than for fentanyl (P < .0001 by analysis of covariance) (i.e., fentanyl is more potent than morphine).

TABLE 2

Values for concentrations of morphine and its two metabolites

<table>
<thead>
<tr>
<th></th>
<th>Minutes after infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Morphine (ng/ml)</td>
<td>825 ± 722</td>
</tr>
<tr>
<td>Morphine-3-glucuronide (ng/ml)</td>
<td>60 ± 65</td>
</tr>
<tr>
<td>% Of corresponding morphine concentration</td>
<td>6.7 ± 3.7%</td>
</tr>
<tr>
<td>Morphine-6-glucuronide (ng/ml)</td>
<td>14 ± 16</td>
</tr>
<tr>
<td>% Of corresponding morphine concentration</td>
<td>1.9 ± 1.1%</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± S.D. Ratio of the two metabolites to the corresponding morphine concentrations did not vary with age.

![Graph](image_url)

**Fig. 4.** Values for (log) \(k_{eo}\) with fentanyl (•) and morphine (○) are plotted against (log) age. Lines are determined by analysis of linear regression; neither was statistically significant. Values for \(k_{eo}\) were larger for fentanyl than for morphine (P < .0001 by Student’s t test for unpaired data).

**Fig. 5.** Values for (log) \(\Delta\) (increase in time to response per \( \mu \text{g/ml} \) concentration of the opioid in the effect compartment) with fentanyl (•) and morphine (○) are plotted against (log) age. Lines are determined by analysis of linear regression. For both fentanyl and morphine, time to response decreased with age; the slope of the regression lines was similar for the two drugs. Values for \(\Delta\) were larger for morphine than for fentanyl (P < .0001 by analysis of covariance) (i.e., fentanyl is more potent than morphine).

TABLE 2

Values for concentrations of morphine and its two metabolites

<table>
<thead>
<tr>
<th></th>
<th>Minutes after infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Morphine (ng/ml)</td>
<td>825 ± 722</td>
</tr>
<tr>
<td>Morphine-3-glucuronide (ng/ml)</td>
<td>60 ± 65</td>
</tr>
<tr>
<td>% Of corresponding morphine concentration</td>
<td>6.7 ± 3.7%</td>
</tr>
<tr>
<td>Morphine-6-glucuronide (ng/ml)</td>
<td>14 ± 16</td>
</tr>
<tr>
<td>% Of corresponding morphine concentration</td>
<td>1.9 ± 1.1%</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± S.D. Ratio of the two metabolites to the corresponding morphine concentrations did not vary with age.

Mainly by an understanding of maturational changes in analgesic properties of these drugs. The present study was designed to provide this information.

We observed that sensitivity to opioid-induced analgesia decreased slightly with age. Our findings are consistent with those of McLaughlin and Dewey (1994), who reported that morphine, meperidine and fentanyl were more potent in suppressing the response to tail-flick and hot-plate tests in neonates than in adult rats. However, McLaughlin and Dewey did not measure plasma concentrations of these opioids and therefore were unable to determine whether opioid sensitivity in neonates resulted from maturational changes in pharmacokinetics or in pharmacodynamics. Our results suggest that differences in sensitivity rather than in either pharmacokinetics or equilibration delays explains the smaller opioid dose requirement in younger patients.

Our present finding of maturational changes in sensitivity to the analgesic effects of opioids differs from our previous finding regarding sensitivity to the ventilatory depressant effects of these drugs. Bragg et al. (1995) infused fentanyl or morphine in neonatal dogs and measured minute ventilation during constant hypercapnia (end-tidal PCO\(_2\) was maintained at 6 to 8 mm Hg above the resting value by adjusting inspired CO\(_2\)). We observed that the effect site concentration of morphine that depresses ventilation 50% (C\(_{50}\)) increased markedly (~80-fold) during the first month of life. This contrasted with the ~3.4-fold change in analgesic sensitivity to morphine during this period (fig. 4). For fentanyl, maturational decreases in sensitivity to the ventilatory (~4.1-fold) and analgesic (~3.9-fold) depressant effects are similar during the first month of life. This suggests that ventilatory depression may be a consistent guide to analgesic effects of fentanyl in neonates. In contrast, the pronounced maturational change in the ventilatory depressant effects of morphine suggests that in the neonate <1 week old, ventilatory depression may occur at opioid concentrations much smaller than those that produce analgesia. Differences in study design limit our ability to compare opioid concentrations producing ventilatory depressant vs. analgesic effects. First, no means exist to compare the effect measures of the two studies: \(\Delta\) determined to quantify analgesia and C\(_{50}\), the concentration depressing ventilation 50%. Second, the studies were performed in two different species of dogs (labradors vs. beagles).

Although sensitivity to each opioid changed with age, the rate of equilibration between plasma concentrations and effect (\(k_{eo}\)) did not vary with age. This is similar to our finding for ventilatory depressant effects of these opioids in neonates. Assuming that both analgesic and ventilatory depressant effects of opioids reflect their brain concentrations, \(k_{eo}\) presumably describes the rate at which each opioid crosses the blood-brain barrier. Our finding that equilibration rates for analgesic and ventilatory depressant effects of both opioids do not vary with age refutes the suggestion by Kupferberg and Way (1963) that the profound toxicity of morphine...
in younger animals resulted from immaturity of their blood-brain barrier. Kupperberg and Way observed markedly different toxicity in different ages (younger animals "exhibited only abortive seizures" and died >4 hr after drug administration, whereas older animals had "severe seizures and deaths generally occurred in less than 3 hours"), possibly limiting their ability to compare morphine toxicity in these two groups. Our findings suggest instead that the larger effect of opioids in neonates results from inherent central nervous system sensitivity. We also note that values for \( k_e \), for analgesia in the present study are similar to those for ventilatory depression that we reported previously (0.06 min\(^{-1}\) for morphine and 0.34 min\(^{-1}\) for fentanyl) (Bragg et al., 1995). This suggests that the time course for onset and offset of analgesia and ventilation is similar for each opioid (but differs between opioids).

Another possible explanation for the results of our study is that the recently proposed active transport mechanism that removes morphine from the central nervous system (Ekblom et al., 1992) is immature at birth. This would explain an increase in morphine dose requirements during the first month of life, as observed in the present study. However, in that our experiment is not conducted at steady state, an increase in the rate of transport should probably result in a maturational change in \( k_e \) rather than in \( D \), which is inconsistent with the results of the present study.

Several aspects of our study design warrant comment. First, to ensure a broad range of time to response values, we gave opioid doses sufficient to achieve the cutoff value for time to response in each animal. Had we chosen a larger value for cutoff, we would have obtained additional information about the concentration-effect relationship, perhaps permitting the use of pharmacodynamic models more complicated than equation 1 (e.g., a sigmoid e-max model). However, by censoring the response at 12 sec, we lose the ability to model e-max (the maximal effect). Therefore, we used a statistical technique that is not often used in analgesia experiments but is often used for other types of survival-type data, assuming that the time at which the animal responds is given by a probability distribution whose median, but not its shape, is affected by the concentration of the opioid at the effect site. The method that we used to model censored data might be applicable to other types of studies in which the response is also censored by a cutoff value.

A second issue of study design regards the potential contribution of the metabolites of morphine to its analgesic effects. At the end of the morphine infusion, concentrations of the 3-glucuronide and 6-glucuronide metabolites averaged 6.7% and 1.9%, respectively, of peak morphine concentrations; later, morphine concentrations decreased more rapidly than those of the metabolites so that 60 min after the infusion, concentrations of morphine-6-glucuronide averaged 16% of morphine. Relatively little is known about the analgesic potency of these metabolites. In adult humans, the 6-glucuronide metabolite has a dose-related ventilatory depressant effect less than that of morphine (Peat et al., 1991); the 3-glucuronide metabolite is also believed to be less potent than morphine, but dose-response data are lacking in neonates. In the absence of data from neonatal dogs regarding the relative analgesic potency of these metabolites and their relative rates of equilibration with the central nervous system, we were unable to incorporate the effects of these metabolites into our pharmacodynamic model. Ignoring the effects of these metabolites resulted in our overestimating the analgesic potency of morphine. However, because concentrations of the metabolites were markedly less than that of morphine at times of peak effect and because the metabolites are probably less potent than morphine, ignoring their contribution presumably minimally altered our estimates of \( D \). In addition, because the relative concentrations of the metabolites did not vary with age, any errors in the estimation of \( D \) should be similar at all ages. Thus, ignoring the contribution of the metabolites to analgesic potency should not alter our conclusions regarding maturational changes in the potency of morphine.

A third issue of study design concerns the additional factors that might influence the response of neonates to opioids. Analgesic effects of these drugs are a function of several factors: absorption, distribution, and elimination of the drugs (i.e., factors that influence the plasma concentration-time curve); rate of equilibration (\( k_{ee} \)) between concentrations in plasma and those at the effect site; and central nervous system sensitivity. Although we examined each of these in the present study, additional factors might influence pharmacokinetics or pharmacodynamics of opioids in neonates. For example, increased intra-abdominal pressure [such as that observed during surgical repair of abdominal wall defects in neonates (Yaster et al., 1988)] markedly reduces clearance of fentanyl (Gauntlett et al., 1988) by decreasing hepatic function rather than liver blood flow (Kuhls et al. 1995). Second, interaction with other drugs or endogenous compounds might influence sensitivity to opioids. Thus, factors beyond those examined in the present study are likely to influence the response to opioids in neonates in the clinical setting.

The final issue of study design concerns our selection of species. Although rats have been used extensively to study analgesic effects in neonates, their small size would not permit repeated sampling of blood, thereby limiting the opportunity to model pharmacokinetics and pharmacodynamics. Thus, we studied dogs, another species reported to be "sensitive" to morphine in the neonatal period.

Coupled with our earlier study of ventilatory depression in neonatal dogs, we now suggest that fentanyl is preferred to morphine in neonates, particularly if spontaneous ventilation is necessary. First, the ventilatory depressant effects of morphine (in dogs) vary markedly during the first month of life (Bragg et al., 1995). If this applies to humans, it would limit the ability of the clinician to select a nondepressant dose a priori. However, administration of small doses repeatedly might permit the clinician to titrate morphine to effect. Second, the marked maturational change in the ventilatory effects of morphine, in contrast to the smaller maturational changes in its analgesic effects, might result in the neonate developing respiratory depression with doses (or concentrations) markedly less than those needed to produce analgesia. In contrast, the ventilatory depressant and analgesic effects of fentanyl mature in parallel in dogs. An alternative explanation for our findings is that morphine concentrations producing analgesic and ventilatory effects are similar at birth.

\(^3\) These data could have been obtained had we performed additional studies in which we administered these metabolites and measured analgesic effects.
and that during the first month of life, ventilatory effects change markedly, whereas analgesic effects vary minimally. This would result in a large margin of safety for morphine at 1 month of age. However, clinical experience does not suggest that this safety margin is particularly large at 1 month of age. In addition, the observed toxicity of morphine in young neonates and warnings against its clinical use in these patients argue against this possibility.

Regardless of the potential benefits of fentanyl over morphine, one should be cautious when administering fentanyl to neonates (and to all patients). Its large \( k_{\text{eq}} \) results in a rapid onset of effect, potentially leading to both apnea and chest wall rigidity in response to bolus administration of large doses. As a result, fentanyl probably should be administered slowly (over several minutes) to neonates in whom tracheal intubation and controlled ventilation have not been accomplished.

In summary, we measured the analgesic effects of morphine and fentanyl in neonatal dogs. For both drugs, equilibration between plasma concentration and effect did not vary with age, although fentanyl equilibrated more quickly than morphine (consistent with its known rapid onset). Both drugs demonstrated maturational decreases in potency, and the magnitude of change with age was similar for morphine and fentanyl. The latter finding contrasts to our previous finding that during the first month of life, whereas that of fentanyl varies minimally. The contrast between maturational changes in the ventilatory depressant effects of morphine and its analgesic effects suggests limited utility of morphine in neonates during spontaneous ventilation. In contrast, the small but parallel maturational changes in the ventilatory depressant and analgesic effects of fentanyl in dogs suggests that it might be an appropriate analgesic in neonates, if administered slowly and with appropriate monitoring of ventilation.

**Appendix: Description of the Weibull Function**

Response of the painful stimulus was modeled using a Weibull function as follows.

**Predicted = Base line + \( \Delta \cdot C e \)**

**Survival = 0.5 \((\text{Observed/Predicted})^{2}\)**

**Density = \(Z \cdot (\text{Observed/Predicted})^{2} \cdot \ln(2)\)**

\[ \cdot \text{Survival/Observed} \]

where Predicted is the median value predicted by the equation, Base line is the value for time to response both before opioid is administered and when opioid effects have dissipated, \( C e \) is the concentration in the effect compartment, \( Z \) is a parameter that governs the shape of the Weibull function and Observed is the measured value for time to response. If Observed is <12 sec, likelihood equals Density. If Observed is \( \geq 12 \text{ sec} \), likelihood equals Survival. For each subject, likelihoods are determined for each observation. The four parameters of the model (Base line, \( k_{\text{eq}} \), \( Z \) and \( \Delta \) ) are then adjusted to maximize the product of these likelihoods.

**Acknowledgments**

Dr. Stuart Beal provided fundamental assistance with the pharmacodynamic analysis. We also thank Dr. Lewis Sheiner (Laboratory Medicine, UCSF) for assistance with the pharmacodynamic analysis, Dr. Howard Fields (Neurology, UCSF) for assisting with study design, Dr. Tony Yaksh (Anesthesia, UCSD) for designing the thermal probe and Drs. Gregory Timmel and Nina Hahn (Animal Care Facility, UCSF) for assisting with care of the animals.

**References**


