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Model-informed Bayesian Estimation Improves the Prediction of Morphine Exposure in Neonates and Infants

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Abstract

Background—Pain control in infants is an important clinical concern, with potential long-term adverse neurodevelopmental effects. Intravenous morphine is routinely administered for post-operative pain management; however, its dose-concentration-response relationship in neonates and infants has not been well characterized. Although the current literature provides dosing guidelines for the average infant, it fails to control for the large unexplained variability in morphine clearance and response in individual patients. Bayesian estimation can be used to control for some of this variability. The authors aimed to evaluate morphine pharmacokinetics and exposure in critically ill neonates and infants receiving standard of care morphine therapy and compare a population-based approach to the model-informed Bayesian techniques.

Methods—The pharmacokinetics and exposure of morphine and its active metabolites were evaluated in a prospective opportunistic pharmacokinetic study using 221 discarded blood samples from 57 critically ill neonates and infants in the neonatal intensive care unit. Thereafter, a population-based pharmacokinetic model was compared to a Bayesian adaptive control strategy to predict an individual's pharmacokinetic profile and morphine exposure over time.

Results—Among the critically ill neonates and infants, morphine clearance showed substantial variability with a 40-fold range (i.e., 2.2 to 87.1, mean 23.7 L/h/70 kg). Compared to the observed morphine concentrations, the population-model based predictions had an R^2 of 0.13 while the model-based Bayesian predictions had an R^2 of 0.61.

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Conclusion—Model-informed Bayesian estimation is a better predictor of morphine exposure than pharmacokinetic models alone in critically ill neonates and infants. A large variability was also identified in morphine clearance. A further study is warranted to elucidate the predictive covariates and precision dosing strategies that use morphine concentration and pain scores as feedbacks.

Keywords

Bayesian estimation; Neonates; Infants; Model-based dosing; Morphine; Precision dosing

BACKGROUND

Morphine is routinely used for the control of post-operative pain in the neonatal intensive care unit (NICU)¹; however, precision dosing schemes do not exist for neonates and infants.² The morphine pharmacokinetic (PK) literature describes considerable unexplained variability in morphine clearance³ and although several informative population PK models have been developed a substantial percentage of the variability remains unaccountable.^{4–10} The unpredictability in morphine clearance leads to dosing designed for the ‘average’ infant without guidance for controlling for interpatient variability. Therapeutic drug monitoring of morphine is currently not performed and clinicians are left with inadequate clinical information to measure effectiveness. Thus, pain may be inadequately treated or infants may be placed at higher risk for adverse effects when on morphine.

Morphine dosing in neonates and infants is titrated to response, but newborn pain is difficult to measure and even when protocols exist they are difficult to follow.¹¹ Pain assessment tools generally rely on some combination of changes in facial expression, behavior, or physiologic parameters but still do not fully characterize the pain experience as measured by cortical activity.¹²

Population PK studies have used data from multiple subjects within a defined population to mathematically determine PK parameters, such as clearance and volume of distribution.¹³ Although the use of covariates, such as age, weight, gender, or organ function, better predicts individual PK parameters, substantial inter-patient variability remains. Bayesian estimation, using one or more measured drug levels as feedback to the model to further improve the prediction of PK parameters, has been proposed as an attractive solution to further control for inter-patient variability and improve dosing regimens.^{14,15} However, it remains unclear whether morphine exposure in infants can be better explained using Bayesian estimation than simpler population PK models.

Ideally, PK models would be integrated with pharmacodynamic (PD) analgesic markers to target an evidence-based exposure range. The exposure range is a moving target that might vary based on a number of factors, including the cause of pain (e.g., surgery type, endotracheal tube discomfort), the time since painful insult, and previous experience with pain and opiates.

The purpose of this study was to prospectively evaluate morphine PK and exposure in critically ill neonates and infants receiving standard of care morphine. We hypothesized that

compared to population-based methods, Bayesian adaptive control strategies could better predict individual PK morphine profiles.

MATERIALS AND METHODS

We conducted a prospective opportunistic PK study using a minimal-risk design and discarded blood samples^{16,17} from neonates and infants in the NICU receiving morphine as part of their standard of care over a 7-month period. The Institutional Review Board at Cincinnati Children's Hospital Medical Center (CCHMC) approved the study protocol. Informed consent was obtained from the parents or legal guardians of the enrolled subjects. All infants receiving IV morphine for at least 24 hours for analgesia in the CCHMC NICU were eligible to participate in this study, except those with severe liver (aspartate aminotransferase (AST) or alkaline phosphatase >5 times the upper limit of normal for age) or kidney disease (creatinine >3 times the upper limit of normal for age), undergoing therapeutic hypothermia, receiving extracorporeal membrane oxygenation, or receiving other opiate medications.

When available, residual blood from blood samples withdrawn for clinical testing was obtained from the clinical lab. All samples were collected from the clinical lab, transferred, processed, and stored in the Cincinnati Bio-Bank Core within 7 days before the measurement of morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) concentrations. The demographic information and clinical data collected from the electronic medical record were medical and surgical history, gestational age, postnatal age, weight, gender, race, serum creatinine, AST, alkaline phosphatase, times and doses of administered morphine, and date and time of blood sample collections.

Standard of Care Dosing

The clinical team decided the timing for treatment initiation with morphine and its dosing. Clinical judgment was performed to determine the need for a continuous morphine infusion and frequency of intermittent bolus doses of morphine. Not all patients received a continuous infusion. In fact, most patients were administered 'as needed' (pro re nata, PRN) intermittent bolus doses of morphine by the nursing staff per protocol. Pain management was guided by the use of the Neonatal Infant Pain Scale,¹⁸ a validated measure of pain in infants. In general, the hospital protocol dictated that infants scoring in the moderate (score 3-4) or severe (score >4) range should first undergo non-pharmacologic interventions to differentiate pain from agitation; however, if the score remained elevated after reassessment, pharmacological interventions were pursued. If analgesia remained insufficient or other clinical concerns arose, the nursing staff would notify the clinical team. A typical starting infusion dose of morphine in the NICU was 0.05 mg/kg/h after a loading dose of 0.05 mg/kg¹⁹ and the usual initial intermittent or as needed IV dose was 0.05 mg/kg.

Assays for Morphine and its Metabolites

Plasma samples were prepared for analysis by solid-phase extraction as recently described.²⁰ Morphine and its two metabolites, M3G and M6G, were quantified with a validated liquid chromatography tandem mass spectrometry assay using stable isotope-labeled internal

standards. The analysis was performed using a LC20AD HPLC system (Shimadzu) coupled to the SCIEX QTRAP 5500 mass spectrometer (Sciex, Concord, Canada). Chromatographic separation of morphine from its metabolites was achieved using a reverse phase C18 LC column (150 × 2.0 mm i.d. 5 µm, Phenomenex). Mobile phase A comprised water/0.1% formic acid/5 mM ammonium formate (v/v/v) while mobile phase B comprised acetonitrile/0.1% formic acid (v/v). The flow rate was 0.5 mL/min with gradient elution and the total run time was 8 minutes. Analytes were detected by tandem MS, with electrospray ionization and positive multiple reaction monitoring (MRM) mode. The optimum MRM transitions m/z 286.1 → 152.1, m/z 462.2 → 286.1, and m/z 462.2 → 286.1 were selected to quantify morphine, M3G, and M6G, respectively. Data were acquired and processed with MultiQuant software version 3.0. The lower limit of quantification for all analytes was 2 ng/mL and the calculated inter-batch accuracies (% bias) ranged from -2.6 – 13% for all concentrations with an overall inter-batch precision lower than 10.3% for the samples used as Quality Controls for the three analytes, morphine, M3G, and M6G.

Population-based Prediction of Individual Morphine PK Profiles

Morphine plasma concentration profiles were simulated and compared to the observations based on the actual dosing history of each patient. A deterministic simulation was performed with a previously published morphine population PK model for neonates and infants using NONMEM (version 7.2, ICON, Ellicott City, MD). In a recent study, we performed an extensive comparison and validation analysis of the published morphine population PK models as part of the development of an electronic health record-embedded decision support platform for morphine precision dosing in neonates.²¹ Several useful models were identified during this analysis. However, the Holford model was selected as the patient demographics in the cohort analyzed were comparable to those of neonates and infants in the NEOPAIN study.⁸ In addition, we opted to use an overall model structure that enabled the separation of growth (weight) and maturation (ontogeny) and other factors that are known to influence morphine clearance, such as mechanical ventilation and prematurity. In the model published by Holford et al.⁸ (See Table 1), morphine clearance in neonates and infants is described as a function of body weight (BW) and postmenstrual age (PMA), with allometric scaling of clearance with a power coefficient of 0.75 and a sigmoidal clearance maturation model as follows:

$$CL_i = CL_{std} \times \left(\frac{BW}{70}\right)^{0.75} \times \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}} \times FDEVCL$$

where CL_{std} is the clearance in an average adult weighing 70 kg, TM_{50} is the PMA at which 50% of adult clearance is reached, and the Hill coefficient is associated with the slope of the developmental profile. Postnatal changes in the volumes of distribution in the central and peripheral compartment were described as:

$$V_i = V_{std} \times \left(\frac{BW}{70}\right) \times (1 - \beta Vol \times \exp(-PNA \times \ln(2)/TVOL)) \times FDEVV$$

where PNA is the postnatal age in days, β VOL is the fractional decrease in volume at birth compared to the mature values, and TVOL is the half-life of the increase in volume. The factors, FDEVCI and FDEVV, were applied to account for the lower clearance observed in the ventilated preterm neonates. The population means for all parameters are summarized in Table 1.

Model-informed Bayesian Analysis

Individual PK parameters were estimated by Bayesian estimation using NONMEM. The goal of Bayesian estimation is to obtain the most probable post-hoc estimates of the PK parameters (posterior) based on the population model (prior) and the concentration measurements used as feedback as described in tutorials on the topic by Mould²² and Bauer^{23,24} (see NONMEM code, Supplemental material). The dosing, demographic, and morphine plasma concentration data were used for the analysis, with the published neonate morphine PK model⁸ as the prior Bayesian model. The Bayesian-predicted individual plasma profile and morphine concentrations were compared to the observed concentration measurements. The percent mean error, computed as a measure of bias, and the percent absolute mean error, computed as a measure of precision, were calculated as follows²⁵:

$$\text{Bias}(\%) = \frac{100}{n} \sum \frac{\text{Pred}_i - \text{Obs}_i}{\text{Obs}_i}$$

$$\text{precision}(\%) = \frac{100}{n} \sum \frac{|\text{Pred}_i - \text{Obs}_i|}{\text{Obs}_i}$$

where n is the number of morphine concentrations, Pred_i is either a population model-based or Bayesian-estimated predicted concentration in the i^{th} individual measurement, and Obs_i is the observed morphine concentration in the i^{th} individual measurement.

Morphine PK Values

Morphine PK parameters, including clearance and volume of distribution, were allometrically scaled to a 70-kg adult based on the previously published PK model⁸; this model combined data from Anand et al.⁷ and Bouwmeester et al.⁴ and included a maturation function for morphine clearance and volume of distribution. According to the authors, the theoretical allometric exponent in combination with the clearance maturation function significantly improved the predictions without introducing substantial error. A factor was applied to premature neonates who were ventilated to further improve prediction; this factor may have been related to the reduced hepatic blood flow observed in ventilated patients.²⁶

Statistical Analysis

Data are expressed as median or mean values with ranges. The correlation between model-based predictions and the observed morphine plasma concentrations was evaluated by linear regression analysis using R version 3.5.0.

Evaluation of the Individual PK Profiles

The stepwise model-informed process was evaluated using a representative case example. PK profiling began with the population model prediction (no measured concentration available) followed by estimation of the individual parameters and PK profile based on the first, and a subsequent follow up concentration result. In addition, individual exposure-time curves were generated where the population PK model and the model-informed Bayesian prediction with all available concentration data were used to illustrate the differences between the two approaches. The cases were selected as general representative examples of different clinical scenarios. To develop the exposure-time curves, population model-based predicted concentration profiles were generated according to the patient-specific dosing data, the covariates of clearance, and the volume of distribution such as body weight, postmenstrual or postnatal age, and whether the case was a ventilated pre-term infant or not. The individual parameters were then generated using Bayesian estimation based on all available data.

RESULTS

Data collected from 57 patients were included in the present analysis, with a total of 221 morphine concentration measurements available for the PK analysis. The number of morphine concentrations available from each patient varied from 1 to 11 samples, with a median of 3 samples per patient over an average 10-day period. The infants' gestational age ranged from 24 to 41 completed weeks while the post-natal age ranged from hours after birth to 153 days of life. Twenty-two of the 57 patients (38.6%) were females. The demographic and clinical data, including diagnosis, surgery, or procedure of patients are summarized in Table 2.

The current trial and error dosing paradigm result in a wide range of morphine exposures as observed with the measured morphine concentrations in Figure 1A. Morphine clearance showed large inter-patient variability (2.2 to 87.1, mean 23.7 L/h/70 kg) as demonstrated by the 40-fold range. Further, a large variability was reflected by the wide range of observed morphine concentrations ranging from 2.6-529.7 µg/L (Figure 1). Morphine volume of distribution displayed substantial variability between patients (7.7 to 141.1, mean 36.0 L/70 kg). Figures 1B and 1C show the large variability in metabolite exposure.

A better correlation was observed between the Bayesian predicted concentration estimates and the observed concentrations ($R^2=0.61$) than between the population-model based predictions and observations ($R^2=0.13$) (Figure 2). The bias and precision for the Bayesian estimated prediction (34.7% and 45.8%, respectively) were smaller than those for the population model-based prediction (134.5% and 159.6%, respectively).

Figure 3 presents a case example depicting the stepwise processes starting with the PK model-informed prediction followed by Bayesian estimation to mimic a clinical scenario. Figure 4 shows the overall predictive performance in representative examples of the population model-based prediction (orange dotted lines) and Bayesian estimation prediction (blue solid lines) of the morphine PK profiles versus the observed concentrations. Figure 4A represents a 42-day old male born at 37 weeks estimated gestational age (GA) with

Hirschsprung disease. Morphine was initiated after laparoscopic G-tube placement and mucus fistula revision while IV bolus morphine was initiated at 0.1 mg/kg every 2-6 h. The 0.05-mg/kg concentration of the bolus morphine injections was additionally administered intermittently based on the patient's pain scores. Figure 4B represents a 1-day old female (39 weeks GA) with a pneumothorax who received bolus injections of 0.1 mg/kg of morphine every 3-16 h after insertion of a chest tube. Figure 4C represents an 80-day old pre-term male (26 weeks GA) diagnosed with colonic strictures with a prior history of necrotizing enterocolitis. After surgery, continuous morphine was initiated at 0.05 mg/kg/h. Additionally, 0.1 mg/kg of an IV bolus injection was administered every 2-8 hours as needed for pain. The infusion rate increased to 0.1 mg/kg/h two hours after the start of infusion and returned to 0.05 mg/kg/h after 3.5 days. Figure 4D represents a pre-term female (GA 26 weeks) aged 110 days. She was first administered morphine at 0.1 mg/kg/h of continuous infusion, with intermittent 0.1 mg/kg of IV bolus injection as needed. The infusion rate increased to 0.15 mg/kg/h two hours after the start of infusion and returned to 0.1 mg/kg/h after more than 4 days.

DISCUSSION

This study confirms the ability of model-informed Bayesian estimation to better predict an individual's PK profile than a population-based method using patient information as covariates without concentration feedback. Compared to the population PK model, the Bayesian estimation model of morphine improves the precision in infants.

Although previous studies have demonstrated a wide variability in morphine concentrations,²⁶ to our knowledge, this is the first study to demonstrate that Bayesian estimation can improve morphine exposure prediction in infants. Such finding is important as the ability to predict exposure leads to the ability to control exposure. A recent commentary by Anderson and van den Anker mentions a tentative range of 10-30 ng/mL; however, they emphasized the lack of a clear indication dependent morphine dose-exposure-response relationship.² Future studies are needed to further explore the morphine and morphine metabolite exposures, pain scores, and other biomarkers to determine potential target concentration ranges. Model-informed Bayesian estimation will be helpful in this process by indicating excessive over- and unnecessary underexposure based on individualized morphine exposure-response profiling in neonates and infants. In a recent analysis of pain scores relative to morphine concentrations in a comparable cohort receiving IV morphine, a large percentage of neonates was exposed to high morphine concentrations relative to the pain scores.²⁷

Per kilogram bodyweight dosing is typically used in neonates and infants. Although some authors make further recommendations based on age,^{3,4,7,26} this has not translated to changes in the standard clinical practice of dosing morphine at many institutions. Pain and analgesia are highly variable complex dynamic pathways and different clinical situations require variable medication exposures.^{28,29} For example, an infant undergoing abdominal surgery post-operative day one will have a different morphine exposure need than an intubated infant with a discomfort related to the endotracheal tube and mechanical ventilation. The inability to harmonize dosing with exposure and clinical response is concerning as very low concentrations will lead to inadequate analgesia, which is both

inhumane and can subsequently influence development, leading to adverse consequences of neonatal pain.³⁰ Emerging literature suggests that the negative long-term consequences of neonatal pain may be prevented with appropriate analgesia.³¹ However, increased morphine exposure is associated with prolonged ventilation, respiratory depression, hypotension, decreased gastrointestinal motility, and subsequent opiate withdrawal.^{32,33} Although it is unclear whether morphine exposure contributes to long-term deleterious developmental effects, a recent long-term follow-up study demonstrated that this does not occur in humans. However, given the small sample size, future studies with larger sample sizes are needed to confirm these findings.

Several PK models exist that describe morphine clearance in infants.^{3,5,7-9} Although these models were evaluated, we chose the model proposed by Holford et al.⁸ as it represents a large previously published data set from Anand et al.⁷ and Bouwmeester et al.⁴ Further, it has been shown to accurately predict the morphine dose rate needed to achieve a target concentration over a wide age range. This data set considers gestational and postnatal ages, prematurity, and bodyweight.

To achieve precision dosing for morphine in the NICU, new strategies must be pursued. One such strategy, coupling PK modeling with Bayesian analysis, involves the calculation of the initial dose using available population-based PK models.³⁴ A logical subsequent step would involve the use of one or more measured morphine (and M3G and M6G) concentration results as an additional feedback into the model to refine the dosing regimen and transition from population-based to truly individual precision dosing.^{15,35,36} The real power of this strategy comes from Bayesian adaptive control, which combines the prior knowledge captured by the population model with new patient-specific information such as a measured concentration to generate an individualized morphine dosing regimen, to maintain morphine exposure within the provider specified desired target range^{14,36}. Bayesian estimation can be conducted prior to reaching a steady-state level and thus could be performed immediately after the initial dose of a medication. A similar strategy has been pursued to effectively and safely dose sirolimus in our NICU.³⁷⁻³⁹ However, a major hurdle in the past is the requirement of a readily available means to measure morphine for use in real time to incorporate into the PK model. With the recent advances in nano-sampling and dried blood spot technology, direct quantitative analysis of therapeutic drugs by mass spectrometry has become feasible.^{40,41} Further, we have developed paper spray assays,^{42,43} including a method that measures morphine concentration at the bedside using a single drop of blood. The results from this assay are available in approximately 2 min and are rapidly inputted in the electronic health record. These results are expected to be used in the Bayesian feedback analysis and are made available to the clinical team to adjust dosing as needed. This process could also be repeated as needed if the clinical results are suboptimal or the patient's condition changes.

The Bayesian estimation techniques, which incorporate the measured morphine concentration into the analysis, better predict the PK profile. The initial dose is determined by the population-based model followed by the plasma morphine drug level. Using the dosing information, the target morphine concentration goal (better determination required), bedside pain score, and morphine concentration value, the decision support tool using

Bayesian adaptive controls recommends a new dosing regimen to ensure the morphine exposure target goal is achieved.²¹

Because of the lack of good predictors of variability in morphine PK in combination with challenges of assessing neonatal pain, clinical teams experience extreme difficulty managing the balance between appropriate morphine exposure and optimal analgesic response. The variability in exposure can be related to illness severity, a decrease in hepatic or renal blood flow as observed in hypotension or mechanical ventilation,²⁶ variations in gestational or postnatal age, fluid status, recent blood transfusion, genetics, ontogeny of enzyme systems,^{44–46} and race.⁴⁷ Although we did not account for these factors in the current study, they underscore the clinical importance of developing precision dosing algorithms to achieve effective pain control while decreasing the risk of adverse effects. Further complicating matters is the variable exposure to the active morphine metabolites, which is important because of the analgesic activity of M6G^{48,49} and the mu opioid receptor antagonism of M3G.^{48,50,51} Although M6G is two to three fold less potent than morphine, it remains clinically relevant as it is present in concentrations that exceed those of morphine.⁵² Therefore, these metabolites must be accounted for in future models.

The inability to assess a target morphine exposure range and the routine use of higher morphine doses than those recommended in the literature are limitations of the present study. The wide range of observed morphine concentrations was partially due to the wide range of morphine doses administered. Further, we could not determine whether apparent lower range exposures provided adequate analgesia or whether increased doses led to increased risks of adverse effects. Patients might however vary in their individual therapeutic requirements and targets based on the type of surgery, time from surgery, tolerance, age, race, differences in pain processing, and other factors.⁵³ Future studies incorporating morphine PD markers, such as pain scores and pharmacogenetics, are thus needed to better define the exposure-response relationship.⁵⁴

Although useful pain biomarkers that enable the titration of morphine to achieve a response should be identified and considered, measuring pain in infants is challenging. Over 40 behavioral and physiological scales exist to assess neonatal pain; however, there is no consensus to determine the pain scale that should be used or when an analgesic intervention is warranted.⁵⁵ Brain oriented approaches, including near-infrared spectroscopy,⁵⁶ functional magnetic resonance imaging,⁵⁷ and electroencephalogram,^{58,59} show promise for pain measurement; however, additional research is required before their translation into clinical practice. Pain PD marker research may help to establish a morphine exposure-response relationship to assist in precision dosing.^{2,29} The use of Bayesian adaptive control for the administration of a pain medication would be of great benefit to PD studies as it reduces some of the inherent age-related differences in morphine PK. Further, its use would help to improve our understanding of neonatal and infant morphine dosing requirements by defining the developmental-specific target concentrations in this population.

CONCLUSION

In critically ill infants receiving standard of care morphine dosing, a model-informed Bayesian approach was found to better predict their PK profiles than population-based models. Additionally, a large variability was identified in the morphine concentrations achieved, ultimately reflecting the wide range of morphine clearances that cannot be explained by clinical factors alone and lack other predictive covariates. The large interpatient variability in morphine disposition suggests that model-based dosing guidelines that allow individualization should be developed to optimize the response of infants to morphine. Thus, therapeutic drug management using model-based Bayesian estimation with real time concentration feedback represents an attractive next step.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A) Observed morphine concentrations in a cohort of 57 patients receiving standard of care pain management. Each symbol represents an individual patient. B) Observed M3G concentrations in the patient population. A total of 292 observed M3G concentrations in a cohort of 57 patients receiving standard of care pain management. C) A total of 245 observed morphine-6-glucuronidation concentrations in a cohort of 57 patients receiving standard of care pain management.

Figure 2.
Predicted vs observed morphine concentrations for A) the population-based model and B)
the Bayesian estimation model.

Figure 3.

Case example of the stepwise model-informed process, starting with the population model prediction (no measured concentration available) followed by the estimation of individual parameters and the PK profile based on one or more concentration results.

A) Population model-based predicted morphine concentration time profile (orange solid line). The first observed concentration measurement (closed circle) indicates that this patient has a concentration that is lower (higher clearance) than that expected according to the population estimate. (B) Individual predicted concentration time profile using Bayesian estimation and the first observed concentration (blue solid line). The population model-based prediction is shown as a dashed line. (C) The second observed concentration was overlaid on the individual prediction, indicating that the individual PK model using Bayesian feedback could predict the later concentration.

Figure 4.

Comparison of the observed morphine concentrations with the population model-based predictions using covariates and model-informed Bayesian estimations in four representative patients. The dashed lines represent the population PK model-based predicted profiles while the solid lines represent the Bayesian estimated profiles using all data. Closed circles represent measured concentrations. (a) 42 days old male at a gestational age (GA) of 37 weeks, (b) 1 day old female at a GA of 39 weeks, (c) 80 days old male at a GA of 26 weeks, and (d) 110 days old female at a GA of 26 weeks.

Table 1.

The neonatal morphine population pharmacokinetic model used in this study.

References	Source patient cohorts	PK model descriptions	Population mean PK estimates
Holford et al. ⁸	NEOPAIN data reported by Anand et al. ⁷ and Bouwmeester data ⁴ reanalyzed using a model with a maturation function.	$CL_i = CL_{std} \times \left(\frac{BW}{70}\right)^{0.75} \times \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}} \times FDEVCL^*$ $V1_i = V1_{std} \times \left(\frac{BW}{70}\right)^*$ $\times (1 - \beta Vol \times \exp(-PNA \times \ln(2)/TVOL)) \times FDEVV$ $Q_i = Q_{std} \times \left(\frac{BW}{70}\right)^{0.75}$ $V2_i = V2_{std} \times \left(\frac{BW}{70}\right)^*$ $\times (1 - \beta Vol \times \exp(-PNA \times \ln(2)/TVOL)) \times FDEVV$	CL_{std} (L/h/70 kg) =86.4 $V1_{std}$ (L/70 kg) =46.8 Q_{std} (L/h/70 kg) =68.6 $V2_{std}$ (L/70 kg) =203 TM_{50} (weeks) =58.1 $Hill$ =3.58 $FDEVCL^a$ =0.479 βVol =0.252 $TVOL$ (days) =20.3 $FDEVV^a$ =0.696

Abbreviations: Pharmacokinetic (PK), individual morphine clearance (CL_i), clearance in an average adult weighing 70 kg (CL_{std}), birth weight (BW), post-menstrual age (PMA), steepness of clearance maturation (HILL), PMA at which 50% of adult clearance is reached (TMA), fraction of clearance in the NEOPAIN group (FDEVCL), individual central volume ($V1_i$), central volume in an average adult weighing 70 kg ($V1_{std}$), fractional decrease in volume at birth compared to mature values (βVol), postnatal age in days (PNA), half-life of the increase in volume (TVOL), Fraction of ($V1 + V2$) in the NEOPAIN group (FDEVV), individual intercompartmental clearance (Q_i), intercompartmental clearance in an average 70-kg adult (Q_{std}), individual peripheral volume ($V2_i$), central volume in an average adult weighing 70 kg ($V2_{std}$)

* FDEVCL and FDEVV, are applied for pre-term ventilated neonates whose gestation age is less than 32 weeks.

Table 2.

Demographic information for the 57 subjects included in the study

Parameters	Median	Min	Max
Gestation age (weeks)	37	24	41
Postnatal age (days) *	2	0	153
Post menstrual age (weeks) *	38	24	52
Birth body weight (kg)	2.60	0.60	4.33
Body weight *	3.00	0.80	6.10
Sex (n)	Female (22), Male (35)		
Race (n)	White (40), Black (6), Asian (1), Others or Unknown (10)		
Diagnosis (n)	CDH (10), TEF/EA (8), Gastroschisis (7), Intestinal perforation (7), Sedation while intubated (6), Hirschsprung disease (2), Pneumothorax (2), CPAM (2), Micrognathia (2), Tracheal rings (2), Imperforate anus (1), SCT (1), NAS (1), Subglottic stenosis (1), Omphalocele (1), Mesoblastic nephroma (1), Intestinal malrotation (1), Vein of Galen (1), Intestinal stricture (1)		

Abbreviations: Congenital diaphragmatic hernia (CDH), tracheoesophageal fistula and esophageal atresia (TEF/EA), congenital pulmonary airway malformation (CPAM), sacrococcygeal teratoma (SCT), and neonatal abstinence syndrome (NAS). The study comprised 41 neonates younger than 4 weeks old and 16 infants.

* At the start of therapy.