The Journal of Clinical Pharmacology
2020, 60(9) 1231–1236

DOI: 10.1002/jcph.1620

Exploring the Relationship Between Morphine Concentration and Oversedation in Children After Cardiac Surgery

Abraham J. Valkenburg, MD, PhD[1]*, Sebastiaan C. Goulooze, MSc[2]*, Chun Yin Ng, BSc[2], Cormac V. Breatnach, MD[3], Dick Tibboel, MD, PhD[4], Monique van Dijk, PhD[4,5], Catherijne A. J. Knibbe, PharmD, PhD[2,6], and Elke H.J. Krekels, MSc, PhD[2]

Abstract

Titrating analgesic and sedative drugs in pediatric intensive care remains a challenge for caregivers due to the lack of pharmacodynamic knowledge in this population. The aim of the current study is to explore the concentration-effect relationship for morphine-associated oversedation after cardiac surgery in children aged 3 months to 3 years. Data on morphine dosing, as well as morphine plasma concentrations, were available from a previous study on the pharmacokinetics of morphine after cardiac surgery in children. Oversedation was defined as scores below 11 on the validated COMFORT–behavioral scale. Population pharmacokinetic-pharmacodynamic modeling was performed in NONMEM 7.3. The probability of oversedation as a function of morphine concentration was best described using a step function in which the EC_{50} was 46.3 ng/mL. At morphine concentrations below the EC_{50}, the probability of oversedation was 2.9% (0.4& to 18%), whereas above the EC_{50} percentages were 13% (1.9% to 52%) (median value [95% prediction interval from interindividual variability]). Additionally, the risk of oversedation was found to be increased during the first hours after surgery ($P < .001$) and was significantly lower during mechanical ventilation ($P < .005$). We conclude that morphine concentrations above approximately 45 ng/mL may increase the probability of oversedation in children after cardiac surgery. The clinician must evaluate, on a case-by-case basis, whether the analgesic benefits arising from dosing regimen associated with such concentrations outweigh the risks.

Keywords

pharmacodynamics, morphine, intensive care unit, pediatrics, adverse effects, cardiac surgical procedures

Titrating analgesic and sedative drugs in the pediatric intensive care unit remains a challenge for caregivers. Before successful titration is achieved, individual patients can suffer from insufficient analgesic efficacy due to underdosing or adverse effects such as apnea and hypotension due to overdosing. With better knowledge of the pharmacokinetics and pharmacodynamics of analgesic and sedative drugs in the individual pediatric patient, starting doses may be optimized to reduce the need for subsequent titration.[1]

For postoperative care after cardiac surgery, morphine is the primary analgosedative drug worldwide.[2] The pharmacokinetics of morphine has been studied extensively, including studies in special populations.[3,4] The pharmacodynamics of morphine has been less extensively examined, which has resulted in a lack of consensus on dosing recommendations for morphine in children after cardiac surgery, with advised doses varying from 10 to 60 μg/kg per hour for a continuous infusion and from 50 to 500 μg/kg for a loading dose.[2] The range of morphine concentrations reported to provide adequate analgesia in children is also very broad at 4 to 65 ng/mL.[5] Even less is known about

[1]Department of Intensive Care, Erasmus University Medical Center, Rotterdam, the Netherlands
[2]Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug ResearchLeiden University, Leiden, the Netherlands
[3]Department of Anaesthesia and Critical Care Medicine, Our Lady's Children's Hospital, Dublin, Ireland
[4]Department of Pediatric Surgery, Erasmus University Medical Center–Sophia Children's Hospital, Rotterdam, the Netherlands
[5]Division of Nursing Science, Department of Internal Medicine, Erasmus University Medical Center–Sophia Children's Hospital, Rotterdam, the Netherlands
[6]St. Antonius Hospital, Department of Clinical Pharmacy, Nieuwegein, the Netherlands

Submitted for publication 27 January 2020; accepted 25 March 2020.

Corresponding Author:
Abraham J. Valkenburg, MD, PhD, Department of Intensive Care, Erasmus University Medical Center, Dr. Molewaterplein 60, 3015 GJ Rotterdam, the Netherlands
E-mail: a.valkenburg@erasmusmc.nl

*Both authors contributed equally to this article.

the relationship between morphine concentration and the probability of adverse effects related to overdosing, which may not be of relevance in the short term and when patients are intubated but could ultimately result in prolonged pediatric intensive care unit stay.[2,6] Additionally, the use of opioids in neonates and infants has been associated with long-term neurodevelopmental effects.[7,8]

Following cardiac surgery and in response to validated pain and sedation scores, additional morphine doses may often be required.[2,9] An important question is whether a morphine concentration can be identified above which the probability of side effects (eg, oversedation) increases. To date, no studies have been performed exploring the relationship between morphine concentration and oversedation. Therefore, the aim of the current study has been to examine the concentration-effect relationship for morphine-associated oversedation after cardiac surgery in children aged 3 months to 3 years.

Methods

Patients and Data Description

This article describes the analysis of the data from an observational prospective study at Our Lady's Children's Hospital, Dublin, that was approved by the local ethics committee.[3] Written informed consent for the study was obtained from the parents preoperatively. The study included children aged between 3 and 36 months, admitted to the intensive care unit after cardiac surgery. The exclusion criteria included preoperative treatment with morphine or midazolam, medical history of cardiothoracic surgery through sternotomy, and preoperative mechanical ventilation. The original study was published and described in detail elsewhere[3] and is briefly summarized below.

For this analysis of oversedation, we used COMFORT-B (Comprehensive Observation and Monitoring for Our Richland Tots–Behavioral) scores collected from the patients from this clinical study, defining oversedation as COMFORT-B score <11, as proposed by Ista et al.[10] The end of the data collection period was marked by 1 of the following events: a switch from intravenous to oral morphine, discharge to the ward, a procedure requiring general anesthesia, and reintubation for any reason other than oversedation.

The analysis considered a total of 565 COMFORT-B observations in 35 individuals, with a median age of 6 months (range 3-31 months) and a median body weight of 6.1 kg (range 3.6-12.9 kg). Twenty individuals (57%) were diagnosed with trisomy 21. Patients underwent surgery for the following congenital heart effects: 1 patient with atrial septal defect, 9 patients with ventricular septal defect, 16 patients with atrioventricular septal defect, and 9 patients with tetralogy of Fallot. Additional information on the patient population and the standardized anesthesia used during surgery can be found in the publication of the original clinical study.[3]

Postoperative Analgosedation Protocol

Children received a standardized general anesthetic regimen without premedication as previously described.[3] After discontinuation of cardiopulmonary bypass, a morphine loading dose of 100 µg/kg was administered, and a morphine infusion was started at 40 µg/kg per hour. COMFORT-B assessments were regularly performed after surgery as part of the postoperative analgosedation protocol. The COMFORT-B scale has been validated for pain and distress assessment in children below 3 years of age, including those with Down syndrome.[11-13] Additional morphine, as 20- to 40-µg/kg bolus doses, was provided when the COMFORT-B score was >16 and numerical rating scale was above >3, indicating moderate to severe pain.[9] A COMFORT-B score >16 in combination with a numerical rating scale <4 was seen as an indication for additional sedation requirements. At this point midazolam was started in addition to morphine. As part of the standard of care, all patients received 3 intravenous doses of acetaminophen for the first 24 hours (7.5 mg/kg for children <10 kg and 15 mg/kg for children >10 kg).

Pharmacodynamic Model Analysis

To describe the probability of oversedation as a function of morphine plasma concentrations, population pharmacokinetic-pharmacodynamic modeling was performed using NONMEM 7.3 (ICON plc, Dublin, Ireland).[13] In the model, morphine plasma concentrations from the previously developed pharmacokinetic models of morphine in this cohort were used.[3] For the patients who also received midazolam, midazolam concentrations from a previously developed pharmacokinetic model for midazolam in this cohort were taken into account (Valkenburg et al, unpublished data). Both direct and indirect pharmacodynamic models were tested to characterize the effect of morphine and midazolam, using the following functions: linear, maximum effect (E_{max}), sigmoid E_{max}, and a step function (created by fixing the value of the Hill parameter in a sigmoid E_{max} formula at 100). The NONMEM code of the final model is provided in the Supplemental Material.

Model selection was based on the objective function value (–2 log likelihood). The patient characteristics of body weight, age, sex, trisomy 21 status, and mechanical ventilation status were tested as covariates to explain the interindividual variability in the risk

Fellows of American College of Clinical Pharmacology: Catherijne A. J. Knibbe, PharmD, PhD

of oversedation and were included in the model if this resulted in a significantly ($P < .01$) better fit of the observed data, using the objective function value and assuming a chi-squared distribution. For model diagnostics, the residuals over time, over morphine concentration, and over midazolam concentration were inspected for the presence of trends in the observed proportion of oversedation and the model's predictions. Details on how these residuals were calculated can be found in the Supplemental Material.

Model Simulations

To visualize the relationship between morphine concentration and probability of oversedation, we simulated this relationship for 1000 individuals using the final model. Additionally, to visualize the morphine concentrations over time that can be expected based on the dosing regimen applied in this study, and to judge the risk of overdosing with this treatment protocol, we simulated the morphine concentrations using the morphine dosing regimen of the original clinical study (100 μg/kg morphine loading dose followed by a continuous morphine infusion at 40 μg/kg per hour for 24 hours), for a population of 1000 children with a body weight of 6.13 kg (median body weight in the study). For this simulation we used the previously published pharmacokinetic model, developed in this patient cohort.[3]

Results

Clinical Data

The analysis considered a total of 565 COMFORT-B observations, with a median number of COMFORT-B observations per patient of 14 (range 6-39). Of the COMFORT-B observations, 74 (13%) were below 11, indicating oversedation. COMFORT-B observations were collected during a median postoperative follow-up of 37 hours (range 12.4-114 hours) after the morphine loading dose. A total of 81% of the COMFORT-B observations were collected while patients were mechanical ventilated.

Postoperative Analgosedation

During the study patients received a median cumulative morphine dose of 1090 μg/kg, with a range of 424 to 4740 μg/kg. Four patients received continuous morphine at an infusion rate higher than the starting infusion rate of 40 μg/kg per hour. The number of morphine rescue boluses per patient ranged from 0 to 13 (median 4). Total morphine dose given as bolus was on average 223 μg/kg (including the 100-μg/kg loading dose) with a range of 100 to 420 μg/kg. Morphine concentrations during COMFORT-B observations ranged from 3.9 to 254 ng/mL (median 28.7 ng/mL). Midazolam was administered to 26 of the patients (74%), with a median cumulative dose of 761 μg/kg in these patients. Midazolam concentrations during COMFORT-B observations ranged from 0 to 1024 ng/mL (median 18.5 ng/mL).

Table 1. Parameter Estimates for the Final Population Pharmacodynamic Model

Parameter [Units]	Estimate (RSE %)
Baseline logit probability (*Base*)Baseline probability [%]	–2.11 (12%)10.8
Mechanical ventilation effect ($Effect_{vent}$) [-]	–1.46 (27%)
Morphine effect	
Morphine E_{max}	1.59 (27%)
Morphine EC_{50} [ng/mL]	46.3 (3%)
Morphine Hill coefficient (n)	100 FIXED
Effect of time after loading dose	
Time effect at t = 0 min ($Effect_{t0}$) [-]	8.9 (27%)
Slope exponential decay time effect ($Slope_{time}$) [min^{-1}]	–0.0082 (23%)
Interindividual variability	
Baseline logit probability (ω^2)	1.15 (62%)

RSE indicates relative standard error of estimate; ω^2, variance of interindividual variability.

The function for the logit probability of oversedation is: $Logit\ P = Base + Effect_{vent} + \frac{E_{max} \times C_{mor}{}^{n}}{C_{mor}{}^{n} + EC_{50}{}^{n}} + Effect_{t0} \times e^{Slope_{time} \times time}$, in which effects of mechanical ventilation ($Effect_{vent}$), morphine concentration (C_{mor}), and time after loading dose (*time*) are included. $Effect_{vent}$ is 0 when patient is not on mechanical ventilation. The probability of oversedation (*P*) is defined as: $P = 100\% \times \frac{e^{Logit\ P}}{e^{Logit\ P}+1}$.

Pharmacodynamic Model Analysis

By use of pharmacokinetic-pharmacodynamic modeling, a correlation of increased probability of oversedation with increased morphine concentrations ($P < .01$) and of decreased probability of oversedation with mechanical ventilation ($P < .005$) was identified. The effect of morphine was best described using a step function, implying that the EC_{10}, EC_{50}, and EC_{90} have similar values: morphine concentration had a very low effect on oversedation at low to moderate concentrations (<45 ng/mL) but quickly reached its E_{max} when concentrations exceeded the estimated EC_{50} of 46.3 ng/mL. In the model, interindividual variability in the probability of oversedation was identified, with a coefficient of variation of 147%. Finally, an exponentially decreasing function over time with an estimated half-life of 85 minutes ($P < .001$) was identified as a predictor of probability of oversedation that characterized the higher observed proportion of oversedation in the first hours after the end of surgery that could not be explained by morphine or midazolam concentrations. During the covariate analysis we found that the addition of sex, age, body weight, midazolam concentration, or trisomy 21 status as predictors of interindividual variability in the probability of oversedation did not significantly improve the model ($P > .01$). Therefore, none of these covariates was included in the final model. The final parameter estimates are shown in Table 1. This final model adequately described the observed data regarding

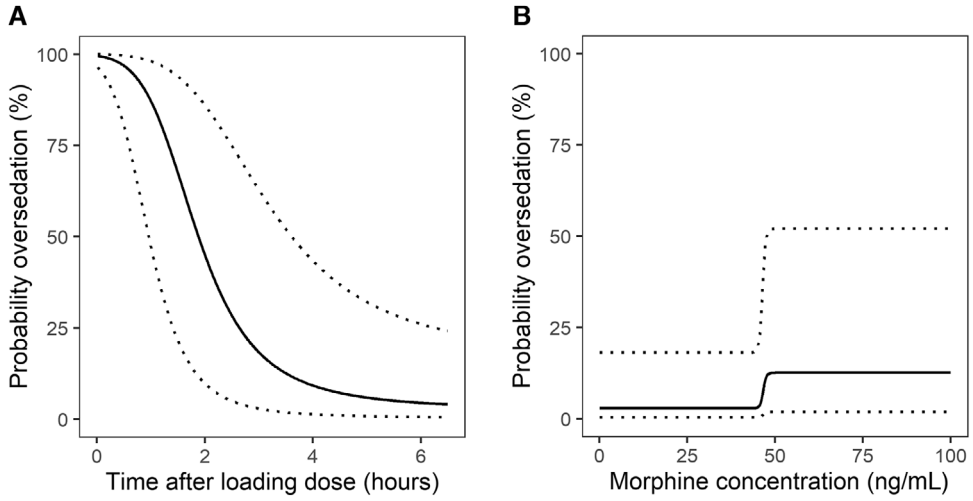

Figure 1. Effects of time after loading dose (A) and morphine concentration (B) on the probability of oversedation after cardiac surgery in pediatric patients. Shown are the median (solid line) and 95% prediction interval (dotted lines) of 1000 children. Simulations in panel A are generated at low morphine concentrations (<45 ng/mL), whereas the simulations in panel B are generated at a time when the initial high probability of oversedation after the loading dose (A) has returned to baseline (>5 hours after loading dose).

oversedation, as there were no systematic differences between the model predictions and observations in the diagnostic plots (Supplemental Figure S1).

Figure 1 shows the influence of time and morphine concentration on the probability of oversedation during mechanical ventilation, depicted as the 95% prediction interval of a population of 1000 simulated individuals. Figure 1A shows that in the first hours after the morphine loading dose, there is a high probability of oversedation, even at low morphine concentrations (<45 ng/mL), which quickly decreases with time toward a baseline probability of oversedation with a median of 2.9% (95% prediction interval 0.4% to 18%). Figure 1B shows the concentration-effect relationship of morphine-associated oversedation. The figure shows that below the EC_{50} of 46.3 ng/mL, the probability of oversedation at baseline was 2.9% (0.4% to 18%) (median value [95% prediction interval]), whereas above the EC_{50} the probability of oversedation increases to 13% (1.9% to 52%). The concentration-effect relationship of morphine-associated oversedation is not shown for patients who are not on mechanical ventilation, as all observations at high morphine concentrations (>46.3 ng/mL) were made during mechanical ventilation only.

In order to establish which proportion of the patients would exceed the EC_{50} of 46.3 ng/mL morphine, at which a steep increase in the probability of oversedation was observed, Figure 2 shows morphine concentration-time profiles for 1000 individuals receiving a loading dose of 100 μg/kg followed by a 40 μg/kg per hour infusion. The figure shows that except for the first hour after the loading dose of 100 μg/kg, a morphine concentration exceeding 46.3 ng/mL is generally not reached without additional bolus doses. These findings are in agreement with the clinical study in which 3 or more additional morphine bolus doses were given to all 9 patients who had 1 or more COMFORT-B assessments with morphine concentrations above 46.3 ng/mL

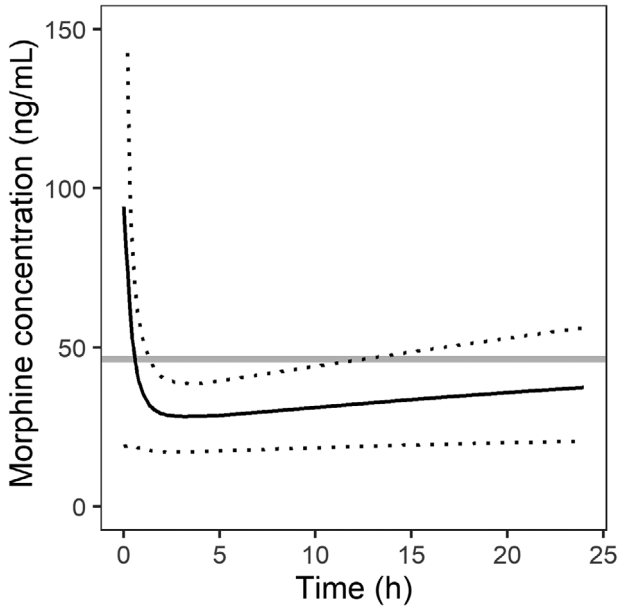

Figure 2. Morphine concentrations over time for 1000 simulated children of 6.13 kg after cardiac surgery receiving a 100-μg/kg morphine loading dose followed by a 40 μg/kg per hour continuous intravenous infusion. The simulation does not include the administration of any additional rescue morphine bolus doses. The black solid and dotted lines indicate the median and 95% prediction interval of the morphine concentrations in the 1000 simulated children, respectively. The gray line indicates the EC_{50} of the pharmacodynamic model (46.3 ng/mL), above which the probability of oversedation strongly increases.

beyond the first few hours after the loading dose. With higher infusion rates of intravenous maintenance morphine (ie, 50 μg/kg per hour), morphine concentrations above 46.3 ng/mL will occur more frequently, even without administration of additional bolus doses (Supplemental Figure S2).

Discussion

In this study we aimed to quantify the concentration-effect relationship of morphine-associated oversedation in a population of children between 3 and 36 months old after cardiac surgery using pharmacokinetic-pharmacodynamic modeling. The probability of oversedation was found to increase at morphine concentrations higher than approximately 45 ng/mL (from 2.9% to 13% in a typical patient) and during the first hours after cardiac surgery (Figure 1).

Our results show that when we used the morphine dose that was used in the clinical study (100 μg/kg morphine loading dose followed by 40 μg/kg per hour continuous infusion), morphine concentrations will generally be below the threshold of 46.3 ng/mL. This suggests that morphine-associated oversedation is particularly of concern when morphine is uptitrated beyond this dosing regimen through the administration of additional morphine boluses or increases of the continuous infusion rate, or in dosing regimens with a starting infusion rate of continuous morphine of 50 μg/kg per hour or higher.

The probability of oversedation was highly variable; in the majority of mechanically ventilated patients, morphine concentrations above 46 ng/mL would still only result in a probability of oversedation of $\leq$20%, which can be considered acceptable if these high concentration are required for adequate analgesia. However, some patients might have very high probabilities of oversedation (>50%) at high morphine concentrations, which would need to be considered in titrating morphine in children after cardiac surgery. Unfortunately, we did not identify any patient characteristics in this study population that could serve as a priori predictors of the probability of oversedation of an individual patient. Future work should quantify the relationship between the morphine concentration and its analgesic effect so that, combined our current results, we might establish the morphine concentration at which the balance between benefits and risks (ie, oversedation) is optimized.

We also identified a high probability of oversedation in the first hours after the morphine loading dose that was administered following the discontinuation of the cardiopulmonary bypass. This increased probability of oversedation could not be explained by the morphine or midazolam concentrations in these patients at that time and was therefore accounted for in the model using an empirical exponentially declining function with a half-life of 85 minutes. This phenomenon might be explained by residual effects of the general anesthesia during surgery (which consisted of remifentanil, isoflurane, sevoflurane, and muscle relaxants[3]). Such a postanesthesia washout has previously been described in pharmacodynamic studies on sedation levels after craniofacial surgery in children who did not receive morphine loading doses or continuous maintenance infusions.[14,15]

We also found that during mechanical ventilation the probability of oversedation was lower than after extubation. The direction of this association was unexpected because a deeper level of sedation can be acceptable or even desirable during mechanical ventilation to avoid autoextubation. The lower probability of oversedation during mechanical ventilation might be explained as the behavioral response to the pain and discomfort of mechanical ventilation, which would increase the COMFORT-B score, lowering the probability of observing COMFORT-B scores below 11. Because of the lack of observations at high morphine concentrations in extubated children, we cannot conclude what the effect of such morphine levels would be on oversedation rates in the absence of the antagonistic effect of mechanical ventilation (shown in Figure 1B).

The current analysis has some limitations. COMFORT-B scores below 11 are used clinically as an indication of oversedation in children during analgesic and sedative treatment but could in theory also be observed during deep sleep.[10] The study included a relatively small number of children, which likely contributed to the fact that the covariate analysis did not identify patient characteristics that could predict part of the large interindividual variability in morphine-associated oversedation. Additionally, midazolam was administered to a subpopulation of the children in this study. However, no statistically significant association between the midazolam concentration and the probability of oversedation could be identified. This might be explained by the fact that in this study midazolam was not administered to all patients but was given only in response to undersedation.

Conclusions

We explored the concentration-effect relationship of morphine-associated oversedation in young children after cardiac surgery and found that the probability of oversedation is increased at morphine plasma concentrations above a threshold of approximately 45 ng/mL. Our analysis indicates that after the first

hour, morphine concentrations above this threshold are almost exclusively expected in children who receive rescue morphine in addition to the standard starting dose regimen of 40 μg/kg per hour or in those exposed to prolonged treatment of more than 12 hours at this dose. Whether or not the analgesic benefits from dosing practices associated with higher morphine concentrations outweigh the risk should be evaluated on an individual basis.

Conflicts of Interest

None of the authors reports any conflicts of interest. Supported by a grant (F/12/4) from the National Children's Research Centre, Dublin, Ireland.

Data Availability

The data presented in this manuscript are not available in any repository. For questions please contact Dr Valkenburg (a.valkenburg@erasmusmc.nl).

References

1. Levy G. Impact of pharmacodynamic variability on drug delivery (1). *Adv Drug Deliv Rev*. 1998;33(3):201-206.
2. Zeilmaker-Roest GA, Wildschut ED, van Dijk M, et al. An international survey of management of pain and sedation after paediatric cardiac surgery. *BMJ Paediatr Open*. 2017;1(1): e000046.
3. Valkenburg AJ, Calvier EA, van Dijk M, et al. Pharmacodynamics and pharmacokinetics of morphine after cardiac surgery in children with and without Down syndrome. *Pediatr Crit Care Med*. 2016;17(10):930-938.
4. Knibbe CA, Krekels EH, van den Anker JN, et al. Morphine glucuronidation in preterm neonates, infants and children younger than 3 years. *Clin Pharmacokinet*. 2009;48(6):371-385.
5. Elkomy MH, Drover DR, Galinkin JL, Hammer GB, Glotzbach KL. Pharmacodynamic analysis of morphine time-to-remedication events in infants and young children after congenital heart surgery. *Clin Pharmacokinet*. 2016;55(10): 1217-1226.
6. Vet NJ, Ista E, de Wildt SN, van Dijk M, Tibboel D, de Hoog M. Optimal sedation in pediatric intensive care patients: a systematic review. *Intensive Care Med*. 2013;39(9):1524-1534.
7. Attarian S, Tran LC, Moore A, Stanton G, Meyer E, Moore RP. The neurodevelopmental impact of neonatal morphine administration. *Brain Sci*. 2014;4(2):321-334.
8. Pollak U, Bronicki RA, Achuff BJ, Checchia PA. Postoperative pain management in pediatric patients undergoing cardiac surgery: where are we heading? *J Intensive Care Med*. 2019:885066619871432.
9. van Dijk M, Peters JW, van Deventer P, Tibboel D. The COMFORT Behavior Scale: a tool for assessing pain and sedation in infants. *Am J Nurs*. 2005;105(1):33-36.
10. Ista E, van Dijk M, Tibboel D, de Hoog M. Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT "behavior" scale. *Pediatr Crit Care Med*. 2005;6(1):58-63.
11. Valkenburg AJ, Boerlage AA, Ista E, Duivenvoorden HJ, Tibboel D, van Dijk M. The COMFORT-behavior scale is useful to assess pain and distress in 0- to 3-year-old children with Down syndrome. *Pain*. 2011;152(9):2059-2064.
12. van Dijk M, de Boer JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. *Pain*. 2000;84(2-3):367-377.
13. Ambuel B, Hamlett KW, Marx CM, Blumer JL. Assessing distress in pediatric intensive care environments: the COMFORT scale. *J Pediatr Psychol*. 1992;17(1):95-109.
14. Peeters MY, Prins SA, Knibbe CA, et al. Pharmacokinetics and pharmacodynamics of midazolam and metabolites in nonventilated infants after craniofacial surgery. *Anesthesiology*. 2006;105(6):1135-1146.
15. Peeters MY, Prins SA, Knibbe CA, et al. Propofol pharmacokinetics and pharmacodynamics for depth of sedation in nonventilated infants after major craniofacial surgery. *Anesthesiology*. 2006;104(3):466-474.

Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.