Size does matter : drug glucuronidation in children

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Chapter 5

Innovative Paediatric Pharmacology; Validation of an Evidence-Based Dosing Algorithm for Morphine in Neonates and Infants

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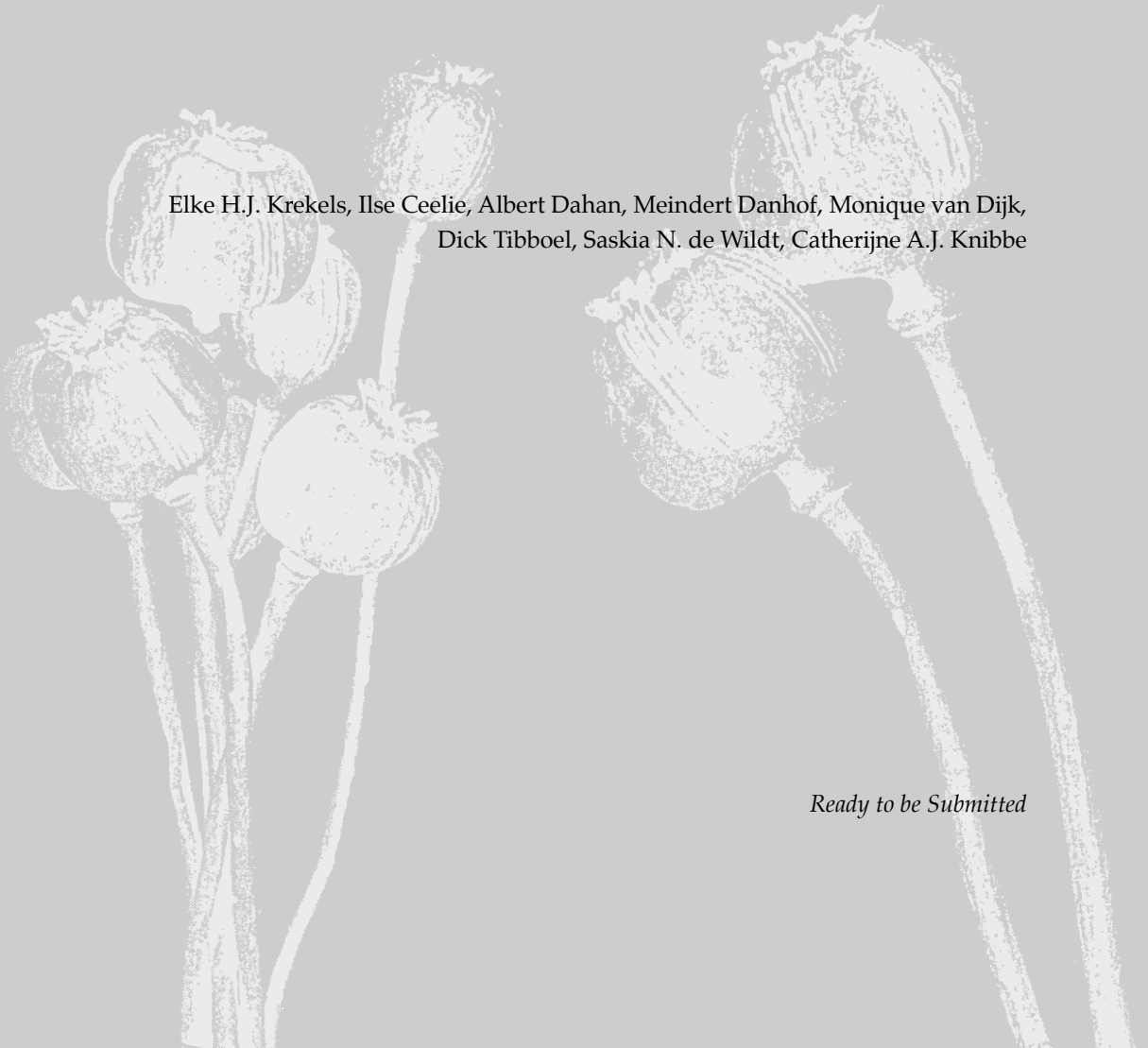

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Abstract

Context: Validated morphine dosing algorithms are lacking for neonates and infants. A paediatric population pharmacokinetic model showed morphine clearance to non-linearly increase with bodyweight and be reduced by 50% in neonates younger than ten days.

Objective: Prospectively evaluate a morphine IV dosing algorithm that was derived from a population pharmacokinetic model, in term neonates up to infants of one year of age.

Design: Single-centre, prospective, study (March 2008 – July 2010, 48 hrs follow-up, www.trialregister.nl: number NTR1438).

Setting: Level III pediatric intensive care unit.

Patients: 38 patients after major non-cardiac surgery, including 18 term neonates younger than ten days and 20 older patients.

Interventions: Postoperative continuous morphine IV infusion of 2.5 $\mu g/kg^{1.5}/h$ in neonates younger than ten days and 5 $\mu g/kg^{1.5}/h$ in older patients. Morphine IV rescue according to a validated age-appropriate pain protocol.

Main outcome measures: 1) morphine rescue dose; 2) average actual morphine infusion rate; 3) morphine and metabolite concentrations.

Results: For young neonates compared to older patients, patients needing morphine rescue was 27.8% *vs.* 90% ($p<0.001$) and total rescue dose was 0 (0 - 539) $\mu g/kg$ *vs.* 193 (0-1183) $\mu g/kg$ (median (range), $p<0.001$). Median actual morphine infusion rate was 4.4 (3.6 – 5.0) $\mu g/kg/h$ *vs* 14.4 (7.4 – 15.7) $\mu g/kg/h$ (median (range), $p<0.001$), and the number of patients needing more than 125% of the initial model-derived infusion rate was 17% *vs* 55% ($p<0.05$). Morphine and metabolite concentrations were accurately predicted by the paediatric population morphine model.

Conclusions: Compared to traditional morphine dosing in $\mu g/kg/h$, the proposed dose in young neonates was lower but still efficacious, while the higher dose in older patients still yielded a substantial need for rescue medication. Improvements seem possible, but the model-based dosing algorithm correcting for age-related differences in morphine pharmacokinetics may prevent overdosing in the youngest neonates and reduce suboptimal dosing in infants.

Introduction

Lack of paediatric dosing information has caused unlicensed and off-label drug prescription to be common practice in the paediatric population, despite the increased risk of suboptimal dosing or adverse drug effects [1]. Population pharmacokinetic and/or pharmacodynamic modeling approaches, also known as non-linear mixed-effects modeling, strongly facilitates the development of evidence-based rather than empiric or consensus-based paediatric drug dosing algorithms [2]. In population analyses, pharmacokinetic and/or pharmacodynamic parameters can be derived from sparse, dense and/or unbalanced data obtained from patients during routine clinical practice. Moreover, the sources of variability in the population can be quantified, and in a covariate analysis patient characteristics that are predictive of this variability, such as for instance bodyweight or age, can be identified [3]. These key patient characteristics form the basis of model-derived dosing algorithms. Before these dosing algorithms are implemented in clinical practice, they should however be prospectively evaluated to ascertain that the observed endpoints obtained with the new dosing algorithm are in agreement with the model-based predictions [2].

A drug that is commonly used in paediatrics is the opioid morphine. Interestingly, although this drug has been used in clinical settings for a very long time, validated dosing guidelines across the paediatric age-range are lacking. Under or overdosing of morphine should be prevented to avoid inadequate pain relief, opioid-related safety issues and opioid-withdrawal symptoms. Recently, a population model for the pharmacokinetics of morphine and its two major metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) was developed for a population of postoperative and ventilated preterm and term neonates up to children of three years of age (Chapter 3). In this model, clearance proved to nonlinearly increase with bodyweight. Additionally, a 50% reduction in morphine glucuronidation was observed in neonates with a postnatal age younger than ten days, which was independent the gestational age. This is similar to what is observed for bilirubin glucuronidation after birth. To ascertain good predictive model performance, this model was extensively validated, both internally and externally (Chapters 3 and 4). From this model it was subsequently derived that dosing morphine maintenance doses on the basis of $\mu g/kg^{1.5}/h$ with a 50% dose reduction in neonates younger than ten days, would yield similar morphine and metabolite concentrations across this population (Chapter 3). Compared to a traditional dosing scheme of 10 $\mu g/kg/h$, this nonlinear dosing algorithm leads to a substantial reduction in morphine infusion rates in neonates (e.g. 4.3 *vs* 10.0 $\mu g/kg/h$ for a young neonate of 3 kg), while infants would receive a higher dose (e.g. 14.1 *vs* 10.0 $\mu g/kg/h$ for an infant of 8 kg). The

current proof-of-principle study prospectively evaluates this model-derived paediatric dosing regimen for morphine over 48 hours in postoperative patients under the age of one year, using the required morphine rescue dose administered according to a validated age-appropriate pain protocol as primary endpoint. Furthermore the average actual morphine infusion rate was evaluated and measured morphine and metabolite concentrations in the patients were compared to concentration predictions by the paediatric morphine pharmacokinetic model (Chapter 3).

Methods

Study Design

In a single-center, double-blind, randomized controlled trial comparing the postoperative analgesic efficacy of morphine and paracetamol over 48 hours in term neonates and infants younger than 1 year [4], the patients allocated to receive morphine as primary analgesic agent were dosed according to the model-derived dosing algorithm (Chapter 3). The current analysis evaluates the efficacy of this new algorithm across the age-range in the morphine arm of this study in terms of required morphine rescue doses and actual average morphine infusion rates. Blood samples for the evaluation of model predicted morphine and metabolite concentrations were obtained from patients in both the morphine and paracetamol arm of the study. As the comparison between the analgesic efficacy of morphine and paracetamol and full details of this study where published elsewhere [4], in the present publication details are summarized as relevant to the current analysis.

Patients

Term neonates and infants under the age of one year, undergoing major abdominal or non-cardiac thoracic surgery between March 2008 and July 2010 at the Erasmus MC – Sophia Children's Hospital in Rotterdam, The Netherlands, were eligible for inclusion. Exclusion criteria were: 1) postconceptual age younger than 36 weeks; 2) bodyweight less than 1.5 kg; 3) extra corporeal membrane oxygenation (ECMO) treatment; 4) neurological or hepatic dysfunction or renal insufficiency; 5) pre- or postnatal administration of opioids or psychotropic drugs for more than 24 hours; 6) known allergy or intolerance for paracetamol or morphine; 7) administration of opioids in the 24 hours prior to surgery.

The study was approved by the Erasmus MC ethics review board and was registered in the Netherlands Trial Register under the number NTR1438 [5]. Written informed consent was obtained from the parents or legal guardians before inclusion of the patients.

Interventions

Patients were stratified by age into one group that was younger than ten days and one group that was older than ten days, as patients in these groups would receive different morphine dosages. All patients received a 100 μg/kg morphine IV bolus dose 30 minutes before the anticipated end of the surgical procedure. In the morphine arm of the study, patients with a postnatal age less than ten days received a postoperative continuous morphine IV infusion of 2.5 $\mu g/kg^{1.5}/h$ and older patients received 5 $\mu g/kg^{1.5}/h$, which was implemented using the dosing table depicted in table I. To maintain the blinding of the morphine *versus* paracetamol study, the patients allocated to the morphine arm of the study also received four times daily placebo saline infusions of the same volume as the paracetamol bolus dose a patient would receive in the paracetamol arm of the study.

Table I. *Dosing table used to implement the model-derived morphine dosing algorithm for continuous infusions in clinical practice. Patients younger than ten days received a dose of 2.5 $\mu g/kg^{1.5}/h$ and patients older than ten days received 5 $\mu g/kg^{1.5}/h$.*

	Model-derived dosing algorithm	
	PNA < 10 days *2.5 $\mu g/kg^{1.5}/h$*	*PNA > 10 days* *5 $\mu g/kg^{1.5}/h$*
Bodyweight (kg)	**Infusion rate μg/kg/h**	**Infusion rate μg/kg/h**
1.5 – 2	3.1	6.1
2 – 2.5	3.5	7.1
2.5 – 3	4.0	7.9
3 – 3.5	4.3	8.7
3.5 – 4	4.7	9.4
4 – 4.5	5.0	10.0
4.5 – 5	5.3	10.6
5 – 5.5	5.6	11.2
5.5 – 6	.	11.7
6 – 6.5	.	12.3
6.5 – 7	.	12.8
7 – 7.5	.	13.2
7.5 – 8	.	13.7
8 – 8.5	.	14.1
8.5 – 9	.	14.6
9 – 9.5	.	15.0
9.5 – 10	.	15.4
10 – 10.5	.	15.8

PNA = postnatal age

During the first 48 hours of postoperative recovery at the intensive care unit, trained nurses assessed patient's pain levels every 2 hours or when the patients appeared to be in discomfort, according to an age-appropriate standardized pain protocol [6], based on COMFORT-behavior scores [7] and Numeric Rating Scale (NRS) pain scores [8]. Open-label morphine rescue medication was administered to patients of both the morphine and paracetamol arm when NRS ≥ 4. Patients younger than ten days received a bolus dose of 10 μg/kg and older patients received 15 μg/kg. Patients were reassessed after 10 minutes and received additional bolus doses when necessary. If analgesia was not adequate after three bolus doses within one hour, the patients received an additional loading dose of 100 μg/kg after which the morphine infusion rate was increased by 1.25 $\mu g/kg^{1.5}/h$ in neonates younger than ten days and 2.5 $\mu g/kg^{1.5}/h$ in older children. When after this increase the patient needed again more than 3 rescue bolus doses within one hour, another loading dose was administered and infusion rates were increased by the same amount again. The morphine infusion was stopped or reduced in case of morphine related adverse events or after 12 hours of adequate analgesia, indicated by an NRS score < 4. In case of discomfort, indicated by COMFORT-behaviour scores of >17 and NRS pain scores of < 4, midazolam was administered.

Outcomes

The nurse-controlled open-label morphine rescue medication in the first 48 postoperative hours was used as the primary efficacy outcome measure. This was expressed as percentage of patients in need of rescue medication, the number of rescue events with an event being an administration of a morphine bolus dose, an additional morphine loading dose or an increase of morphine infusion rate, and the total morphine rescue dose. The two age-groups were analyzed separately and compared. Additionally, the average actual morphine infusion rate over the duration of the postoperative infusion for each patient was compared between these groups. Since there were bodyweight and age-related differences in the model-derived morphine dosing algorithm, the average morphine infusion rate in each individual patient was also compared to the initial model-derived infusion rate for that patient, by calculating the percentage of patients that had an average morphine infusion rate within or outside 25% of the prescribed dose (as in bioequivalence studies, this is considered to be clinically significant) and the percentage of patients that required more than double the initial model-derived infusion rate.

Blood samples to determine morphine and metabolite concentrations were obtained to determine the accuracy of the concentration predictions by the pharmacokinetic model (Chapter 3) in the current set of patients that were dosed according to the model-derived dosing algorithm in table I. A maximum of eight blood samples or a total 5% of the blood volume of a patient, were obtained from an indwelling arterial catheter

when present. When possible a blood sample was taken prior to a morphine rescue dose or prior to a scheduled paracetamol or placebo bolus dose. Additional samples were taken when possible at various times, to obtain information on a wide range of the concentration-time curve. Blood samples were centrifuged at 3000 rpm and plasma was subsequently stored at -80°C till further analysis.

Statistical Analysis

To statistically compare the analgesic efficacy of the model-derived morphine dosing algorithm between neonates younger than ten days and patients of ten days or older, the Fisher exact test was used for the dichotomous endpoints (need for rescue mediation, actual morphine infusion rate within or outside 25% of the prescribed dose, actual morphine infusion rate more than 200% of the prescribed dose). The Mann-Whitney test was used for the other categorical and continuous endpoints (number of rescue events per patient, morphine rescue dose, average actual morphine infusion rate).

To ascertain that the patients of whom pharmacokinetic samples were obtained could be regarded as a representative sample of the patients that were analyzed for the analgesic efficacy, the demographics and clinical characteristics of the patients in these groups were statistically compared. For this also the Fisher exact test was used for the dichotomous data (sex, location of surgery, need for postoperative ventilation) and the Mann-Whitney test was used for the continuous data (postnatal age, bodyweight, duration of surgery).

Pharmacokinetic Blood Sample Analysis

The frozen plasma samples were allowed to thaw at room temperature. Proteins in 200 μl samples were precipitated with 700 μl acetonitrile which contained ^{2}H3-Morphine ($^{2}H_3$-M), ^{2}H3-Morphine-3-glucuronide ($^{2}H_3$-M3G), and ^{2}H3-Morphine-6-glucuronide ($^{2}H_3$-M6G) (Cerilliant, Texas, USA) as internal standards and 100 μl 1 mM zinc sulphate. The samples were mixed for 2 minutes and centrifuged for 5 minutes at 13000 rpm. 200 μl of the supernatant was dried under a gentle stream of nitrogen at 50°C. The residues were reconstituted in 100 μl of 0.1 % (v/v) formic acid in water and 20 μl of this sample was injected into the HPLC system, which contained an Ultimate 3000 autosampler (Dionex, Amsterdam, The Netherlands), a HPG680 pump (Dionex, Amsterdam, The Netherlands), and a 3 μm, 120Å, 50 x 2.1 mm YMC-pack ODS-AQ column (YMC Inacom, Overberg, The Netherlands) with an ODS precolumn (Phenomenex, Utrecht, The Netherlands) at 30°C. The mobile phase consisted of 0.1 % formic acid in water with 3% acetonitril (Lichosolv) (Merck B.V., Amsterdam, The Netherlands) as modifier and the flow rate was 0.5 ml/min. The system was controlled by Chromeleon (Dionex, Amsterdam, The Netherlands). The eluent of the HPLC system was monitored by a Quattro micro API tandem mass

spectrometer (Waters, Etten-Leur, The Netherlands). Peak areas of reaction ions from morphine, M3G, M6G and the internal standards $^{2}H_{3}$-M, $^{2}H_{3}$-M3G and $^{2}H_{3}$-M6G were obtained in the multiple reaction mode and integrated by data software Masslynx 4.1 (Waters, Etten-Leur, The Netherlands). m/z was 165.0 (285.9>165.0) for morphine and 286.0 (461.9 >286.0) for M3G and M6G. For the internal standards m/z was 165.0 (288.9>165.0) for $^{2}H_{3}$-M and m/z (464.9>289.0) for $^{2}H_{3}$-M3G and $^{2}H_{3}$-M6G. All analytes could be analyzed in one run and all samples were analyzed in triplo. The sample concentrations were calculated by the internal standard method with weighing factor $1/(Y^{2})$.

Blank pooled human serum was used for control samples and serum spiked with morphine, M3G, and M6G (Cerilliant, Texas, USA) in methanol/water were used for the calibration curve and quality controls.

Model-Based Pharmacokinetic Predictions

NONMEM VI (ICON, Ellicott City, MD, USA) was used to obtain model-based concentration predictions. In predicted *versus* observed plots, the available morphine and metabolite concentrations were visually compared to both the individual and population concentration predictions by the paediatric population pharmacokinetic model for morphine (Chapter 3). Individual predicted concentrations were based on a model fit of the individually observed concentrations to the model, based on the administered dose, bodyweight and postnatal age of the patient. Population predicted concentrations were obtained using the population parameter values of a typical individual to simulate concentrations based on the administered dose, specified bodyweight and postnatal age of the patient.

Results

Patients and Sampling

Figure 1 shows the inclusion diagram for this study. Thirty-nine patients were allocated to receive morphine as primary analgesic (morphine arm) of which 38 patients actually received continuous morphine infusions according to the model-derived dosing algorithm. These 38 patients were included in the current analysis of the analgesic efficacy of the new morphine dosing algorithm. Morphine and metabolite concentrations were available for 8 of these 38 patients, due to the limited number of patients with an arterial line. In the paracetamol arm, 33 patients were included, of which the analgesic efficacy was assessed in a separate study [4]. For a total of 7 of the 33 patients in the paracetamol

arm, morphine concentrations were available resulting upon the standard loading dose of morphine that was administered in all patients at the end of surgery and morphine rescue boluses when indicated by the standardized pain protocol.

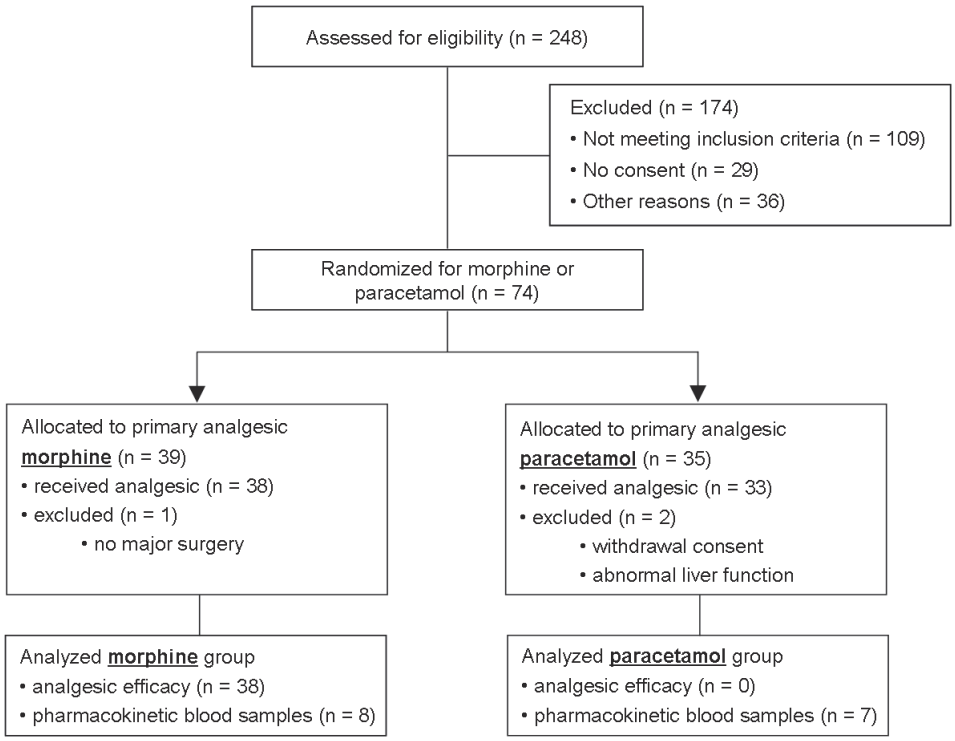

Figure 1. *Inclusion diagram for the current analysis.*

Table II summarizes the demographics and clinical characteristics of the patients in the group analyzed for analgesic efficacy and in the group analyzed for model predictions of morphine and metabolite concentrations. The table shows that the group of patients of whom blood samples were obtained represents the overall group analyzed for morphine efficacy well, as there were no statistically significant differences in demographics and patient characteristics between these groups.

Table II. *Demographics and clinical characteristics of the patients in the analysis of the analgesic efficacy of the morphine dosing algorithm and the patients in the analysis of the pharmacokinetic model predictions of morphine and its metabolite concentrations in the current study.*

	Patients analyzed for analgesic efficacy of the morphine dosing algorithm (n = 38)	**Patients analyzed for pharmacokinetics of morphine (n = 15)**	**p-value**
Postnatal age (days, median (range))	20 (0 – 355)	3 (0 – 200)	0.56 †
Bodyweight (kg, median (range))	3.6 (2.0 – 9.8)	3.3 (1.6 – 8.0)	0.42 †
Sex (n, M / F)	26 / 12	7 / 8	0.21 ‡
Location of surgery (n, thorax / abdomen)	11 / 27	5 / 10	0.75 ‡
Duration of surgery (min, median (range))	139 (27 - 480)	149 (69 – 480)	0.30 †
Postoperative ventilation (n, %)	14 (37%)	7 (47%)	0.55 ‡

† Mann-Whitney test, ‡ Fisher exact test

Analgesic Efficacy

An overview of the need for morphine rescue medication in patients younger and older than ten days dosed according to the model-derived morphine dosing algorithm is provided in table III.

Table III. *Analgesic efficacy of the model-derived morphine dosing algorithm, expressed as need for rescue medication.*

Patient group	**n**	**Patients in need of rescue medication**	**Rescue events #**	**Total rescue dose (μg/kg) #**
Total	38	23 (60.5%)	2 (0 – 14)	20 (0 – 1183)
0 – 10 days	18	5 (27.8%)	0 (0 – 10) ‡	0 (0 – 539) †
10 – 365 days	20	18 (90.0%)	4.5 (0 – 14) ‡	193 (0 - 1183) †

median (range), † $p < 0.05$, ‡ $p < 0.001$

Overall, 60.5% of all patients needed rescue medication, with four out of 18 neonates younger than ten days (27.8%) needing rescue medication, compared to 18 out of 20 patients (90%) who were ten days or older ($p<0.001$, Fisher exact test). In neonates younger than ten days compared to the older children, the number of rescue events per

patient (median (range)) were 0 (0-10) *versus* 4.5 (0 – 14) (p<0.001, Mann-Whitney test) and the total rescue dose (median (range)) was 0 (0-539) μg/kg *versus* 193 (0 – 1183) μg/kg (p <0.001, Mann-Whitney test). Considering only the patients in need of rescue medication, the average number of rescue events per patient was 6 (2 – 10) *versus* 5.5 (1 – 14) in patients younger and older than ten days (p=0.97, Mann-Whitney test). While the median rescue dose in neonates younger than ten days who were in need of rescue medication was lower than the median rescue dose in the older children that needed rescue medication 140 (20 – 539) μg/kg *versus* 228 (15 – 1183) μg/kg, this difference did not reach statistical significance (p=0.53, Mann-Whitney test).

The average actual morphine infusion rate (median (range)) calculated over the duration of the post-operative infusion, consisting of the initial model-derived morphine infusion rate according to table I and additional morphine rescue doses that where required according to the standardized pain protocol, was 4.4 (2.5 – 24.6) μg/kg/h in neonates younger than ten days and 14.4 (7.9 – 39.3) μg/kg/h in older patients (p<0.001, Mann-Whitney test). In figure 2, the average morphine infusion rate during the duration of postoperative infusion is depicted for each individual patient (symbols) together with the model-derived morphine infusion rates which differentiates between children older and younger than ten days (solid lines). Different symbols are used for patients younger and older than ten days.

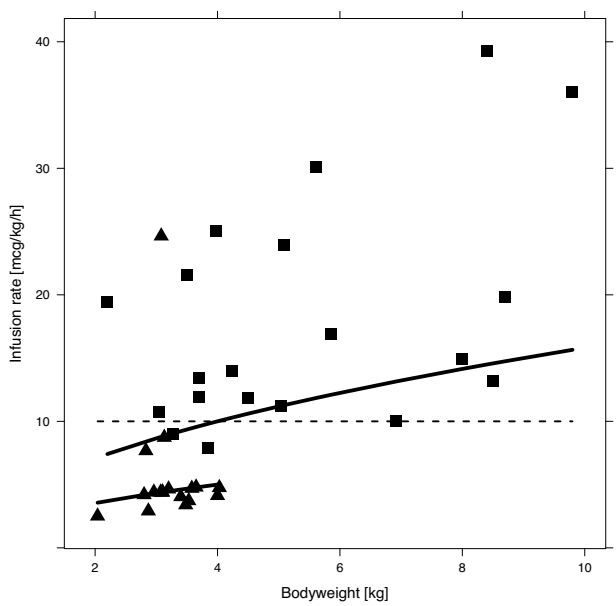

Figure 2. *Average actual postoperative morphine infusion rates during the postoperative infusion* time

for each individual patient with triangles (▲) representing neonates younger than ten days and squares (■) representing older children, and initial infusion rates according to the model-derived dosing algorithm (solid lines) in patients younger than ten days (2.5 $\mu g/kg^{1.5}/h$) and older than ten days (5 $\mu g/kg^{1.5}/h$). The dashed line represents the infusion rates according to the traditional dosing regimen in our facilities.

Three out of 18 neonates (17%) required less than 75% of the initial infusion rate *versus* none of the 20 older patients (p=0.10, Fisher exact test), 12 out of 18 neonates (67%) *versus* 9 out of 20 older patients (45%) had actual infusion rates within 25% of the initial dose (p=0.21, Fisher exact test), 3 out of 18 neonates (17%) required more than 125% of the initial infusion rate *versus* 11 out of 20 older patients (55%) ($p<0.05$, Fisher exact test), and 1 out of 18 neonates required more than twice the initial infusion rate *versus* 7 out of 20 older patients ($p<0.05$, Fisher exact test). For unknown reasons, a 1 day old boy required on average 5.6 times the initial morphine infusion rate during his 38 hour postoperative infusion. Of the older patients that need more than twice the initial morphine infusion rate none required more than three times the initial infusion rate.

In figure 2 a reference line representing the traditional intravenous morphine dose for the patient population in the current study in our unit (10 ug/kg/h – dashed line) was also added. This shows that initial morphine IV infusion rates were lower than the traditional dose in neonates younger than ten days and higher than the traditional infusion rate for infants older than ten days and heavier than 4 kg.

Morphine and Metabolite Concentrations

Figure 3 shows the plots of predicted *versus* observed concentrations of morphine (left), M3G (middle), and M6G (right). In the upper panels of figure 3, individual predicted *versus* observed concentrations are shown, which are based on the model fitting to the data. These plots indicate no bias and adequate precision of the concentration predictions. The graphs of the population predicted *versus* observed concentrations (lower panels) indicate no bias around the line of unity, suggesting the simulated predictions to be accurate in this patient population. The spread of data points around the line of unity in these plots indicates that the inter-individual variability in morphine pharmacokinetics in the population is considerable.

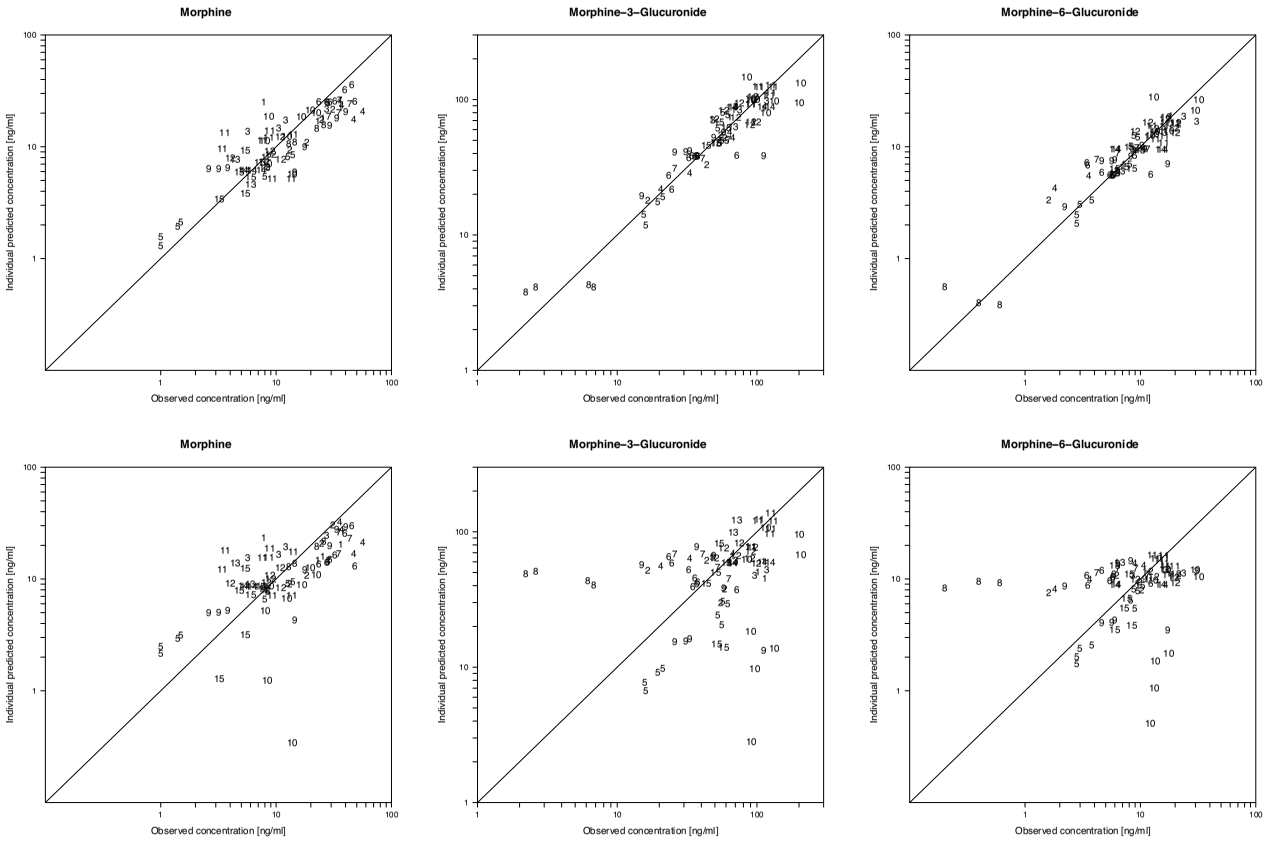

Figure 3. *Model predicted versus observed concentrations for morphine (left), morphine-3-glucuronide (middle), and morphine-6-glucuronide (right). Individual predictions (top) are based on the individual model fit of the observed concentrations, whereas population predictions (bottom) are simulated concentrations for a typical patient with a specified bodyweight and age. Different numbers are used to indicate data points of different individuals.*

Discussion

The current study prospectively evaluated a model-derived dosing algorithm for morphine in term neonates to infants of one year of age. According to this algorithm initial morphine maintenance infusion rates were 2.5 $\mu g/kg^{1.5}/h$ for neonates younger than ten days and 5 $\mu g/kg^{1.5}/h$ in older patients (table I), resulting in a reduction between 50% and 75% in neonates younger than ten days compared to the traditional morphine dose in our unit of 10 $\mu g/kg/h$, while children older than ten days and heavier than four kilograms received up to 150% of our traditional morphine dose. The limited need for rescue medication in the very young suggests the reduced morphine dose in this age-group to still be efficacious, while the increased dose in the older patients still does not appear to yield adequate analgesia in most of these patients (table III). Figure 2 further illustrates that the morphine infusion rate according to the model-derived dosing algorithm gives a good reflection of the actual morphine need in children younger than ten days. In older patients, the variability in average morphine consumption is higher, and in this group the percentage of patients requiring more than twice the prescribed morphine dose is also higher (35% compared to 6% in the young neonates, $p<0.05$). Moreover, figure 2 proves the morphine IV infusion rates according to the traditional dosing guideline to be too high for young neonates.

The morphine dosing algorithm that was evaluated in the current study was derived from a population pharmacokinetic model in which bodyweight and a postnatal age of less than ten days were identified as key patient characteristics that are predictive of the inter-individual variability in the clearance and distribution of morphine and its main metabolites (Chapter 3). Thorough external evaluation of the population pharmacokinetic model with four independent datasets from four different centers previously established confidence in the predictions by this model (Chapter 4). Blood samples obtained from a limited number of patients in the current study further confirm the accuracy of the model predictions in patients that were dosed according to the new dosing regimen (figure 3). It is thereby confirmed that the model-derived dosing algorithm indeed corrects for the developmental changes in morphine pharmacokinetics in this population, yielding similar steady state concentrations for morphine and its metabolites across the full age- and weight-range in the current study.

According to the pharmacokinetic model, continuous morphine IV infusion rates should be dosed on the basis of $\mu g/kg^{1.5}/h$, with a 50% reduction in neonates younger than ten days, to correct for age-related differences in morphine clearance. However, target concentrations needed to determine the infusion rate have not been firmly established for morphine in the paediatric population, although concentrations

around 20 ng/ml have been suggested in postoperative neonates and infants [9,10]. The infusion rate in the current study was derived from clinical experience in our own unit. Our traditional dosing guideline for continuous morphine IV infusions for neonates and children up to three years of age is 10 μg/kg/h irrespective of the age of the patient, which is in the lower range of literature reported postoperative morphine IV infusion rates of 10 – 40 μg/kg/h [11]. Previous research suggested this infusion rate to be relatively high for neonates and young children, but often insufficient for older patients [12]. Based on these results a morphine dose amount of 2.5 μg/kg$^{1.5}$/h in neonates younger than ten days and 5 μg/kg$^{1.5}$/h in older patients was selected for the current study as this leads to a reduced dose in neonates and an increased dose in older heavier patients, compared to our traditional dosing guideline. Upon these doses, average steady state concentrations of approximately 10 ng/ml are anticipated throughout the entire study population from term neonates and infants to the age of one year. Even though this concentration is lower than the previously suggested 20 ng/ml, the results show that this target concentration is sufficient, particularly for neonates.

To our knowledge no prospectively validated paediatric morphine dosing algorithms have been published that are based on a thorough investigation and understanding of the developmental changes in the pharmacology of morphine in this population. However, when pharmacokinetic models are used as the sole basis for paediatric dosing corrections, it is implicitly assumed that the pharmacodynamics of that drug remain constant within this population. This assumption is acceptable when: 1) pathophysiological processes are similar throughout the population, 2) the exposure-effect relationship can be assumed independent of age based on the mechanism of action, and 3) the same clinical endpoints for treatment are used throughout the populations [13]. It has not been proven that morphine meets the first two criteria in the current study population.

The pain protocol in the current study has been specifically developed and validated for the population included in the current study [7,8], thereby making rescue medication and total morphine consumption an appropriate and objective endpoints for analgesic efficacy in the current study. The model-derived morphine dosing algorithm evaluated in the current study corrects for age-related difference in morphine pharmacokinetics leading to similar concentrations throughout the population. The observed difference in rescue medication and morphine consumption between younger and older patients therefore suggests age-related differences in either pain perception or analgesic efficacy of morphine. The latter can for instance be caused by differences in effect-site distribution and/or differences in sensitivity to morphine and its pharmacologically active metabolites. Although evidence-based corrections for age-related differences in morphine pharmacokinetics already contributed to improving

paediatric morphine dosing, an investigation into morphine pharmacodynamics in this population could be used to further refine the morphine dosing algorithm by defining age-specific target concentrations.

Medicine always strives to expose patients to the lowest possible drug doses that are clinically effective. It is now recognized that neonates, even extreme premature ones, are able to experience pain that requires treatment [14–18]. With respect to short-term outcome measures expressed using various clinical endpoints like mortality, pain, duration of ventilation, or general clinical outcome measures, results on the potential benefit of morphine or opioid administration in general have been contradictory, while acute respiratory, gastro-intestinal, cardiovascular, and neurological side effects as well as the occurrence of tolerance, dependence and withdrawal symptoms are well known. Animals studies have raised concerns about the long-term effects of both pain and morphine exposure in neonates on endpoints like brain structure, (hormonal) stress response, and behaviour later in life [19–21]. Data in humans are scarce, however recent long-term follow-up studies in cohorts of children that were exposed to morphine for the treatment of pain or for ventilatory support during the neonatal period showed limited to no difference between these children and controls on outcome measures like intelligence, behaviour, motor skills, memory, chronic pain, and health-related quality of life [22–24].

The number of patients in the current study is too small to establish the influence of the reduced morphine dose in young neonates on the occurrence of acute morphine-related side-effects, dependence or withdrawal, but it is expected that a morphine dose reduction positively influence these endpoints. Similarly, it could not be established whether the increased morphine dose in older children, yielded significant increases in the occurrence of acute morphine side-effects, dependence or withdrawal, however exposing these patients to ineffective or suboptimal doses of morphine can be regarded as equally unethical as over-dosing. It is also expected that optimization of the paediatric morphine dosing algorithm positively influences potential long-term effects that morphine exposure or untreated pain may have.

In conclusion, the development of evidence-based dosing regimens in the paediatric population is complicated by practical, ethical, and legal constraints. However population modeling now makes it possible to obtain drug dosing algorithms for the paediatric population with a similar level of scientific evidence as has been the standard requirement for the adult population for a long time [3]. It is envisioned that this methodology can be extended to other vulnerable patient populations as well.

For morphine, the development of a paediatric dosing algorithm that corrects for developmental changes in the pharmacokinetics yielded a 50% to 75% dose reduction in initial infusion rates in neonates younger than ten days that was still efficacious for the

majority of the patients. For children of ten days or older, the developed dosing algorithm prescribed an increased dose compared to the traditional dose, that still required rescue dosing in the majority of patients, although the total morphine requirement was still within 25% of the prescribed dose for almost half of the patients. Overall, the new morphine dosing algorithm reduces the risk of over-exposure in the youngest neonates as well as the risk of exposing older patients to suboptimal doses.

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