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Quantifying the Pharmacodynamics of Morphine in the Treatment of Postoperative Pain in Preverbal Children

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Abstract

While the pharmacokinetics of morphine in children have been studied extensively, little is known about the pharmacodynamics of morphine in this population. Here, we quantified the concentration-effect relationship of morphine for postoperative pain in preverbal children between 0 and 3 years of age. For this, we applied item response theory modeling in the pharmacokinetic/pharmacodynamic analysis of COMFORT-Behavior (COMFORT-B) scale data from 2 previous clinical studies. In the model, we identified a sigmoid maximal efficacy model for the effect of morphine and found that in 26% of children, increasing morphine concentrations were not associated with lower pain scores (nonresponders to morphine up-titration). In responders to morphine up-titration, the COMFORT-B score slowly decreases with increasing morphine concentrations at morphine concentrations >20 ng/mL. In nonresponding children, no decrease in COMFORT-B score is expected. In general, lower baseline COMFORT-B scores (2.1 points on average) in younger children (postnatal age <10.3 days) were found. Based on the model, we conclude that the percentage of children at a desirable COMFORT-B score is maximized at a morphine concentration between 5 and 30 ng/mL for children aged <10 days, and between 5 and 40 ng/mL for children >10 days. These findings support a dosing regimen previously suggested by Krekels et al, which would put >95% of patients within this morphine target concentration range at steady state. Our modeling approach provides a promising platform for pharmacodynamic research of analgesics and sedatives in children.

Keywords

morphine, pediatric pharmacology, pharmacokinetic-pharmacodynamic modeling, postoperative pain

Morphine is frequently used in children to treat postoperative pain.[1] As both under- and overdosing of morphine may have detrimental effects, many studies on the optimization and individualization of morphine dosing in children have been performed. This has led to ample evidence on the pharmacokinetics (PK) of morphine from preterm neonates to adolescents.[2–4] From these studies, dosing advices could be obtained that will lead to similar morphine concentrations in children of different ages.[5] Given these important steps forward, the next step is to study the pharmacodynamics (PD) of morphine across the pediatric age range to define the target concentration throughout childhood.[6–8]

Morphine target concentrations for the treatment of postoperative pain in neonates and infants have previous been suggested to lie between 4 and 27 ng/mL but were lacking the support of knowledge on the concentration-effect relationship.[7,9,10] The quantification of the concentration-effect relationship of morphine in children has proven difficult, with different studies reporting no statistically or clinically significant relation between morphine concentration and reduction in pain levels.[3,11,12] Factors that may complicate

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PK/PD analyses of morphine in children may, apart from age-related variation in morphine PK, include the large interchild variability in pharmacodynamic response to morphine, variable pain trajectories over time, and the difficulty of pain assessment in preverbal children.[3,6,7,13] For the latter, observational scales that quantify pain-associated behavior and symptoms in children, such as the COMFORT-B and the Premature Infant Pain Profile, have been developed and are currently in use in pediatric clinical practice.[14–16] These composite scales, consisting of the sum of multiple subscores or items, are not only used to guide titration of morphine in clinical practice but have also opened new avenues for analyzing morphine PD using advanced PK/PD modeling approaches.

Item response theory is a data analysis technique that can be used to analyze item-level data (ie, scores for individual items of a scale) of composite clinical scales instead of the total composite score data. Compared with more traditional data analysis of total score data, item response theory modeling has improved statistical power, which might enable a more precise quantification of a concentration-effect relationship of morphine.[17,18] This was recently demonstrated by Välitalo et al,[11] who used item response theory to analyze item-level data from the COMFORT/COMFORT-B scales to characterize the PD of morphine in mechanically ventilated preterm neonates.

The goal of this study is to quantify the PD of morphine for the treatment of pain after major noncardiac surgery in preverbal children aged 0 to 3 years. This is done using item response theory modeling in the PK/PD analysis of COMFORT data collected in 2 previous clinical studies.[19,20] Using the final PK/PD model, we identify a target concentration for morphine for the treatment of postoperative pain in children aged <3 years.

Methods

Clinical Studies

This secondary study analyzes COMFORT and COMFORT-B data obtained from children between ages 0 and 3 years during their stay at the pediatric intensive care unit after major noncardiac surgery in 2 clinical studies performed at the Erasmus Medical Centre–Sophia Children's Hospital in Rotterdam, The Netherlands.[19,20] Both studies were approved by the hospital's institutional review board and their procedures were in accordance with the Helsinki declaration. Written informed consent was obtained from parents or legal representatives. A pain management protocol based on the COMFORT-B scores was used in both studies for the titration of morphine dosing in children during the study period.

Data in the 2 studies were collected using the COMFORT scale (van Dijk et al[20]) and COMFORT-B scale (Ceelie et al[19,20]), respectively. The COMFORT scale contains 6 behavioral and 2 physiological items that quantify pain-associated behavior and symptoms as a proxy for the level of pain.[15,20,21] The response of each item ranges from 1 (low distress/pain) to 5 (high distress/pain). The behavioral items are *calmness and agitation*, *crying* (only measured in absence of mechanical ventilation), *facial tension*, *physical movement*, *muscle tension*, *alertness*, and *respiratory response* (measured only during mechanical ventilation), while the physiological items are blood pressure and heart rate. The COMFORT-B scale only contains the behavioral items of the COMFORT scale and has been validated for use in postoperative pain assessment in preverbal children.[15] The item-level scores (ie, scores for each item of the scale) of the COMFORT-B scale or the scores from the behavioral items in the COMFORT scale, can be summed to yield the total COMFORT-B score. The total COMFORT-B score ranges from 6 to 30, for which scores of 11 to 16 reflect adequate treatment and are clinically aimed for during titration.[22] COMFORT-B scores above 16 are an indication for undertreatment, and would be a reason to administer additional morphine or other analgesics or sedatives. COMFORT-B scores below 11 are more ambiguous and could indicate not only deep sleep but also overtreatment with morphine or other analgesics or sedatives.

Study 1: Van Dijk et al. This study included 204 term neonates and infants aged 0 to 3 years who underwent major noncardiac surgery.[15,20] Subjects received a 100-μg/kg bolus dose of morphine at the end of surgery. Subjects were randomized to receive a 10-μg/kg/h continuous morphine infusion or a 30-μg/kg morphine bolus every 3 hours, with rescue morphine in both arms based on the pain management protocol. In the present study, we included the 185 subjects from whom both COMFORT scores and morphine concentration data were available.

Study 2: Ceelie et al. This study included 71 term neonates and infants aged 0 to 1 year who underwent major noncardiac surgery.[19] Subjects received a 100-μg/kg bolus dose of morphine at the end of surgery. Subjects were randomized to receive either continuous intravenous morphine or 4-times-daily intravenous paracetamol (30 mg/kg/d), with rescue morphine in both arms based on the pain management protocol. Subjects randomized for continuous morphine started on a model-based infusion rate of 2.5 μg/kg$^{1.5}$/h for subjects aged <10 days and 5 μg/kg$^{1.5}$/h when ≥10 days. This dosing regimen implies a higher infusion rate per kilogram of body weight with increasing body weight

(see Table S1).[5,23] In the present study, we included the 13 subjects for whom both COMFORT-B scores and morphine concentration data were available. Of these 13 subjects, 6 were randomized to paracetamol as the primary analgesic in the study. The trial was registered at www.trialregister.nl under NTR1438.

Model Development

The model development consisted of 2 steps. In step 1, we estimated the item characteristic curves of the item response theory model, which quantify the relationship between the probability of observing item-level scores and an unobserved latent variable representing the level of pain.[18] The second step of the analysis was the development of a longitudinal PK/PD model that describes how this latent variable changes as a function of morphine concentration, time, and other covariates. The model development of both steps was done using NONMEM 7.3 (ICON plc, Dublin, Ireland), with the Laplacian estimation method.[24]

Estimation of Item Characteristic Curves of Item Response Theory Model

The distribution of the latent variable, which represents the level of pain as a continuous variable, was assumed to follow a standard normal distribution that represents the deviation from the mean level of pain in the current study population, such that a value of 0 represents the mean level of pain in the population and a value of –1 represents a level of pain that is 1 standard deviation lower than the mean. An increase in the value of the latent variable reflects an increase in the level of pain and is associated with an increased probability of observing a higher score on an item of the COMFORT(-B) scale: the probability of observation y of item j being scored as score k during the i^{th} observation can be calculated from the latent variable LV_i and the item characteristic curve shown in Equations 1 and 2.

$$p\left(y_{ij} > k\right) = \frac{e^{a_j\left(LV_i - b_{jk}\right)}}{e^{a_j\left(LV_i - b_{jk}\right)} + 1} \quad (1)$$

$$p\ \left(y_{ij} = k\right) = p\left(y_{ij} > k - 1\right) - p\left(y_{ij} > k\right) \quad (2)$$

where a_j is the discrimination parameter of item j, and b_{jk} is the difficulty parameter of grade k of item j. For the purpose of estimating the parameters a and b of the item characteristic curves, a single value of the latent variable is estimated for each COMFORT observation and used to fit all item scores collected during this COMFORT observation according to Equations 1 and 2.[11,25]

Longitudinal Morphine PK/PD Model

For the longitudinal model, all parameters of the item characteristic curves as estimated above were used to model the change in latent variable within individuals as a function of time, morphine concentration, and/or patient characteristics.

Informed by morphine plasma concentration measurements in each individual patient (on average 3.5 measurements per patient), individual morphine concentrations over time during the entire study period were predicted using a previously published and externally validated population PK model.[26] The model resulted from a nonlinear mixed-effects analysis of observed morphine concentrations from several studies, including the 2 studies analyzed in the current analysis. From this model, considering the individual patient's covariates, dosing history, and PK observations, we obtained the individual post hoc predicted plasma concentrations of morphine. These individual morphine concentrations were used as input (ie, driver of the PD effect) in the longitudinal morphine PK/PD model.

The longitudinal model was developed by starting with a base model that only included a constant value for the latent variable including interindividual variability. Effects of time and morphine concentration were added to this base model in a stepwise manner and only included in the model if this resulted in a significantly better fit ($P < .01$), as indicated by a drop in the objective function value of >6.63 points for 1 additional parameter.

Different PD models (ie, linear, exponential, maximal efficacy [E_{max}], and sigmoid E_{max}, relationships in a direct effect model or effect compartment model) were tested to relate the individual morphine concentrations to the latent variable. Morphine concentrations in each individual over time were obtained from the observed morphine concentrations and dosing information in each individual resulting in individual PK model parameters for each patient.[19,20,26]

After finding the appropriate functions to describe the effect of time and morphine concentration on the latent variable, we included interindividual variability of the model's parameters in a stepwise manner, until inclusion of interindividual variability of an additional parameter did not further improve the model. We also explored the inclusion of covariance between the interindividual variability of 2 parameters. Finally, we investigated whether the model could be improved by adding patient characteristics as covariates to explain part of the interindividual variability on the model parameters. The following covariates were selected to be tested, based on physiological plausibility and on the availability of covariate data in both studies: postnatal age, body weight, sex, surgical stress score, and whether or not the patient was on mechanical ventilation during the observation.

Model Evaluation

The goodness of fit of the item characteristic curves was assessed by comparing the model-estimated item characteristic curves (Equations 1 and 2) with a nonparametric estimation of these curves, which was created with a generalized additive model for ordered categorical data using the "mgcv" package, version 1.8-27, package in R (R Foundation for Statistical Computing, Vienna, Austria).[11] The goodness of fit of the longitudinal model was assessed by comparing the observed (OBS) and predicted total COMFORT-B scores, where the predicted total COMFORT-B score (PRED) was calculated by:

$$PRED = \sum_{j=1}^{6} \sum_{k=1}^{5} p\left(y_{ij} = k\right) \times k \quad (3)$$

where $p(y_{ij} = k)$ is the predicted probability that a score of k is observed for item j at observation i (Equation 2). Residuals were calculated as the difference between OBS and PRED.

Model-Based Simulations

Using the final PK/PD model, simulations were performed to visualize the concentration-effect relationship of morphine on the COMFORT-B score, with a constant time after surgery (T = 0). We plotted the predicted total COMFORT-B score (Equation 3) over the morphine concentration between 5 and 60 ng/mL for 10 000 simulated subjects. Morphine concentrations outside this range were not simulated, as there were limited observations at these concentrations. In the same morphine concentration range, we also simulated discrete COMFORT-B observations using the probabilities calculated using Equation 2. Subsequently, each simulated observation was classified as 1 of 3 categories: potentially overtreated (COMFORT-B <11), adequately treated (COMFORT-B = 11-16), or undertreated (COMFORT-B >16).[22] This latter simulation was repeated 40 times (each with 10 000 simulated subjects) with different sets of parameter values (sampled from the covariance matrix, representing the uncertainty of the parameter estimates in the final model PK/PD model), to derive a confidence interval of the predicted probabilities.

Finally, a previously published PK model was used to calculate the steady-state morphine concentrations that would be expected when using the previously proposed morphine maintenance dosing regimen (Table S1) that was used in study 2.[26]

Results

Patients and Data

Data from a total of 198 children from the 2 clinical studies were available for analysis. Baseline patient characteristics are provided in Table 1. The 67 neonates (median postnatal age of 2 days; range, 0-30 days) in the data set were born from pregnancies with a median duration of 38 weeks (interquartile range, 36-40). In total, item-level data from 2319 COMFORT/COMFORT-B observations after major noncardiac surgery were available. The total scores of the COMFORT-B observations (and the sum of the behavioral item scores of the COMFORT observations) were within the clinically desirable window of 11 to 16 in 54% of the observations, <11 in 21% of the observations (ie, potentially overtreated), and >16 in 25% of the observations (ie, undertreated for pain or distress). The individual predicted morphine concentration during these COMFORT(-B) observations ranged from 0.1 to 185.2 ng/mL, with a mean and standard deviation of 14.1 and 14.4 ng/mL, respectively.

Table 1. Summary of Patient Characteristics (N = 198) Included in the Analysis

Demographic	Median (IQR) or N (%)
Postnatal age, wk	13.3 (0.8-39.3)
Neonates	67 (34)
Body weight, kg	4.5 (3.1-8.0)
Male sex	114 (58)
Surgical stress score	9 (8-11)

IQR, interquartile range.

Model Development and Evaluation

The item characteristic curves characterize the relationship between the latent variable, which is a continuous measure of the level of pain, and the probability of observing specific scores on particular items of the COMFORT scale. Figure 1 shows the item characteristic curves of the item response theory model for each item (dashed lines) and shows an adequate goodness of fit, as the model-estimated item characteristic curves generally match the nonparametrically estimated curves (although deviations between the 2 are visible in certain items). Higher values of the latent variable are associated with higher scores on the items of the COMFORT scale, especially in the behavioral items, which were more informative for the estimation of the latent variable than the physiological items (Figure 1, Table S2). The parameter estimates of the item characteristic curves are shown in Table S2.

A longitudinal morphine PK/PD model was developed in a second step to predict the changes in latent variable for each individual as a function of time, morphine concentration, and/or patient characteristics. Model development started with a baseline model for the latent variable (BASELINE), after which functions describing the effect of morphine ($EFFECT_{morphine}$) or

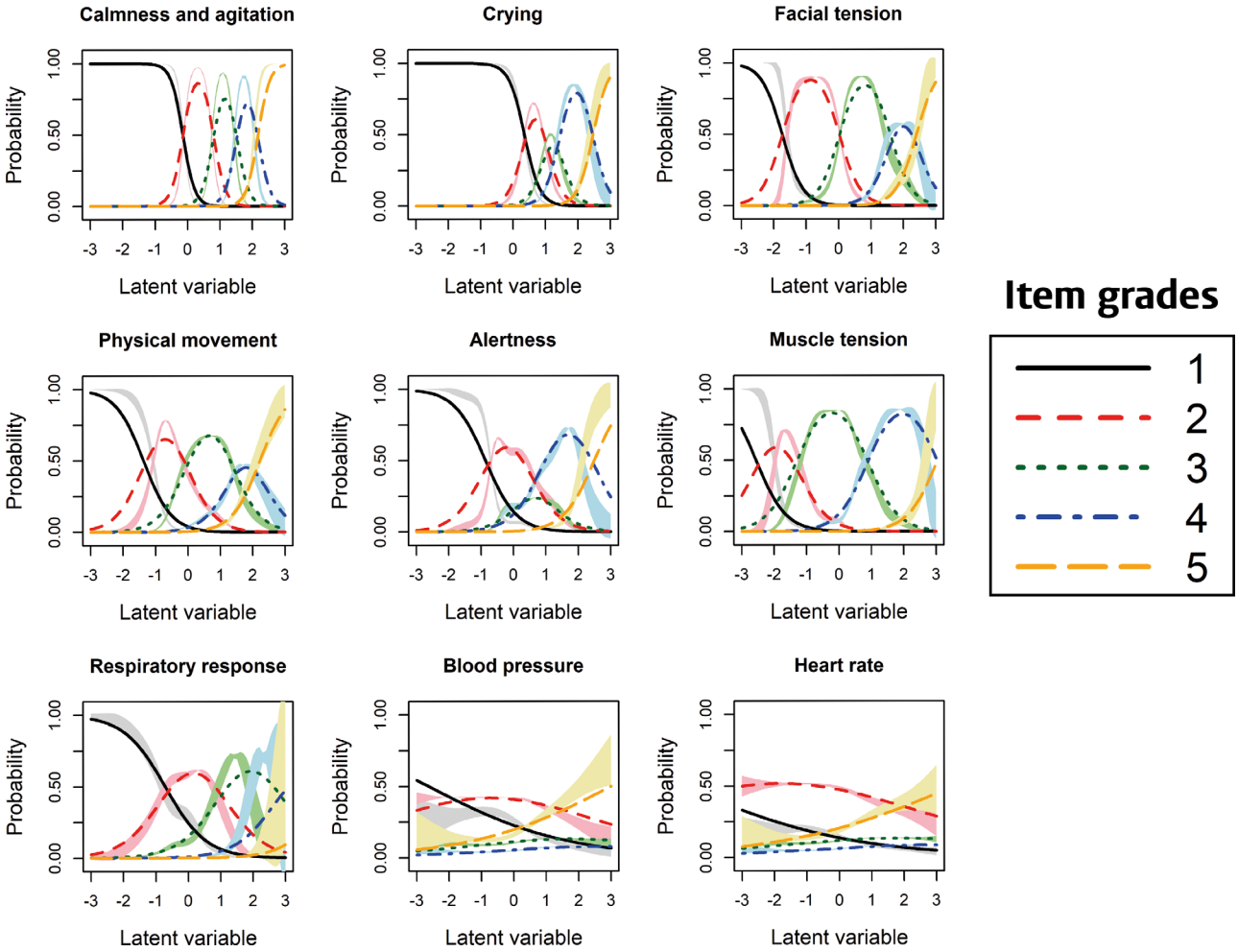

Figure 1. Diagnostic plots of the item characteristic curves of the item response theory model. The lines depict the model estimated item characteristic curves of the item response theory model, which characterize the probability of an item being scored a particular grade (1-5) as a function of the value of the latent variable, which represents a continuous measure of pain. The shaded areas depict nonparametric smoother of the item-characteristic curves from the item-level data, which can be considered as observed data against which the model-estimated item characteristic curves can be compared. The latent variable for each observation is estimated on an arbitrary scale, where 0 represents the mean of the latent variable in the present study. Latent variable values of −1 and 1 represent a value that is 1 standard deviation lower or higher than the mean, respectively. Each child is scored for either crying (for non–mechanically ventilated children) or respiratory response (for mechanically ventilated children).

time ($EFFECT_{time}$) on the latent variable were added to the model when these significantly improved the fit of the observed COMFORT data. The final model included besides the baseline model (BASELINE), a linear relation between time after surgery and the latent variable ($EFFECT_{time}$) for which a parameter $SLOPE_{time}$ was estimated, and a sigmoid E_{max} model to describe the effect of morphine on the latent variable ($EFFECT_{morphine}$) (Table 2). The sigmoid E_{max} model was parameterized as a truncated sigmoid E_{max} model according to Bachman et al, to improve stability of parameter estimation, without affecting the estimated relationship between concentration and effect.[27] The truncated sigmoid E_{max} model consists of 3 estimated parameters: the effect at a morphine concentration of 40 ng/mL (the effect of morphine at a concentration of 40 ng/ml [E_{40}], which is estimated instead of the E_{max} parameter); the sensitivity parameter for the effect of morphine in the truncated E_{max} model, which determines the sensitivity to morphine and replaces the EC_{50} parameter; and the Hill factor, which determines the steepness of the concentration-effect relationship (Table 2).

Interindividual variability could be quantified for 3 parameters in the PK/PD model: baseline latent variable (BASELINE), the slope in the linear function for the time-effect ($SLOPE_{time}$), and the morphine effect (E_{40}). The model also included covariance between the interindividual variability of the parameters' morphine effect and baseline latent variable (Table 2). This positive covariance reflects that patients with an above-average baseline latent variable, reflecting above average

Table 2. Parameter Estimates of the Longitudinal Morphine PK/PD Model in Which the Latent Variable Consists of BASELINE – $EFFECT_{morphine}$ + $EFFECT_{time}$

Parameter	Estimate (RSE%)
BASELINE $= Base_{<age\ switch} + EFF_{age} \times \frac{age^N}{age^N + age_{switch}^N}$	
$Base_{<age\ switch}$	0.027 (351)
EFF_{age}	0.426 (25)
$ln(age_{switch})$	2.33 (2.2)
age_{switch}, days	10.3
N	20 (fixed)
EFFECT$_{morphine}$ $= (B_{40}{}^{HILL} + 1) \times \frac{(E_{40} \times CMOR^{HILL})}{40^{HILL} + B_{40}{}^{HILL} \times CMOR^{HILL}}$, *if responder* = 0, *if non − responder*	
$Ln(E_{40})$	–0.95 (19)
E_{40}	0.3867
B_{40}	0.419 (23)
HILL	4.16 (8.7)
P(responder)	0.735 (7.6)
EFFECT$_{time}$ $= SLOPE_{time} \times time$	
$SLOPE_{time}$, $days^{-1}$	–0.265 (20)
Interindividual variability[a]	
ω^2 BASELINE (variance)	0.684 (11)
ω^2 E_{40} (variance)	3.23 (23)
ω^2 $SLOPE_{time}$ (variance)	0.506 (12)
Correlation BASELINE,E_{40}	0.35 (34)
Correlation BASELINE, $SLOPE_{time}$	–0.84 (12)
Correlation E_{40}, $SLOPE_{time}$	–0.27 (43)

age, in days postnatal age; age_{switch}, postnatal age at which the baseline latent variable increases with EFF_{age}; B_{40}, sensitivity parameter for the effect of morphine in the truncated E_{max} model; $Base_{<age\ switch}$, baseline latent variable for an individual below the age of age_{switch}; BASELINE, baseline model; CMOR, morphine concentration in ng/mL; CV, coefficient of variation; E_{40}, effect of morphine at a concentration of 40 ng/mL; EFF_{age}, effect of age being above age_{switch} on the baseline latent variable; $EFFECT_{morphine}$, effect of morphine; $EFFECT_{time}$, effect of time; HILL, Hill factor that describes the steepness of the morphine concentration-effect curve; N, slope of age effect on baseline around age_{switch}, fixed to 20 to resemble a step function; P(responder), a priori probability of an individual being a responder to morphine up-titration; RSE, relative standard error of estimate; $SLOPE_{time}$, slope of latent variable over time in a typical individual.

[a] Interindividual variability on BASELINE and $SLOPE_{time}$ were considered to be normally distributed, interindividual variability of E_{40} was considered log-normally distributed.

levels of pain at baseline, were also more likely to have an above-average response to morphine.

During the covariate analysis, we identified an effect of age on the baseline latent variable, indicating a lower latent variable (ie, a lower estimate of pain) at baseline in children younger than an estimated 10.3 days postnatal age. The age effect was best described with a sigmoidal function, for which the hill coefficient N was fixed to 20 to create an approximately discrete switch in baseline for children younger or older than the estimated age switch of 10.3 days postnatal age (Table 2). Estimation of the Hill coefficient N did not further improve the model ($P > .05$).

Finally, as we observed that a significant part of the patients had a very low or negligible individual estimate for the effect of morphine (E_{40}), we incorporated a mixture model that allows for a subpopulation of patients in which no concentration effect relationship can be established (nonresponders to morphine up-titration).[28] This addition improved the fit of the data significantly (objective function value = –15.3; $P < .001$) and was therefore included in the model. The final model estimated that 26% of the patients were non-responders to up-titration of morphine. None of the tested covariates were associated with the probability that a patient would be a nonresponder to morphine up-titration.

The parameter estimates of the final model are provided in Table 2. Exclusion of the 6 subjects from study 2 randomized to paracetamol from the analysis had a negligible effect on the parameter estimates of the model (data not shown). The goodness-of-fit plots indicated that the model generally characterized the observed data well (Figure S1).

To illustrate the concentration-effect relationship of morphine for the treatment of postoperative pain in preverbal children that we identified in our study, simulations with the final PK/PD model were performed. Figure 2 illustrates that for morphine concentrations between 5 and 20 ng/mL the predicted COMFORT-B scores are on average within the clinically desirable window of 11 to 16. Individuals aged <10 days had generally lower scores compared to individuals older than 10 days (median COMFORT-B scores of 15.5 vs 13.4 at 10 ng/mL, respectively, Figure 2 left column vs right column). At morphine concentrations above 20 ng/mL, COMFORT-B scores slowly decrease with increasing morphine concentrations in children who are responders to morphine up-titration (Figure 2, upper row). By definition, the concentration-effect relationship is a horizontal line in nonresponding children (Figure 2, bottom row). In all panels of Figure 2, the prediction interval is wide, which reflects the large interindividual variability of the PD of morphine in this population.

Figure 3 shows the percentage of simulated observations in children WHO in clinical practice would be considered potentially overtreated (COMFORT-B <11), adequately treated (COMFORT-B 11-16), or undertreated (COMFORT-B >16) as a function of morphine concentration. Similar to Figure 2, it can be seen that at concentrations above 20 ng/mL, the percentage of potentially overtreated patients increases, while the percentage of undertreated children decreases. Overall, the percentage of children who are adequately treated (COMFORT-B = 11-16) remains relatively stable and maximized between 5 and 30 ng/mL for children aged <10 days, and between 5 and 40 ng/mL for children >10 days. At the same concentration of morphine, the probability of being considered undertreated according to the defined

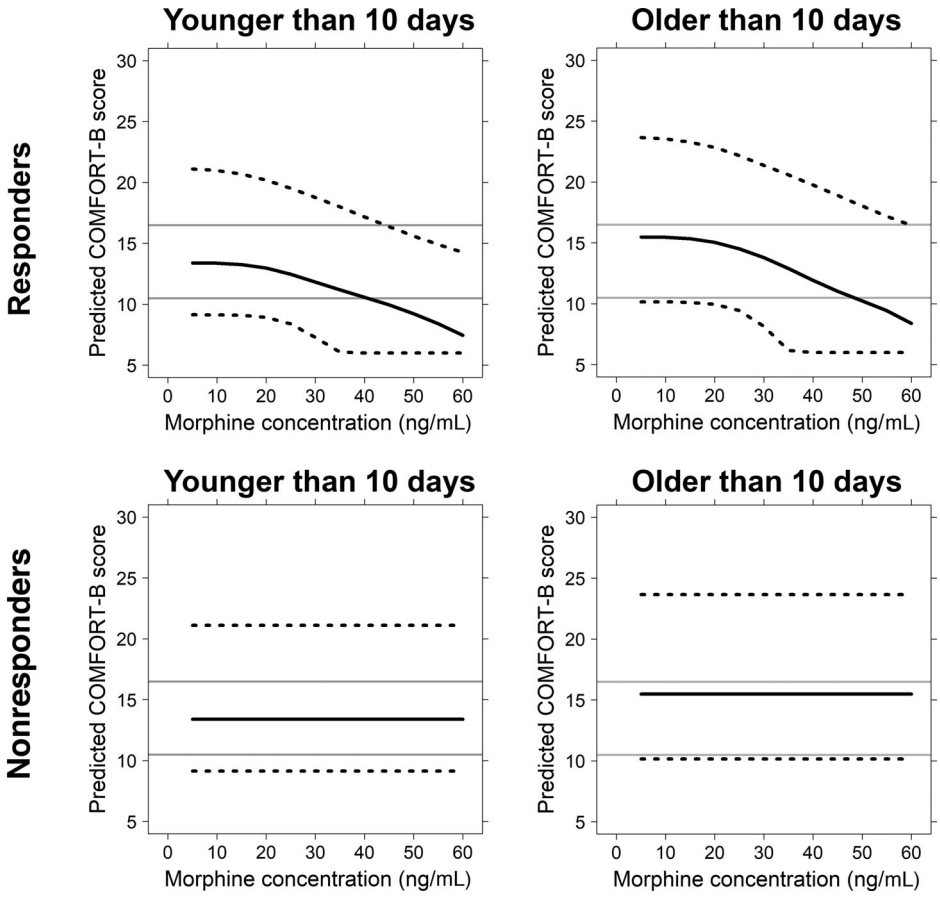

Figure 2. Concentration-effect relationship of morphine in children after major noncardiac surgery for children younger (left panels) and older than 10 days of age (right panels) and for responders (74% of the population, upper row) and nonresponders (26% of the population, bottom row) to morphine up-titration. Shown are the median (solid black line) and 90% prediction interval (dashed lines) of the predicted total COMFORT-B score in 10 000 simulated individuals. The horizontal gray lines drawn at 10.5 and 16.5 illustrate the window of COMFORT-B scores between 11 and 16, which indicates adequate treatment.

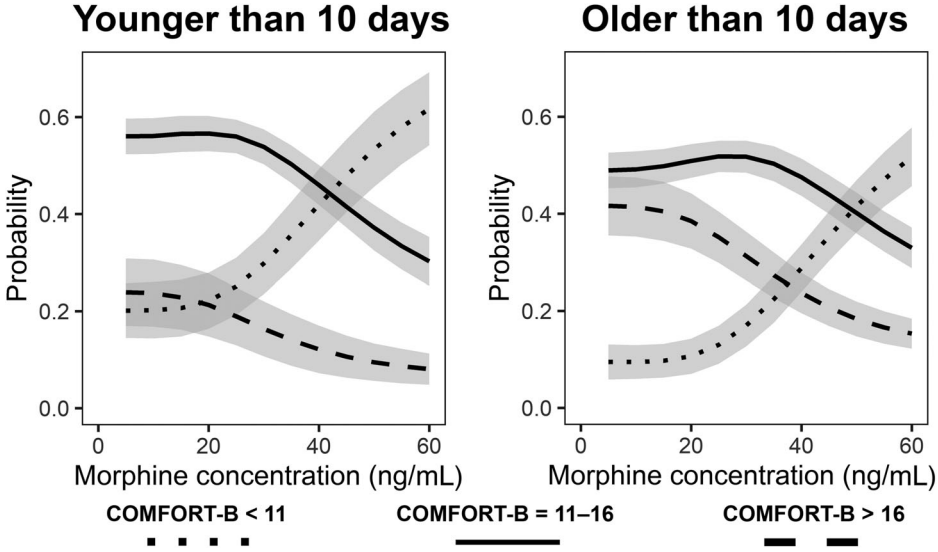

Figure 3. Predicted COMFORT-B observations vs morphine concentrations. COMFORT-B observations were divided in categories, that is, of potential overtreatment (COMFORT-B $<$ 11), adequate treatment (COMFORT-B $=$ 11-16), and undertreatment (COMFORT-B $>$ 16). The predicted probabilities (shown as black lines) were calculated as the proportion of simulated observations that fall in a particular category. The gray shaded area indicates the confidence interval originating from the uncertainty of the model parameter estimates. The simulated individuals included both responders and nonresponders to morphine up-titration.

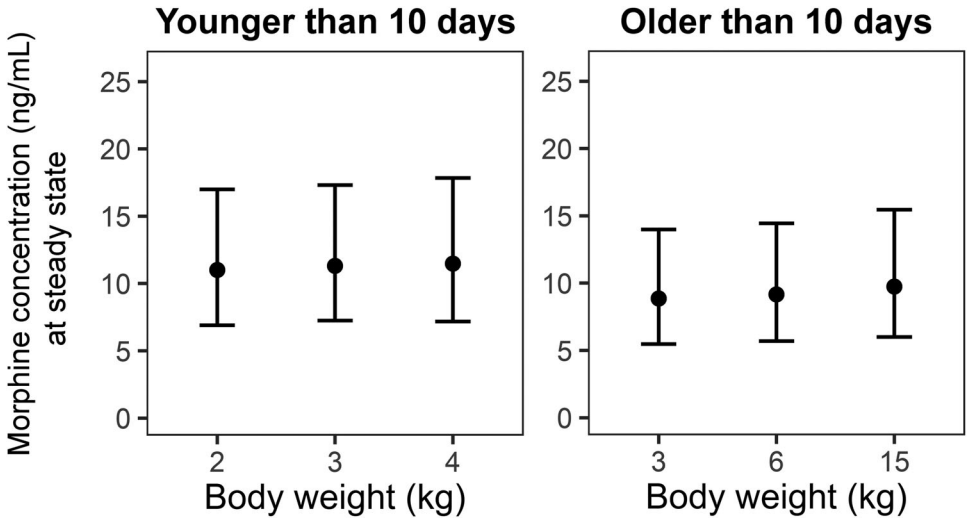

Figure 4. Morphine concentrations at steady state upon a continuous intravenous infusion of 2.5 μg/kg$^{1.5}$/h for children younger than 10 days of age and infusion of 5 μg/kg$^{1.5}$/h in children older than 10 days (see Table S1 for dosing table). Shown are the median and 95% prediction interval of 10 000 simulated children with a previously published externally validated population pharmacokinetic model of morphine.[24]

COMFORT-B thresholds is generally lower for children aged <10 days, compared with older children (Figure 3).

Figure 4 illustrates the morphine concentrations at steady state that can be expected upon the morphine dosing regimen that was used in study 2, that is, 5 μg/kg$^{1.5}$/h, with a 50% dose reduction in neonates aged <10 days (see Table S1 for the dosing table for this regimen). In Figure 4, it can be seen that for a variety of ages and body weights, the 95% prediction interval of the morphine concentration at steady state would fall completely within the range of morphine concentrations that maximize the probability of adequate treatment in Figure 3.

At morphine concentrations >25 ng/mL, COMFORT-B observations collected in nonresponders to morphine up-titration (N = 138) are significantly more likely to indicate undertreatment than observations (N = 252) in responders (29% vs 14%; $P = .0005$) and the item-level scores of most items are significantly higher in the nonresponders to up-titration (Table S3), with the exception of the items respiratory response, blood pressure, and heart rate. Interestingly, these latter 3 items have been found to be least informative in the item response theory model (Table S2).

Discussion

We applied item response theory modeling within a PK/PD model framework to quantify the concentration-effect relationship of morphine for postoperative pain in preverbal children. In the model, we identified a sigmoid E_{max} model for effect of morphine, lower baseline scores in younger children (postnatal age <10.3 days), and a subpopulation (26%) of children that showed no change in effect with increasing morphine concentration (nonresponders to morphine up-titration). Using the obtained concentration-effect relationship, we show that the probability of adequate treatment (COMFORT-B 11-16) is maximized within a morphine concentration range of 5 to 30 ng/mL for children aged <10 days, and between 5 and 40 ng/mL for children aged >10 days.

We observed a lower baseline latent variable and ≈2 points lower COMFORT-B scores at baseline in children during the first 10 days of life, even after accounting for differences in morphine concentrations. This means that this influence comes on top of the previous finding that morphine clearance is reduced by ≈50% in neonates during the first 10 days of life.[23,26] The finding that the change in baseline latent variable happens around the same time at which morphine clearance changes might be considered a coincidence, since the maturation of UDP-glucuronosyltransferase 2B7 metabolism, which is believed to be responsible for the change in morphine clearance during the first 2 weeks of life,[23] is not expected to also affect baseline pain levels.

Because this lowered baseline latent variable means a lower probability for younger children of being undertreated (Figure 3, left panel), a lower need for rescue morphine might be expected in neonates aged <10 days compared with older children. This is in line with findings from Krekels et al, who showed that the need for rescue morphine was indeed lower in younger children (<10 days) compared with older children (10-365 days), despite using the PK

model-based starting dosing regimen for morphine to give a similar morphine exposure for both age groups. These lower COMFORT-B scores and reduced morphine requirements during the first 10 days of life might be explained as a difference in development between the younger and older children, as older children are more likely to express behavioral responses to noxious stimuli,[29–31] and are more aware of their environment with increasing age, which could increase the level of distress experienced in the pediatric intensive care unit.[20] Although one might expect that age also affects the response to morphine, we did not identify any association between age and the parameters that characterize the effect of morphine in the model (E_{40}, sensitivity parameter for the effect of morphine in the truncated E_{max} model, Hill factor, or probability of being a nonresponder to morphine up-titration).

An interesting finding of our analysis is that approximately one-quarter of children are nonresponders to morphine up-titration, meaning that COMFORT-B scores do not decrease with increasing morphine concentrations. Populations of nonresponders to opioid treatment of postoperative pain have been described before in adults as well, although the mechanism behind nonresponse to morphine is still poorly understood and definitions of what constitutes a nonresponder differ across studies.[32] Another possibility is that nonresponders to up-titration had high COMFORT-B scores due to anxiety or distress rather than pain, and these patients might therefore benefit more from sedative treatment than from further morphine up-titration. Our analysis did not result in the identification of patient characteristics that could help predict a priori if a patient will be responsive to morphine. However, the possibility that a patient might be nonresponsive to increased morphine concentrations, is a phenomenon that should be taken into account during the treatment of postoperative pain.

Morphine target concentrations for the treatment of postoperative pain in neonates and infants have previous been suggested to lie between 4 and 27 ng/mL but were lacking the support of the knowledge on the concentration-effect relationship.[7,9,10] Based on our findings, morphine concentration ranges of 5 to 30 and 5 to 40 ng/mL—for children younger or older than 10 days, respectively—maximize the percentage of children with a clinically desirable COMFORT-B score. To reduce the risk of morphine-related adverse effects, it may be optimal to target the lower end of these concentration ranges in pediatric dosing guidelines. For example, we showed that with a previously proposed dosing scheme for morphine maintenance dosing (Table S1), both neonates and infants (<3 years, body weights 2-15 kg) would be expected to have steady-state morphine concentrations between 5 and 20 ng/mL (Figure 4).

It is important to note that individual patients might require higher morphine concentrations due to interindividual differences in postoperative pain and morphine effect. For example, at a morphine concentration of 20 ng/mL, there might still be undertreatment for postoperative pain in about 22% of children aged <10 days and 38% in older children (Figure 3). To identify these undertreated patients, frequent monitoring of pain using validated clinical scales and administration of additional morphine may be required during the postoperative period, as the baseline pain varies within a patient over time. To improve the predictive performance of the model, additional covariates might be incorporated into the PK/PD model to better predict the morphine requirements of individual patients. For the current study, only a limited set of physiologically plausible covariates were tested in the analysis, but future studies may consider extending these to include other patient demographics and pharmacogenetic polymorphisms believed to be related to pain or morphine efficacy.[33] Similarly, it would be of interest to explore whether the metabolites of morphine, morphine-3-glucuronide and morphine-6-glucoronide, could explain the interindividual differences in morphine efficacy.

An important limitation of the current study is that the model is not very well informed on the effect of morphine at low concentrations (<5 ng/mL), because all patients started with a 100-μg/kg morphine bolus after surgery and most patients started on a maintenance morphine regimen. This limitation means that 2 aspects of the model should be interpreted with additional care. First, although the estimated concentration-effect relationship of morphine was practically flat between 5 and 15 ng/mL (Figure 2), this should not be interpreted as evidence that there is no efficacy of morphine at these concentrations (which would be the case if the concentration-effect relationship remains flat down to morphine concentration of 0 ng/mL). Similarly, we identified a population of patients who did not respond to morphine up-titration to *higher* morphine concentration (ie, >15 ng/mL), but we do not know how these patients would have responded if they had not received any morphine at all.

In this study, we identified a concentration-effect relationship for morphine from COMFORT(-B) data in preverbal children. It is important to note that the lack of a true gold standard for pain assessment in preverbal children makes it difficult to disentangle pain and other causes of distress. Morphine has both analgesic and sedative properties, and the concentration-effect relationship identified in this study is likely reflecting a combination of both properties on pain- and distress-related behavior. Current insights suggest that pain and sedation assessment with the COMFORT-B scale is

best performed in combination with a numerical rating scale reflecting the expert opinion of the nursing staff, which also takes contextual factors into account. In addition, because the majority of the patients in this study did not receive paracetamol (192/198), the optimal morphine concentration range for postoperative pain treatment may be different for clinical settings with routine use of paracetamol, as paracetamol can reduce morphine requirements for the treatment of postoperative pain in children.[19] Another limitation of the current study is the lack of simulation-based diagnostics (such as the visual predictive check), which could not be generated due to the complex morphine-titration scheme used in the clinical studies. As a result, some aspects of the model, such as the amount of variability, could not be conclusively evaluated.

Conclusion

We used item response theory modeling to quantify the concentration-effect relationship of morphine for the treatment of postoperative pain in preverbal children. We identified a lower baseline COMFORT-B scores in children aged <10 days, and a population of children who do not respond to increasing morphine concentrations. Based on the model, we conclude that the percentage of children at a desirable COMFORT-B score (11-16) is maximized at a morphine concentration between 5 and 30 ng/mL for children aged <10 days, and between 5 and 40 ng/mL for children aged >10 days. Our modeling approach provides a promising platform for PD research of analgesics and sedatives in children.

Conflicts of Interest

The authors declare no potential conflicts of interest. Catherijne A.J. Knibbe was supported during this study by Innovational Research Incentives Scheme (Vidi grant, June 2013) of the Netherlands Organization for Scientific Research. One of the clinical studies analyzed here (study 2, by Ceelie et al) was supported by ZonMw Priority Medicines for Children grant 40-41500-98.9020. Remaining support was provided from institutional and departmental sources.

Data Availability

The data presented in this article are not available in any repository. For questions, please contact Prof. Catherijne Knibbe, c.knibbe@antoniusziekenhuis.nl

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