Does it still hurt? Perioperative opioid analgesia in different patient populations

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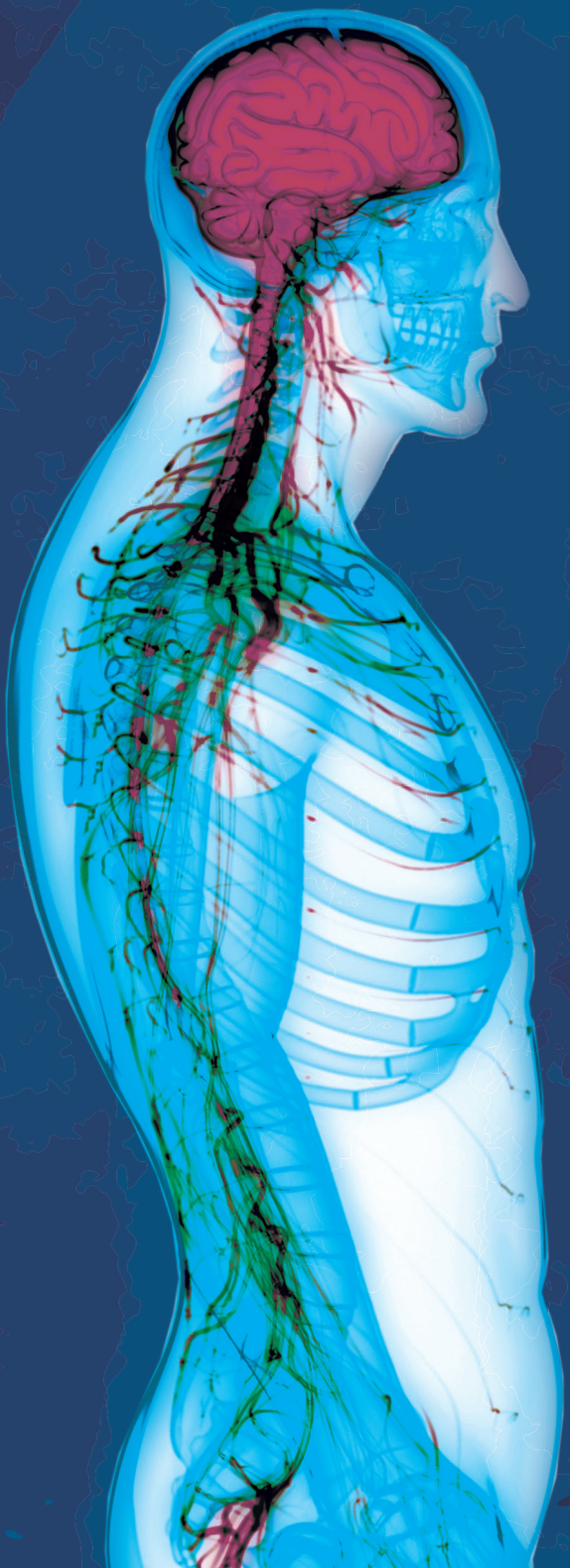

Section III

Opioids after paediatric cardiac surgery

Chapter 7

Postoperative breakthrough pain in paediatric cardiac surgery is not reduced by increased morphine concentrations

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Abstract

Background

Morphine is commonly used for postoperative analgesia in children. Here, we studied the pharmacodynamics of morphine in children after cardiac surgery receiving protocolized morphine.

Methods

Data on morphine rescue requirements guided by validated pain scores in children (n = 35, 3 to 36 months) after cardiac surgery receiving morphine as loading dose (100 μg/kg) with continuous infusion (40 μg/kg/h) from a previous study on morphine pharmacokinetics were analysed using repeated Time-to-Event (RTTE) modelling.

Results

During the postoperative period (38 (IQR 23 to 46) hours), 130 morphine rescue events (4 (IQR 1 to 5) per patient) mainly occurred in the first 24h (107/130) at a median morphine concentration of 29.5 ng/ml (range 7-180 ng/ml). In the RTTE model, the hazard of rescue morphine decreased over time (half-life 18 hours; $p<0.001$), while the hazard for rescue morphine (21.9% at 29.5 ng/ml) increased at higher morphine concentrations ($p<0.001$).

Conclusion

In this study on protocolized morphine analgesia in children, rescue morphine was required at a wide range of morphine concentrations and further increase of the morphine concentration did not lead to a decrease in hazard. Future studies should focus on a multimodal approach using other opioids or other analgesics to treat breakthrough pain in children.

Introduction

Even though opioids are commonly used for pain treatment after major surgery in children, there is no consensus on the type and dose of analgesics to be used. Ineffective postoperative pain management increases the risk of delayed recovery, adverse behavioural and physiological responses[1]. A recent international survey of management of pain and sedation after paediatric cardiac surgery showed a large worldwide variability in choice and dosing of analgesics and sedatives after cardiac surgery in children[2]. The most commonly used drug was morphine, with a wide variation in continuous infusion dose from 10 to 60 µg/kg/h in children aged 0 to 36 months.

The pharmacokinetics of morphine have been studied extensively across the paediatric population in different kind of settings[3], including cardiac surgery[4,5]. Morphine is primarily metabolized through glucuronidation by UGT2B7[6]. Elimination of morphine directly reflects the formation of its two pharmacologically active metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Even though cardiac surgery is associated with changes in hepatic blood flow and tissue perfusion, no difference was reported in elimination clearance in children after major cardiac surgery compared to non-cardiac surgery[4]. Despite all the pharmacokinetic data of morphine, there are only a handful of reports studying morphine pharmacodynamics by relating morphine concentrations to pharmacodynamic endpoints. Two studies investigated the effect of morphine on pain during endotracheal tube suctioning in preterm neonates[7,8]. One study did not find a relation between morphine concentrations and changes in heart rate or the preterm infant pain profile (PIPP), while the other study with the use of Item Response Theory modelling found a weak relationship between morphine concentrations and procedural pain reduction, as established with COMFORT-B and VAS assessments. Recently, Elkomy et al. described the pharmacodynamics of morphine when given as repeated bolus doses in infants and young children after cardiac surgery, by modelling the repeated time-to-event (RTTE) of morphine administration[9]. This methodology quantifies the hazard for events, with in this study the hazard being defined as the expected number of rescue morphine doses per hour in an individual patient. Translating these events into a hazard allows us to demonstrate if factors like time, morphine concentrations or age have impact on the efficacy of morphine reflected by the expected number of rescue doses.

To date there is a paucity of data on the pharmacodynamics of morphine in young children after cardiac surgery when given as continuous infusion with rescue boluses. The objective of this study is to analyse using RTTE modelling the

analgesic efficacy of morphine when given as maintenance and rescue analgesic within the context of a standardized postoperative pain protocol with regular pain and distress measurements.

Methods

Clinical study

Data were collected during an observational, prospective study in 3 to 36-months-old children, which was performed at the Department of Anaesthesia and Intensive Care Medicine of Our Lady's Children's Hospital, Dublin[5]. The study protocol was approved by the local ethics committee and written informed consent for the study was obtained from the parents preoperatively. The main results including the population pharmacokinetic analysis of the morphine concentration time samples of 35 children have been reported before[5].

In short, patients with and without Down syndrome were included when between 3 and 36 months of age and scheduled for cardiac surgery with cardiopulmonary bypass for atrial septal defect (ASD), ventricular septal defect (VSD), atrioventricular septal defect (AVSD), or tetralogy of Fallot (TOF) repair. Exclusion criteria were epilepsy, cerebral palsy or birth asphyxia, history of cardiothoracic surgery through sternotomy, preoperative mechanical ventilation, preoperative treatment with morphine or midazolam, and extracorporeal membrane oxygenation treatment after cardiopulmonary bypass.

All patients received standardized anaesthesia during cardiac surgery as well as standardized postoperative pain and distress management guided by pain and distress assessments by the caregiving nurse with a numeric rating scale (NRS) and the COMFORT-Behaviour scale (COMFORT-B). Morphine was administered as the primary analgesic agent at the end of surgery as a loading dose (100 μg/kg), followed by a continuous infusion of 40 μg/kg/h. In addition to morphine, intravenous acetaminophen was administered three times daily in the first 24 hours after surgery in a dose of 7.5 or 15 mg/kg, depending on weight (i.e. below or above 10 kg, respectively). In case of unacceptable pain (i.e. score combinations of COMFORT-B greater than 16 and NRS greater than 3), additional morphine boluses (20 to 40 μg/kg) were administered, and/or morphine maintenance infusion rates were increased. For rescue sedation, midazolam boluses (0.05 to 0.1 μg/kg) as needed was available. If further escalation for sedation was needed midazolam infusion (0.06 to 0.15 mg/kg/h) or enteral chloral hydrate (25 to 50 mg/kg every 6 h) was started. During the stay at the paediatric intensive care unit (PICU), the morphine dose was gradually decreased. Data collection was stopped

when intravenous morphine was switched to oral morphine, or on discharge from the PICU. Further details are described in the original article[5].

Repeated Time to Event modelling

In the present study, we used a repeated time-to-event (RTTE) model to estimate the hazard for a morphine rescue event during protocolized analgesia after cardiac surgery. The input data for a RTTE analysis consists of the times at which patients experience a morphine rescue event, which was defined as an additional bolus of morphine, an increase in infusion rate of the morphine infusion, or a restart of the infusion after a minimum break of 15 minutes and the times at which patient follow up stops (i.e. censoring event). Depending on the hazard model, the likelihood (L) of the observed event and censoring data is defined by:

$$L(event) = h(t) \times e^{-cumh(t)}$$

$$L(censoring) = e^{-cumh(t)}$$

Where *h(t)* is the hazard of needing rescue for an individual patient at the time of the event, and *cumh(t)* is the area under the hazard-time curve between the time of the previous event (or the time of follow-up start if the patient did not experience an event before time *t)* and the time *t* (the time of the event or the time of censoring).

Structural hazard model and covariate model

For the structural hazard model, baseline hazard models such as the constant hazard, Gompertz and Weibull models were tested to describe the effect of time after surgery on the hazard throughout the study period[10]. In addition, circadian-variation of the hazard after surgery was explored[11]. Morphine, M3G, and M6G concentrations as measured in the participants of the study and published before[5] were tested for their influence on the effect on the hazard for a morphine rescue event using immediate or delayed (i.e. with an effect compartment) drug effect models based on Emax or exponential functions. Finally, we explored the influence of covariates age, Down syndrome (yes/no), mechanical ventilation (yes/no) as predictors of inter-individual variability of the hazard. Potential covariates were tested in the repeated time-to-event model using the likelihood ratio test in a stepwise forward inclusion (α=0.05) and backwards elimination (α=0.01) procedure[12].

Model evaluation

Modelling was performed using NONMEM 7.3. Discrimination between models was made by the likelihood ratio test using the objective function value (OFV, i.e., -2

log likelihood [-2LL]). A decrease of 3.84 in the OFV value between nested models with one degree of freedom, representing a P-value of ≤ 0.05, was considered statistically significant. In addition, the kernel-based visual hazard comparison (kbVHC) was used to evaluate the model's ability to characterize the mean hazard over time[13]. In this method, CV_{target} controls the smoothness of the non-parametric hazard estimate of the kbVHC and this was set to 30%.

Results

Clinical study results

An overview of patient characteristics is shown in Table 1. The median age of the 35 children at surgery was 5.7 months (interquartile range (IQR) 4.3 to 8.3 months). The median postoperative study period at the PICU was 38 hours (IQR 23 to 46). During the first 24 hours, the median total dose of morphine was 940 μg/kg (IQR 116 to 183) or 31.3 μg/kg/h (24 to 36). On day 2, the median morphine dose was 320 μg/kg (IQR 102 to 524) or 16 μg/kg/h.

Figure 1 illustrates the median individual concentrations of morphine in the children over time. The figure shows that as a result of the postoperative pain protocol consisting of a loading dose with continuous infusion, the morphine concentrations are the highest directly after surgery and reached steady state after about 200 minutes. In the first 3 to 4 hours after surgery, morphine concentrations decreased from an average of 60 to 25 ng/ml (Figure 1). Overall these concentrations are, particularly in the first 24h hours, higher than a previously proposed target range for morphine of 10 to 20 ng/ml.

Over the study period, a total of 130 rescue morphine events were identified. The majority of events (n = 107) occurred in the first 24 hours, while the remaining events (n = 23) were in the second 24 hours. A total of 30 (86%) patients received a rescue dose of morphine, with a median of 4 rescue events (IQR 1-5) per patient. Of the 130 rescue events, 114 events (88%) concerned rescue boluses, 9 events (7%) were an increase in infusion rate and 7 patients (5%) received a bolus followed by an increase in infusion rate. Median time between events was 2.6 hours (IQR 1.1 to 4.5 hour). Of the 100 events that occurred after a previous event, 24% occurred within one hour of the previous event. Figure 2 shows the time points of the rescue morphine events with the corresponding morphine concentrations. Median morphine concentrations immediately prior to a rescue event were 29.5 ng/ml (IQR 23 to 43) with a range of 7 to 180 ng/ml. In total, 111 (85%) events occurred above a concentration of 20 ng/ml.

Table 1. Patient characteristics and details of postoperative administration of IV morphine

Variable	Patients (n = 35)
Male	15 (42.9)
Gestational age, weeks	39.0 (38.0 to 40.6)
Age at surgery, months	5.7 (4.3 to 8.3)
Weight at surgery, kg	6.1 (5.2 to 7.7)
Height at surgery, cm	65 (60 to 68)
Trisomy	21 (55.3)
Indication of surgery	
Atrial septal defect	1 (2.9)
Ventricular septal defect	9 (25.7)
AVSD	16 (45.7)
TOF	9 (25.7)
Morphine, day 1 (0 to 24 h), n = 35 patients	
Mean infusion rate, μg/kg/h	31.3 (24.1 to 36.1)
Total morphine, μg/kg	940 (784 to 1040)
Events	107 (82.3)
Morphine, day 2 (24 to 48 h), n = 25 patients*	
Mean infusion rate, μg/kg/h	16.0 (12.0 to 21.5)
Total morphine, μg/kg	320 (102 to 524)
Events	23 (17.7)
Midazolam	
Boluses per patient	4 (0 to 7)
Patients with infusion	13 (37.1)
Chloral hydrate boluses	0 (0 to 1)

*Data collection stopped according to protocol when patients were switched to oral morphine or discharged from the PICU
Data are presented as median (interquartile range) or number (%).
AVSD, atrioventricular septal defects; TOF, Tetralogy of Fallot.

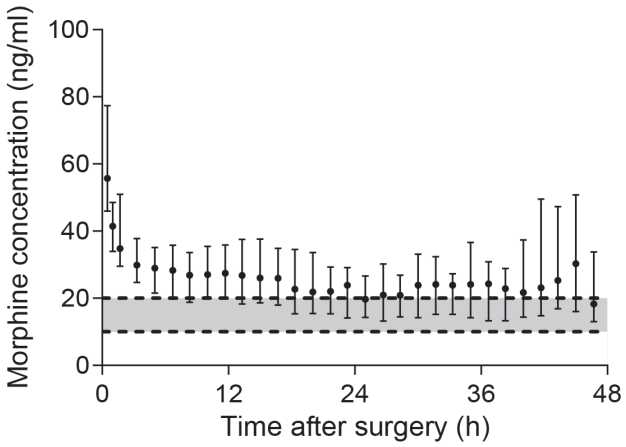

Figure 1. Median morphine concentrations versus time after surgery.
The whiskers indicate interquartile range. The number of patients is decreasing over time according to protocol when patients were switched to oral morphine or discharged from the PICU. The grey area indicates an earlier proposed therapeutic range of morphine (10 to 20 ng/ml)[15]. Data was derived from the earlier published PK model[5] that was based on the patients of the current study. The median postoperative study period at the PICU was 38 hours (IQR 23 to 46).

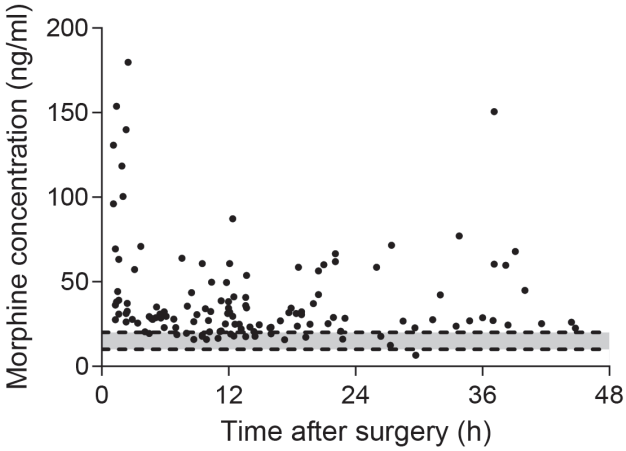

Figure 2. Morphine concentrations immediately prior to a rescue event versus time after surgery.
Solid black circle: rescue event which was defined as an additional bolus of morphine, an increase in infusion rate of the morphine infusion, or a restart of the infusion after a minimum break of 15 minutes. The grey area indicates an earlier proposed therapeutic range of morphine (10 to 20 ng/ml)[15].

Repeated Time to Event modelling

For the structural model describing the base hazard for a morphine rescue event, a Gompertz model was identified of which the parameters can be found in Table 2. The addition of morphine concentration as a predictor of individual deviations in the hazard, resulted in a statistical significant improvement of the model fit ($p<0.001$, Table 2). The hazard for rescue morphine increased at higher morphine concentrations (21.9% at the median concentration of 29.5 ng/ml).

Table 2. Parameter estimates of final pharmacokinetic-pharmacodynamic model of rescue morphine

Parameter (unit)	Submodel	Estimate (RSE)
Gompertz hazard	$HAZ_{base} \times e^{(HAZ_{slope} \times time_{since\ start})}$	
HAZ_{base} (h^{-1})		0.138(0%)
HAZ_{slope} (h^{-1})		-0.0387 (5%)
Morphine effect	$e^{(EFF_{morphine} \times C_{mor})}$	
$EFF_{morphine}$ (ml ng^{-1})		0.0067 (20%)
Inter-individual variability	$e^{(\eta i)}$	
Frailty ω^2 (-)		0.303 (30%)

Hazard is defined as expected number of events per time unit. The final hazard model is:

$$HAZ_{base} \times e^{(HAZ_{slope} \times time_{since\ start})} \times e^{(EFF_{morphine} \times C_{mor})} \times e^{(\eta i)}.$$

Where $Hazard_i$ = individual hazard estimate of subject i; HAZ_{base} = base hazard when $time_{since\ start}$ is 0; HAZ_{slope} = exponential slope base hazard over time; $time_{since\ start}$ = hours since patient started initial morphine infusion; $EFF_{morphine}$ = slope of exponential morphine effect; C_{mor} = morphine concentration in ng ml^{-1}; ηi = posthoc estimate of the individual frailty term of subject i; Frailty ω^2 = variance of frailty term; RSE = relative standard error

Figure 3 illustrates the identified exponential influence of morphine on the hazard showing that only small changes are expected below a morphine concentration of 100 ng/ml. At higher concentrations, the hazard for rescue medication increases more rapidly, however the number of observations are small. This results in a wider confidence interval at morphine concentrations higher than 50 ng/ml, indicating large uncertainty of the obtained function at higher concentrations.

For morphine and metabolite concentrations, adding an effect compartment or other drug effect models (i.e. Emax or exponential) did not improve the model (deltaOFV > 3.84).The model did also not improve significantly when circadian variation or the concentration of M3G or M6G were implemented as predictors for variability ($p>0.05$). Covariates such as age, Down syndrome and mechanical ventilation were not identified as a covariate with statistically significant impact on the model fit. The parameter estimates of the final model describing the hazard for rescue morphine in children after cardiac surgery are listed in Table 2. Figure

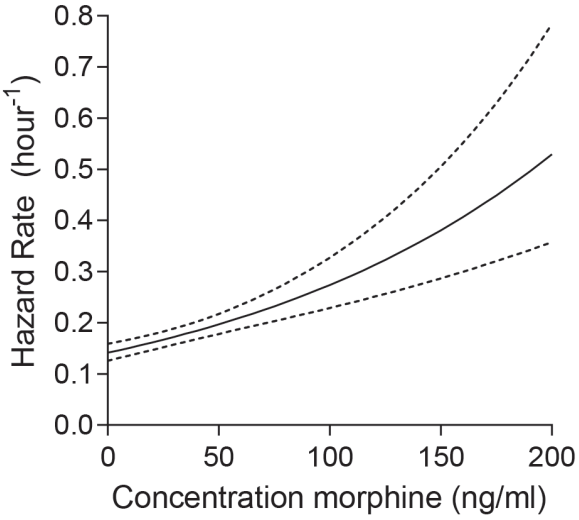

Figure 3. Hazard versus concentration of morphine
Concentration-effect relationship of morphine on the hazard of rescue morphine in children after cardiac surgery as estimated with the final repeated time-to-event model. The dotted lines demarcate the 95% confidence interval.

4 shows the results of the model validation plot kbVHC which illustrates that the hazard directly after surgery (HAZ_{base}) decreases over time after surgery (HAZ_{slope}, $p<0.001$) with a half-life of 18 hours. The figure also shows the comparison of the mean individual predicted hazard obtained with the final model versus the non-parametric kernel-based hazard. While the model-predicted and the non-parametric hazard both decreased over time, implying a good description of the data, the peak in the non-parametric hazard at 24 hours is not captured well by the model (Figure 4).

Discussion

In this study, data were analysed from 35 children aged 3 to 31 months after cardiac surgery who were treated according to a postoperative pain protocol consisting of a morphine loading dose of 100 µg/kg at the end of surgery followed by a continuous infusion of 40 µg/kg/h. Morphine rescue doses were given as bolus doses and/or increased continuous infusions. Prior research on the pharmacodynamics has mainly focussed on the relation between morphine concentrations and pain scores, experimental pain models, or surrogate endpoints such as pupil size[14]. In contrast, the current analysis uses the administration of rescue morphine as a clinically relevant event or indicator for lack of effect of the

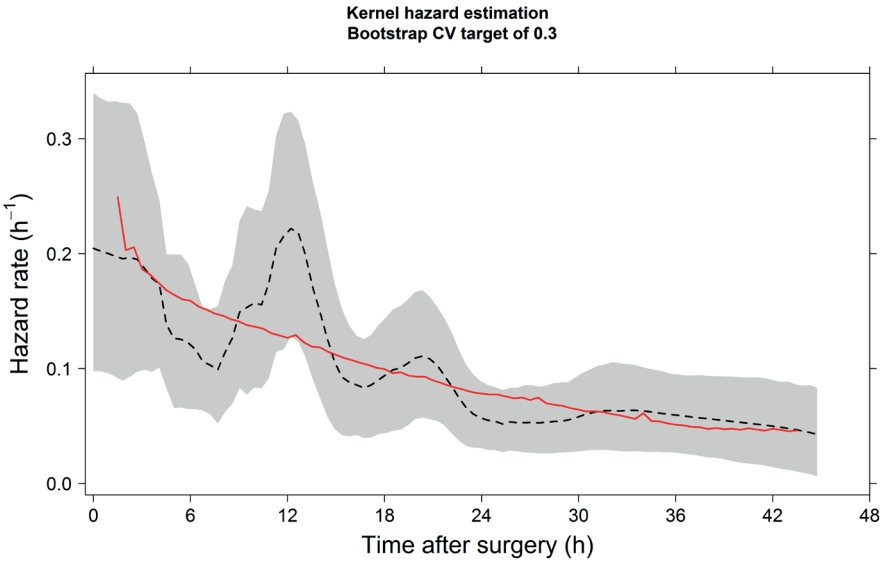

Figure 4. Model evaluation of the final PKPD model using the kbVHC.
Red solid line represents the mean of the model predicted individual hazard estimates. The black dashed line depicts the non-parametric kernel-based hazard in the data and the grey shaded area the 95% confidence interval.

current morphine dose. To this end, rescue events were identified and related to the corresponding morphine concentration, which was found to vary widely. RTTE modelling revealed that the hazard for rescue morphine decreased over time and increased when the morphine concentration increased ($p<0.05$). Here, we discuss the occurrence of rescue events in relation to the morphine concentration, the results of the RTTE analysis and the use of morphine for the treatment of breakthrough pain.

In our study, we identified 130 morphine rescue events during which rescue morphine was given following a standardized pain protocol, which was guided by COMFORT-B and NRS scores. These events of confirmed presence of pain were observed upon a standardized loading dose at the end of surgery followed by a continuous infusion. The concentrations of morphine that were found in this study were relatively high (Figure 1). Previously, a steady state target plasma concentration of morphine after major surgery in children and neonates of 10 to 20 ng/ml has been suggested[15]. The upper limit of 20 ng/ml is mainly based on one study where respiratory effects were reported after morphine infusion (median time of 20 h) in 30 children, aged 2 days to 1.6 years, undergoing cardiac surgery[16]. In another study in neonates and infants (0 to 52 weeks) after abdominal or thoracic

surgery, it was concluded adequate analgesia in neonates was provided with morphine trough concentrations between 15.4 and 22 ng/ml, whereas this was between 1.0 and 7.5 ng/ml for infants older than 4 weeks[17]. In the current study, concentrations of morphine were on average higher than 20 ng/ml, particularly in the first 3 to 4 hours after surgery. Comparing these concentrations is difficult without knowledge on the required target for different surgical procedures and populations. In our study, median morphine concentrations immediately prior to an event were 29.5 ng/ml with a range of 7 to 180 ng/ml with the majority of events (n = 111 (85%)) occurring above 20 ng/ml (Figure 2). These results indicate that more morphine is unlikely to reduce the number of events in patients. It therefore seems that, for now, titrating on effect is the only reasonable advice we can provide. In this respect, it would be interesting to investigate what the role is of individuals that are unlikely to respond to morphine rescue (i.e. non-responders). In other fields of research such as cancer patients or postoperative adult patients, non-response to morphine has been described[18–20]. The underlying mechanism of non-response is not known nor which patients are more prone to have absence of response to morphine or other opioids.

When focusing on the relationship between morphine concentration and the hazard for events which was analysed using RTTE modelling, we could not identify a reduction in hazard for rescue dosing upon an increase in morphine concentration. On the contrary, we identified an increased hazard for rescue medication upon higher morphine concentrations. However, as Figure 3 shows, the confidence interval in the steep part of the curve is wide, indicating that the actual increase in hazard as a result of increased morphine concentration could in fact also be small and/or confused by the delay in effect of morphine when given for breakthrough pain resulting in repeated dosages without awaiting the full effect. A recent study by Elkomy et al. investigated the pharmacodynamics of morphine in 20 children between 3 days to 5 years of age after cardiac surgery when using morphine boluses only[9]. In their study, a morphine concentration of 19.6 ng/ml resulted in a 50% reduction of the hazard for redosing with a wide 95% confidence interval of 5.9 to 49.5 ng/ml. The difference between their results and the concentration-effect relationship of morphine in our study might be related to the difference in study design, with Elkomy et al. studying morphine effects without continuous morphine infusion. The results of our study were obtained in the context of a morphine protocol consisting of both continuous and rescue doses, which reflects the current practice of postoperative care in children after cardiac surgery. The wide confidence intervals found for the concentration – effect relation of morphine in the two studies may indicate that the relation between the concentration of morphine and its efficacy is likely not very strong when studied

in the direct postoperative phase after cardiac surgery in children. Theoretically, opioid tolerance as well as opioid induced hyperalgesia could have played a role regarding the hazard that increases with increasing morphine concentrations. However, there are no studies in postoperative cardiac surgery infants that support this hypothesis.

Breakthrough pain is ideally treated by a fast-acting and highly effective analgesic. Our data shows that of the 100 events that occurred after a previous event, 24 (24%) events occurred within 1 hour of a previous event. This suggests that many of the rescue morphine dose given during the previous event did not adequately address the pain. In line with these observations, the results of our RTTE analysis demonstrated that an increase in morphine concentration does not result in a decrease in the hazard for rescue events, and could even result in an increase in hazard for a rescue event. One explanation for these results could be that morphine has a relatively long time to analgesic action, particularly when compared to short-acting opioids such as fentanyl and alfentanil[21]. While the concentration of morphine has been reported to reach its maximum as early as 20 minutes after intravenous bolus injection, the reported delay between peak blood drug concentration and peak pharmacodynamic effect reflected by a $t_{1/2ke0}$ is 1.6 to 3.9 h in volunteers and 1.7 h in postoperative patients, while for alfentanil and fentanyl a much shorter $t_{1/2ke0}$ (i.e. 1 and 6 min, respectively) has been reported[22,23]. Administration of more morphine as rescue treatment within a protocol of a continuous infusion of morphine should therefore be reconsidered, particularly in those cases where multiple rescue events occur within a short time frame. Instead, multimodal strategies should be further explored for the treatment of breakthrough pain in children[24].

From these results, it seems that studies aiming improving postoperative pain management should compare different dosing strategies (bolus dose versus increasing continuous infusion rate or both), the use of other opioids for breakthrough pain and/or the use of other non-opioid analgesics, such as nonsteroidal anti-inflammatory drugs[25] or acetaminophen. Optimal use of intravenous acetaminophen is currently being studied in combination with, or as replacement for, morphine with the goal of improving postoperative pain management for children[26].

This study has potential limitations. First, this was a single centre, observational study which has its known limitations. Second, our analysis rests on the assumption that morphine reliefs pain in infants after cardiac surgery while this topic is still under debate, despite morphine being the most used analgesic after cardiac surgery[2]. In addition, the effect of morphine in this study is determined

by the events that are identified by nurses giving additional morphine rescue according to their protocol. Therefore, adherence to the pain protocol was of extra importance, while pain assessment in children is generally difficult. In our opinion, this reflects daily practice on the PICU and therefore it is not expected that this substantially influences our conclusions. In addition to this, it may well be that other factors such as requirements for sedation during mechanical ventilation and the treatment of discomfort have played a role. Pain assessment in children can be extremely challenging and while current measurement instruments like the COMFORT scale are validated[27], it is still difficult to differentiate between pain and agitation or distress in infants. Another limitation is that we could not identify a delay in morphine effect in relation to morphine concentration or a diurnal variation in the hazard that is suggested in the observations (Figure 4). Finally, the original study design has its own limitations such as unknown impact of altered PK after cardiopulmonary bypass, systemic inflammation, haemodilution, low cardiac output or impaired liver/kidney function. Also, the requirements of inotropics/vasopressors were not noted[5].

In conclusion, in this study on protocolized morphine analgesia in children, rescue morphine was required at a wide range of morphine concentrations and further increase of the morphine concentration did not lead to a decrease in hazard. Therefore, future research should focus on a multimodal approach using other opioids or other analgesics to treat breakthrough pain in children.

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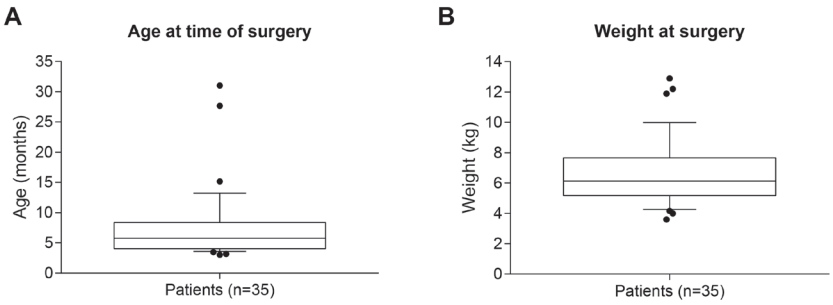
Supplemental Material



Supplemental Figure 1. Age (A) and weight (B) distribution of the included patients (n = 35). Whiskers indicate the 10 and 90th percentile.

Supplemental file – NONMEM model code of final model

```
$SUBROUTINE ADVAN13 TOL=9

$MODEL
COMP    ; (CENTRAL,DEFOBS)              ; Morphine central compartment
COMP    ; (M3G)
COMP    ; (M6G)
COMP    ; (PERIPH)
COMP    ; (CENTRAL,DEFDOSE)             ;Midazolam central compartment
COMP    ; (PERIPHERAL)
COMP    ; (METAB-1_OH)
COMP     ;(METAB -1OHG)
COMP    ; (METAB, PERIP-1OHG)
COMP    ; (METAB -4OH)
COMP ; (CUMHAZ1)                        ; Cum. hazard of morphine rescue


$PK
IF (A_0FLG.EQ.1) THEN
A_0(5)=0
ENDIF
V1        = MORF_V1
QM3F    = MORF_QM3F
QM3E    = MORF_QM3E
V2        = MORF_V2
QM6F = MORF_QM6F
QM6E = MORF_QM6E
V3        = MORF_V3
Q12       = MORF_Q1
V4        = MORF_V4
CL3       = MIDA_CL3
V5        = MIDA_V1
CL1       = MIDA_CL1
Q56       = MIDA_Q
V6        = MIDA_V2
CL2       = MIDA_CL2
V9         = MIDA_V5
V8         = V9
```

```
VSS      = V5+V6
V7       = MIDA_V3
V10      = V7
Q89      = MIDA_Q1
CL4      = MIDA_CL4
CL5      = MIDA_CL5

K12 = QM3F/V1
K20 = QM3E/V2
K13 = QM6F/V1
K30 = QM6E/V3
K14 = Q12/V1
K41 = Q12/V4

K56=Q56/V5
K65=Q56/V6
K57=CL1/V5
K78=CL2/V3
K80=CL3/V7
K89=Q89/V9
K98=Q89/V9
K510=CL4/V5
K100=CL5/V7

VSS = V1 + V2
S1=V1
;S2=V2
S3=V3
S4=V4
S6=V6
S7 = V7
S8 = V8
S9 = V9

TALPHA = THETA(1)/60
ALPHA1= TALPHA *EXP(ETA(1))
SLPE = THETA(2)
TSLOPE=THETA(3)/60
```

```
$DES
DELT = T - START + 0.001
IF (DELT.GT.0) THEN
HAZNOW = ALPHA1 * EXP(SLPE * (A(1)/V1))* EXP(TSLOPE*DELT)
ELSE
HAZNOW = 0
ENDIF

DADT(1) =K41* A(4)- (K12+ K13+K14)*  A(1)
DADT(2) =K12* A(1)-  K20* A(2)
DADT(3) =K13* A(1)-  K30* A(3)
DADT(4) =K14* A(1)-  K41* A(4)
DADT(5) =-A(5) * K57-  A(5)* K56+  A(6)        *  K65    -  K510  *  A(5)     ;
DADT(6) =K56* A(5)-  K65* A(6)
DADT(7) =K57* A(5)-  K78* A(7)
DADT(8) =K78* A(7)-  K80* A(8)-  K89  *  A(8)+K98 * A(9)
DADT(9) =K89* A(8)-  K98* A(9)
DADT(10) =K510  * A(5)-  K100* A(10)
DADT(11) = HAZNOW

$ERROR
Cmida=A(5)/V5
CM3G = A(2)/V2
CM6G = A(3)/V3
Cmor=A(1)/V1 ;
PerMorf = A(4)

CUMHAZ1=A(11)

DELTAT = TIME - START + 0.001
IF (DELTAT.GT.0) THEN
HAZ1 = ALPHA1*EXP(TSLOPE * DELTAT)* EXP(SLPE * Cmor)
ELSE
HAZ1 = 0
ENDIF

PHAZ = TALPHA*EXP(TSLOPE * DELTAT)* EXP(SLPE * Cmor)
IF(NEWIND.NE.2) CUMLAST=0
CUMDIFF = CUMHAZ1 - CUMLAST
```

```
IF(DV.EQ.0.AND.MDV.EQ.0) THEN
Y=EXP(-(CUMHAZ1-CUMLAST))
ENDIF

IF(DV.EQ.1.AND.MDV.EQ.0) THEN
Y=EXP(-(CUMHAZ1-CUMLAST)) * HAZ1
CUMLAST = CUMHAZ1
ELSE
CUMLAST=CUMLAST
ENDIF

PX= Y
$THETA
(0.00001, 0.15) ; HAZbase
(-0.05) ; EFFmorphine
(-0.02) ; HAZslope

$OMEGA
0.567
```