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Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants

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Background. To investigate clinical variables such as gestational age, sex, weight, the therapeutic regimens used and mechanical ventilation that might affect morphine requirements and plasma concentrations of morphine and its metabolites.

Methods. In a double-blind study, neonates and infants stratified for age [group I 0–4 weeks (neonates), group II ⩾4–26 weeks, group III ⩾26–52 weeks, group IV ⩾1–3 yr] admitted to the paediatric intensive care unit after abdominal or thoracic surgery received morphine 100 μg kg^{-1} after surgery, and were randomly assigned to either continuous morphine 10 μg kg^{-1} h^{-1} or intermittent morphine boluses 30 μg kg^{-1} every 3 h. Pain was measured using the COMFORT behavioural scale and a visual analogue scale. Additional morphine was administered on guidance of the pain scores. Morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) plasma concentrations were measured before, directly after, and at 6, 12 and 24 h after surgery.

Results. Multiple regression analysis of different variables revealed that age was the most important factor affecting morphine requirements and plasma morphine concentrations. Significantly fewer neonates required additional morphine doses compared with all other age groups ($P<0.001$). Method of morphine administration (intermittent *vs* continuous) had no significant influence on morphine requirements. Neonates had significantly higher plasma concentrations of morphine, M3G and M6G (all $P<0.001$), and significantly lower M6G/morphine ratio ($P<0.03$) than the older children. The M6G/M3G ratio was similar in all age groups.

Conclusions. Neonates have a narrower therapeutic window for postoperative morphine analgesia than older age groups, with no difference in the safety or effectiveness of intermittent doses compared with continuous infusions in any of these age groups. In infants >1 month of age, analgesia is achieved after morphine infusions ranging from 10.9 to 12.3 μg kg^{-1} h^{-1} at plasma concentrations of <15 ng ml^{-1}.

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Morphine is the most frequently used agent for postoperative analgesia in neonates, infants and children.[1–5] Therapeutic plasma concentrations of morphine depend on factors such as route of administration, total body clearance and volume of distribution. These are affected by the age, hepatic function, renal function and clinical condition.[6–9] As a result of these factors, studies of morphine pharmacokinetics report a noticeable variability between patients.[10] While preterm neonates are regarded as a separate group with regard to serum half-life and morphine clearance, the distinction between term newborns and older infants is less clearly defined.[10] In addition, the pharmacodynamics of morphine may change rapidly during infancy, being influenced by sex,[11] the maturation of opioid receptors,[12–14] earlier experiences of pain,[15] as well as social and cultural factors.[16]

Despite the reported variability, most previous studies have investigated the effects of morphine only in 4–20 patients within the different age groups,[10] thus precluding their ability to examine the effects of underlying clinical and demographic factors.

We designed a prospective study including larger numbers of patients in each age group, enabling us to elucidate the impact of various clinical and demographic variables on both morphine requirements and morphine pharmacokinetics. We have recently reported the effects of morphine administration on hormonal and metabolic stress responses following major surgery in the same patient population.[17]

Methods

After approval from the Medical Ethics Committee for the Erasmus MC, Rotterdam, written consent was obtained from all parents. We included 204 children aged 0–3 yr admitted to the paediatric surgical intensive care unit following non-cardiac thoracic and abdominal surgery. Patients were excluded if they had received morphine <6 h before surgery, or suffered from hepatic, renal or neurological disorders. Patients were stratified into four age groups: group I 0–4 weeks, group II 4–26 weeks, group III 26–52 weeks, group IV 1–3 yr. They were randomly assigned to receive either i.v. continuous morphine (CM) or intermittent morphine (IM). The pharmacist prepared all study drugs and strata-specific schedules for randomization. For each age group, the boxes containing the study drugs were numbered consecutively and used in sequence. Each patient received a study number consisting of a number of the age group (I–IV) and a sequence number (1–68).

Anaesthetic management was standardized in all patients. Anaesthesia was induced with i.v. thiopental 3–5 mg kg^{-1} or, when i.v. induction was impossible, by inhalation of halothane in oxygen (<5% of patients). After the insertion of an i.v. line, the anaesthetic procedure was similar for all patients. Fentanyl 5 μg kg^{-1} was given before orotracheal intubation, which was facilitated with atracurium 0.5–1 mg kg^{-1} or succinylcholine 2 mg kg^{-1}. Ventilation was controlled and anaesthesia was maintained with isoflurane 0.5 minimum alveolar concentration in nitrous oxide 60% in oxygen or air in oxygen. Perioperative fluids were standardized to maintain a glucose infusion rate of 4–6 mg kg^{-1} min^{-1}. Body temperature was kept within normal ranges. A peripheral artery was cannulated and the measured mean arterial pressure (MAP) and heart rate (HR) data served as preoperative baseline data. Patients received a second dose of fentanyl 5 μg kg^{-1} before surgical incision and additional doses of fentanyl 2 μg kg^{-1} when HR and/or MAP were 15% above the baseline values. At the end of surgery, the neuromuscular block was antagonized and the tracheal tube removed. Mechanical ventilation was continued in patients who required ventilatory assistance after surgery.

The anaesthetist and the surgeon then jointly computed the surgical stress score (SSS).[18] This measure takes into account seven items: amount of blood loss, site of surgery, amount of superficial trauma, extent of visceral trauma, duration of surgery, associated stress factors (hypothermia, localized or generalized infection, and prematurity) and cardiac surgery. The total scores in this study (excluding cardiac surgery and prematurity <35 weeks) could range from 3 to 24.

Directly after surgery, all patients received an i.v. loading dose of morphine hydrochloride 100 μg kg^{-1} in 2 min. For children in the CM group this was followed by a morphine infusion 10 μg kg^{-1} h^{-1}, combined with 3-hourly i.v. placebo (saline) boluses. Children in the IM group received 3-hourly i.v. morphine 30 μg kg^{-1}, combined with a continuous placebo infusion (saline). The amount of glucose and the volume of fluid was the same in both treatment groups. The clinical staff were blinded to the study group allocation until data collection was complete. The continuous infusion was started within 30 min after the loading dose; the first intermittent bolus (morphine or placebo) was given 3 h after surgery.

Pain was assessed by nurses trained in the use of the behavioural part of the COMFORT scale (CS),[19 20] the total score of which can range from 6 to 30, and a 0–10 visual analogue scale (VAS). The modified CS counts six behavioural items: alertness, calmness, respiratory response (for mechanically ventilated children) or crying (for non-ventilated children), movement, muscle tone and facial tension.[20] VAS scores were taken after the 2-min observation periods needed for the CS. Additional analgesia was given when there were signs of pain, indicated by VAS score ⩾4. During the first hour after surgery, one-third of the loading dose of morphine could be repeated every 15 min, and thereafter morphine 5 μg kg^{-1} every 10 min if required. Nursing interventions included pain assessment, blood sampling and administration of intermittent bolus (placebo or morphine) medication, and then nursing as needed. No other analgesic or sedative drugs were used. Arterial blood samples were taken after induction of anaesthesia (baseline), at the end of surgery, and at 6, 12,

and 24 h after surgery for measurement of blood gas values and plasma concentrations of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Respiratory depression was defined by the presence of apnoea or arterial Pa_{CO_2} $\geqslant$7.3 kPa in spontaneously breathing patients.[21] Blood samples were taken at time points corresponding with trough plasma morphine concentrations in the IM group.

Morphine and metabolite assay

The blood samples (1.4 ml) were centrifuged at 3000 rpm for 10 min and the serum was stored at –20°C until analysis. Serum aliquots (0.6 ml) were extracted with the Baker-10 extraction system (Baker Chemicals, Deventer, the Netherlands) fitted with 1-ml disposable cyclohexyl cartridges (Baker, Chemicals, Deventer, the Netherlands). The extraction column was conditioned with two column volumes methanol, two column volumes water and diammonium sulphate 1 ml 500 mM, pH 9.3. The serum (0.6 ml) was diluted with diammonium sulphate 0.6 ml 500 mM, pH 9.3 before being introduced into the extraction column. It was washed with diammonium sulphate 2 ml 50 mM, pH 9.3, after which it was allowed to dry for 15 s. The elution was carried out with KH_2PO_4 buffer 0.5 ml 0.01 M, pH 2.1 containing acetonitrile 11%. From this elute 50 µl was injected onto the analytical column.

The HPLC system comprised a Spectroflow 400 solvent delivery system (Kratos, Rotterdam, the Netherlands) equipped with a degasser (Separations, HI-Ambacht, the Netherlands), a Marathon auto sampler (Separations, HI-Ambacht, the Netherlands), a Spectroflow 773 UV detector at λ=210 nm (Separations, HI-Ambacht, the Netherlands), in sequence with an ESA electrochemical detector (ESA, Kratos, Rotterdam, the Netherlands) equipped with an analytical cell (Model 5010). All compounds leave the UV detector chemically intact and so the electrochemically active components can be oxidized in the electrochemical cell. This type of electrochemical cell contains two separate analytical cells, which makes it possible to create a small window of applied potential. The detector 2 potential was set at 0.4 V, while the detector 1 potential was 0.3 V. This minimizes interfering peaks because only compounds with an oxidation potential of 0.3–0.4 V are recorded. Chromatographic separations were achieved using a Cp-Sper C8 column (250×4.6 mm) (Chrompack, Bergen op Zoom, the Netherlands). The mobile phase was KH_2PO_4 buffer 0.01 M, pH 2.1 containing acetonitrile 11% and heptane sulphonic acid 0.4 g litre^{-1}.

For the measurement of M3G, M6G and morphine, calibration samples contained all three compounds. In serum, all three calibration graphs (six data points) were linear in the concentration ranges 25–580 ng ml^{-1} (r=0.9992) for M3G, 5–100 ng ml^{-1} (r=0.9982) for M6G and 5–90 ng ml^{-1} (r=0.9963) for morphine. The quantification limit was 5 ng ml^{-1} for morphine and M6G and 25 ng ml^{-1} for M3G. However, in individual samples, the chromatogram allowed for a lower threshold. As we used median values in this study, these are not affected by the values under the detection limit. In this concentration range, the intra- and inter-day precision was less than 10% for all compounds and the accuracy was about 5% (Table 1).[22 23]

Standardized automated laboratory analysers were used to measure plasma concentrations of bilirubin and creatinine.

Table 1 Intra-day (n=5) and inter-day (n=8) coefficients of variation (% CV) of spiked morphine and its metabolites in human serum *in vitro*. Accuracy is the ability to measure the quantity of the compound being determined. Precision: a method is precise if it yields the same results for a series of replicate determinations

	Compound	Concentration added (ng ml^{-1})	Concentration measured (ng ml^{-1})	Precision (% CV)	Accuracy (%)
Intra-day	M3G	574	561	1.8	2.3
		306	293	3.1	4.2
		158	161	1.9	1.9
	M6G	203	195	3.1	3.9
		108	101	5.0	6.5
		56	54	3.7	3.6
	Morphine	159	154	5.2	3.1
		85	80	6.3	5.9
		44	42	4.8	4.5
Inter-day	M3G	574	564	2.5	1.7
		306	299	3.4	2.3
		158	162	2.2	2.5
	M6G	203	201	3.7	1.0
		108	105	5.4	2.8
		56	56	5.4	0.0
	Morphine	159	156	4.4	1.9
		85	81	5.4	4.7
		44	43	3.9	2.3

M3G=morphine-3-glucuronide, M6G=morphine-6-glucuronide.

Table 2 Patient data and details of surgery in the four ages groups (I 0–4 weeks, II ⩾4–26 weeks, III ⩾26–52 weeks, IV ⩾1–3 yr). Data are mean (SD) unless stated otherwise

	Group I		**Group II**		**Group III**		**Group IV**	
	CM (*n*=31)	**IM (*n*=32)**	**CM (*n*=32)**	**IM (*n*=33)**	**CM (*n*=16)**	**IM (*n*=14)**	**CM (*n*=18)**	**IM (*n*=21)**
Median age (days) (range)	4 (0–28)	2 (0–17)	90 (29–173)	95 (30–179)	273 (185–351)	267 (187–330)	613 (368–1070)	574 (393–1067)
Study weight (kg)	3.2 (0.7)	2.9 (0.5)	5.0 (1.5)	4.7 (1.8)	6.9 (1.6)	7.3 (1.3)	11.1 (1.9)	11.1 (2.5)
Birth weight (kg)	3.1 (0.7)	2.9 (0.5)	2.9 (1.2)	2.7 (1.2)	2.7 (0.9)	2.6 (1.0)	2.7 (0.7)	3.1 (0.9)
Gestational age (weeks)	38 (3)	38 (2)	37 (4)	37 (5)	37 (5)	37 (5)	38 (2)	38 (3)
Boys/girls (*n*)	19/12	18/14	20/12	22/11	9/7	9/5	9/9	9/12
Plasma creatinine concentration (μmol litre^{-1})	46 (22)	47 (25)	26 (18)	23 (14)	31 (36)	54 (45)	28 (36)	27 (16)
Plasma total bilirubin (μmol litre^{-1})	91 (67)	108 (56)	23 (39)	35 (55)	15 (31)	7 (3)	6 (2)	7 (3)
Plasma bilirubin glucuronide concentration (μmol litre^{-1})	6 (4)	9 (8)	14 (26)	23 (42)	12 (32)	2 (1)	3 (1)	3 (1)
Mechanical ventilation before surgery (*n*)	10	5	3	0	0	0	0	0
Mechanical ventilation >24 h after surgery (*n*)	22	14	4	7	0	1	2	2
Surgical stress score	9.8 (2.9)	9.7 (2.8)	9.3 (3.3)	9.6 (2.5)	8.4 (3.1)	10.0 (2.8)	10.6 (2.9)	9.8 (3.5)
Surgery (*n*)								
Thoracic	1	8	6	4	0	2	5	1
Thoracic combined with abdominal	0	2	0	0	0	0	3	2
Abdominal high/low	19/11	7/13	6/19	8/19	8/8	3/9	6/2	5/9
Superficial	0	2	1	2	0	0	2	4

CM=continuous morphine, IM=intermittent morphine.

Statistical analysis

Relations between age and plasma concentrations of morphine, M3G and M6G were investigated using ANOVA. We applied multiple regression analysis to determine the effects of the gestational age, sex, birth weight, study weight, preoperative and postoperative mechanical ventilation, preoperative plasma concentrations of creatinine and total bilirubin, SSS, location of surgery, morphine treatment and a history of previous surgery, in addition to age on morphine requirements and plasma concentrations of morphine and its metabolites. In all analyses, the morphine and metabolite plasma concentrations were transformed logarithmically in order to approximate normal distribution. Relations between the various factors and the need (yes/no) for extra morphine were assessed by logistic regression analysis.

All 204 patients were included in an intention-to-treat analysis. Seven had to be excluded from morphine data analysis (4 in CM, 3 in IM): five had detectable morphine plasma concentrations at baseline as a result of previous morphine administration (congenital diaphragmatic hernia, *n*=4; meconium peritonitis, *n*=1), one patient died within 3 h after surgery (vessel loop and therapy-resistant pulmonary hypertension), and another patient required neuromuscular blockade after surgery (hemi-hepatectomy). Logistic and laboratory problems resulted in missing data for several of the 197 included patients. Spearman's rho was used for correlation coefficients and the other statistical tests used are given in the text. To control the α-error for the multiple statistical tests performed, the level of significance was set at P=0.01, instead of the conventional P=0.05. The power analysis for the comparative randomized trial was given in the original article.[17] In the present paper the effects of age and various other factors are investigated with respect to morphine requirements and plasma concentrations. With a study group of 200 infants, correlations as small as r=0.25 are detectable (α=0.01) with a power greater than 80%.

Results

Table 2 gives the clinical and surgical characteristics of the 197 enrolled patients, stratified by age group and randomized treatment group (97 in the CM group and 100 in the IM group).

Patient characteristics and clinical variables within the four age groups were similar in the two randomized groups. Although the surgical procedures varied, the age and treatment groups had similar SSS.

Table 3 Morphine requirements up to 24 h after surgery (group I 0–4 weeks, group II ⩾4–26 weeks, group III ⩾26–52 weeks, group IV ⩾1–3 yr). Values are percentages, or median (interquartile range). *P<0.001, group I *vs* groups II, III and IV; P=0.011 group II *vs* IV (χ^2-test). †P<0.001 group I *vs* groups II, III and IV (ANOVA). ‡Excluding the loading dose of 100 μg kg^{-1}

	Group I (n=63)	Group II (n=65)	Group III (n=30)	Group IV (n=39)
*Patients with extra morphine (%)	38	91	87	72
† ‡Morphine requirement (μg kg^{-1} h^{-1})	10.0 (10.0–10.7)	12.3 (10.6–16.6)	11.9 (10.4–15.3)	10.9 (10.0–14.3)

Overall, there were significant differences in the use of extra morphine between the age groups (P<0.001), but not between the treatment groups.

Table 3 shows the need for extra morphine and the total requirement for morphine (excluding the loading dose) in the four age groups. Only 38% of neonates (group I) required additional morphine, a significantly lower percentage than in all older age groups. Significantly more infants aged 4–26 weeks required additional morphine than the children aged 1–3 yr.

Multiple logistic regression analysis of all variables showed that age group, plasma concentrations of total bilirubin and the SSS were the most important factors affecting the need for additional morphine. The percentage of patients needing extra morphine was significantly higher in group II than in group I (91% *vs* 38%, P<0.001). In all age groups, increases in plasma bilirubin concentrations reduced the need for extra morphine (P=0.01) whereas a higher SSS increased the need for extra morphine (P=0.007).

During the first hour after the loading dose, the need for additional morphine was only related to age. A significantly higher percentage of patients in group II than in group I (P=0.01) needed extra morphine in this period. There was no consistency in the need for extra morphine during the first hour after surgery and/or between the other time periods (1–6, ⩾6–12, ⩾12–18 and ⩾18–24 h after surgery). Figure 1 shows the percentage of patients needing additional morphine during each of these periods.

The age of the child and type of morphine administration significantly affected the morphine dosage (kg^{-1} day^{-1}) required. However, inherent to the protocol design, the dosage in the CM group was always 30 μg kg^{-1} higher than in the IM group. Disregarding this in the CM group, there was no difference between the groups. Group I needed significantly less morphine than the other age groups (ANOVA, P<0.001) (Table 3).

Analysis of morphine plasma concentrations 6 h after surgery revealed a significant difference between age groups depending on the type of morphine administration. Therefore, the effect of age groups was evaluated within the treatment groups separately. Plasma concentrations at 12 and 24 h after surgery were no longer dependent on type of treatment.

Table 4 gives the plasma concentrations of morphine and its metabolites M3G and M6G, and the differences between

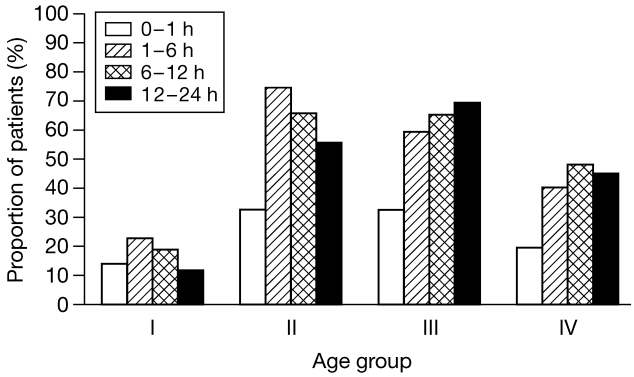

Fig 1 Percentages of patients in the four age groups (I 0–4 weeks, II ⩾4–26 weeks, III ⩾26–52 weeks, IV ⩾1–3 yr) needing additional morphine during the first 24 h after surgery.

age and treatment groups at 6, 12 and 24 h after surgery. Plasma concentrations were significantly higher in group I than in the other groups, and in group II *vs* group IV (Table 4). ANOVA showed that morphine plasma concentrations were significantly affected by the total morphine dose administered (P<0.001). Plasma morphine concentrations in the CM neonatal group (at 12 and 24 h after surgery) were significantly correlated with plasma creatinine concentrations (r=0.5, P=0.01; r=0.4, P=0.04, respectively), and with plasma bilirubin concentrations (both r=0.6, P=0.001).

Difficulties in detection of M3G plasma concentrations in the neonatal group (interfering spikes) resulted in many missing values for M3G in this group (n=32). ANOVA of M3G and M6G plasma concentrations revealed that the age group and the administered dosage of morphine significantly affected these plasma concentrations (both P<0.001). Although plasma concentrations of M3G and M6G were higher after CM than after IM, this difference was only significant for M3G at 6 h after surgery. M3G and M6G plasma concentrations were significantly higher in group I than in the other groups, and in group II *vs* group IV at 12 and 24 h after surgery (all P<0.001) (Table 4). M6G plasma concentrations correlated significantly with plasma creatinine only in the neonates, and only in CM at 12 and 24 h after surgery (r=0.5, P=0.01 and r=0.5, P=0.002, respectively). No such correlation was found for M3G.

Figure 2 shows the median plasma concentrations of morphine, M3G and M6G in the four age groups for CM and

Table 4 Plasma concentrations (ng ml^{-1}) of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) at 6, 12 and 24 h after surgery, according to age (group I 0–4 weeks, group II ⩾4–26 weeks, group III ⩾26–52 weeks, group IV ⩾1–3 yr) and treatment group. Data are median (interquartile range). *Age group I higher than all other age groups (CM and IM) ($P<0.001$); †Group II higher than IV (CM and IM) ($P<0.001$); **CM higher than IM in all age groups ($P<0.007$); ‡Group I higher than groups III and IV (CM and IM) ($P<0.003$) (ANOVA)

	Time after surgery (h)	Group I				Group II				Group III				Group IV			
		CM	*n*	IM	*n*	CM	*n*	IM	*n*	CM	*n*	IM	*n*	CM	*n*	IM	*n*
Morphine	6	25.0* (14.3–32.0)	29	16.5* (10.7–23.8)	28	8.5 (5.0–10.9)	28	5.7 (1.8–14.9)	27	8.6 (4.7–20.0)	14	2.9 (1.0–6.0)	14	5.2 (4.2–6.5)	18	1.0 (1.0–2.5)	17
	12	23.0* (12.0–31.0)	29	15.7* (9.6–22.8)	28	7.9† (5.5–12.3)	28	7.6† (2.0–17.8)	25	5.6 (4.7–10.0)	15	1.1 (1.0–12.7)	13	4.9 (3.8–5.7)	16	1.7 (1.0–5.0)	18
	24	22.0* (15.1–29.5)	29	15.4* (9.9–19.1)	25	7.4† (5.3–13.4)	27	7.5† (1.1–22.9)	24	6.4 (4.2–9.0)	15	1.0 (1.0–3.8)	13	4.8 (3.7–5.6)	17	2.3 (1.0–7.9)	17
M3G	6**	106.0‡ (63.0–151.0)	19	73.0‡ (39.3–87.8)	12	75.0† (53.0–123.8)	26	67.5† (40.0–101.5)	26	77.0 (52.5–116.5)	13	42.0 (22.1–75.8)	14	43.0 (31.0–61.0)	18	30.0 (16.7–55.0)	17
	12	105.0* (64.0–126.0)	19	73.5* (48.0–123.8)	12	77.0† (46.3–112.0)	26	58.0† (28.0–77.0)	23	56.0 (40.3–87.5)	14	26.0 (22.5–54.0)	13	34.0 (23.0–57.0)	16	26.5 (21.3–80.3)	18
	24	90.0* (67.0–116.0)	19	79.0* (46.0–131.0)	11	54.5† (34.8–102.8)	26	45.0† (30.5–69.0)	24	46.0 (38.3–71.8)	14	31.0 (19.8–37.5)	13	39.0 (28.5–51.0)	17	39.0 (18.3–69.0)	17
M6G	6	17.0* (12.8–23.5)	29	12.2* (8.9–16.0)	29	11.8† (8.3–21.0)	29	8.8† (6.0–14.7)	30	12.6 (7.8–17.1)	14	5.2 (3.7–11.1)	14	6.9 (4.5–8.8)	17	3.2 (2.1–6.1)	17
	12	18.6* (14.5–21.6)	29	14.6* (10.5–19.7)	29	12.6† (7.9–16.4)	29	10.8† (4.4–16.6)	27	7.8 (5.9–12.1)	15	4.9 (3.7–7.0)	13	6.2 (4.5–8.1)	15	4.9 (2.9–9.4)	17
	24	16.0* (12.6–21.6)	29	13.2* (10.3–19.0)	26	13.4† (7.0–17.5)	27	7.1† (4.5–12.5)	27	7.6 (6.1–10.9)	15	6.0 (3.6–6.6)	13	6.8 (4.8–10.6)	16	5.5 (2.8–10.7)	16

CM=continuous morphine; IM=intermittent morphine.

IM at 6, 12 and 24 h after surgery. Table 5 gives the ratios of morphine and its metabolites at 24 h after surgery, and the significant differences between age groups. The M6G/M ratio showed significant differences between age groups but not between the different treatments. The M6G/M ratio was lower in group I than in all other groups. Neither age nor treatment at any time point had any significant effect on the M6G/M3G ratio (Table 5).

Eleven spontaneous breathing patients (8 in the IM group, 3 in the CM group) developed postoperative respiratory insufficiency; seven of them required intubation (5 in the IM group, 2 in the CM group). Details of age, treatment, surgical procedure, requirement of morphine and complications are given in Table 6.

Table 7 gives an overview of studies reporting requirements and plasma concentrations of morphine after non-cardiac surgery, including the present data.[24–26]

Discussion

In this clinical study we investigated (i) the effects of various variables on the morphine dose required in infants, and (ii) the age-related changes in morphine and metabolite concentration. Age was the most important factor differentiating dose requirements between neonates and infants older than 4 weeks. In a recent meta-analysis, a continuous infusion rate of 7 μg kg^{-1} h^{-1} was calculated for term neonates, assuming a desired steady-state plasma concentration of 15 ng ml^{-1} for all ages.[27] Neonates in our current study received higher infusion rates and the concentrations are proportionally similar. Because more than 60% of the neonates had adequate analgesia with the minimal dose of 10 μg kg^{-1} h^{-1} (median concentration 22 ng ml^{-1}), it is likely that a lower dose of morphine would have sufficed for the neonates. Significantly more morphine was used in the older children, with requirements ranging from (median) 10.9 to 12.3 μg kg^{-1} h^{-1}. Even with the additional morphine, the required dose was lower than the recommended dosage of 20 μg kg^{-1} h^{-1}.[27–31] Remarkably, of the age groups older than 4 weeks, children aged 1–3 yr needed the lowest dosage of morphine (NS). They also had the lowest plasma concentrations of morphine, which suggests that their clearance was the highest.

Because concentration is directly proportional to dose, we need to determine clearance in order to predict dose. The wide range of neonatal plasma concentrations reported in the literature was as expected, given the variability in interindividual clearance (Table 7). In our study, plasma concentrations of morphine in neonates (n=63) provided adequate analgesia between 15.4 (trough) and 22 ng ml^{-1}, and, in infants older than 4 weeks (n=134), between 1.0 and 7.5 ng ml^{-1}. These low plasma concentrations of morphine apparently produced effective analgesia, as evidenced by the low postoperative CS and VAS scores. It seems that plasma concentrations as high as 15 ng ml^{-1} are not necessary for adequate postoperative analgesia in infants >4 weeks of age. Although at the time of surgery all patients had been without morphine therapy for more than 6 h, plasma morphine was still detectable in five neonates. This indicates that clearance in this age group is low (approxi-

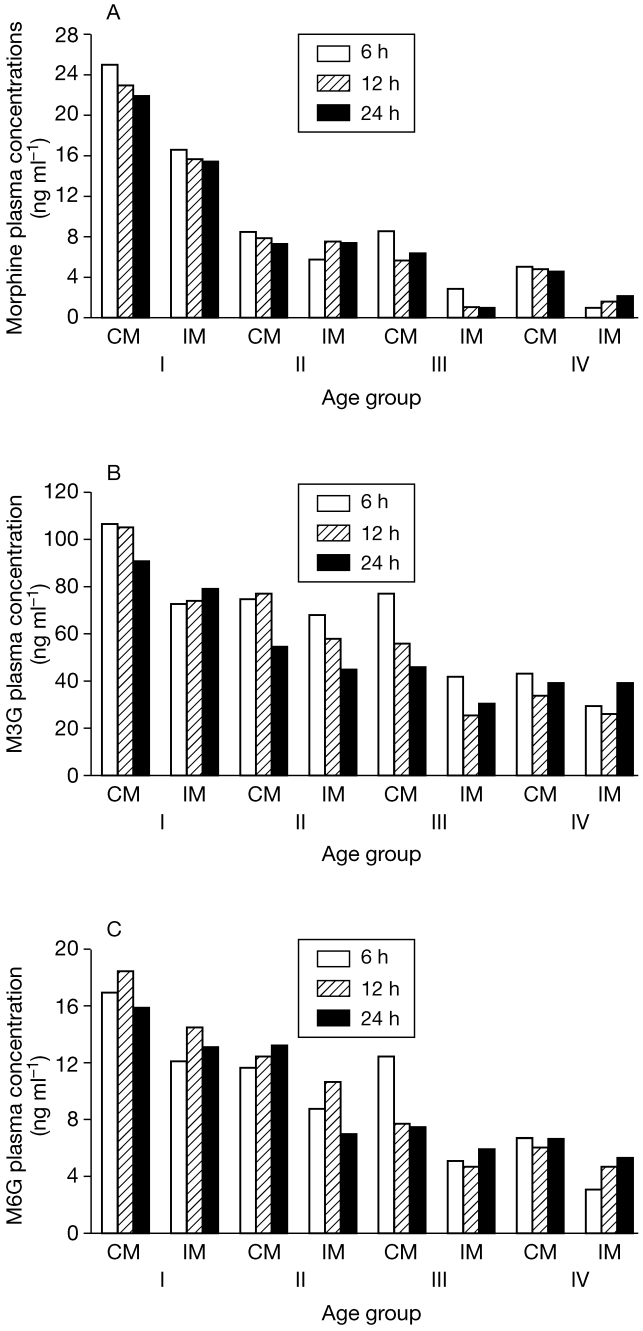

Fig 2 (A) Morphine, (B) morphine-3-glucuronide (M3G) and (C) morphine-6-glucuronide (M6G) plasma concentrations (median) in the four age groups (I 0–4 weeks, II ⩾4–26 weeks, III ⩾26–52 weeks, IV ⩾1–3 yr) at 6, 12 and 24 h after surgery. CM=continuous morphine, IM=intermittent morphine.

mately 9 ml kg^{-1} min^{-1}).[9] Plasma morphine concentrations were significantly dependent on age, bearing in mind that patients with renal impairment were not included. Differences between treatment groups were only found at 6 h after surgery. Extra morphine dosages, given by nurses on the basis of observational pain scores, resulted in similar plasma concentrations in CM and IM from 12 h after surgery. In the CM group, median concentrations decreased from 7.4 to 6.4 to 4.8 ng ml^{-1} with increasing age in groups II, III and IV. These data are consistent with an increase in plasma clearance over the age range investigated.

Plasma concentrations of morphine that should produce effective analgesia in neonates and older children have been reported to range from 3.8 (SD 2.5) to 125 (9) ng ml^{-1}.[26 32–34] This wide range results from the various pain stimuli or sedation end-points, differences in pain perception and pain assessment, and variations in the children's clinical state (severe illness, mechanical ventilation, needing sedation or analgesia, tolerance, etc.). As reported earlier, the relation between morphine requirement and plasma concentrations is also dependent on the type of surgery, which leads to different results after cardiac or non-cardiac surgery.[6 34]

Morphine is mainly metabolized in the liver into M3G and M6G by uridine diphosphate glucuronyltransferase (UDG2B7). The kidneys excrete these metabolites, as well as a portion of the unchanged morphine. Developmental maturation, associated with increasing renal clearance and decreasing drug half-life, starts in the early neonatal period and goes on for 2 yr. Using the three-quarters power model, adult levels of clearance were reached at an earlier age (2–6 months).[35]

High morphine plasma concentrations and low M3G/M and M6G/M ratios, as were found in the neonates, might indicate a low glucuronidation capability. However, from 12 h after surgery, the highest plasma concentrations of M3G and M6G were found in the neonates, showing that they were able to glucuronidate morphine. Nevertheless, hepatic induction of these enzyme systems cannot be ruled out. The high plasma concentrations of morphine metabolites in the neonates were the result of low renal clearance, which was confirmed by the significant correlation between serum creatinine and M6G in this age group. The decreased clearance of morphine explains its increased analgesic effect in neonates, contributed to by the active metabolite M6G. While the M3G/M and M6G/M ratios increased with age, indicating improved morphine metabolism, the M3G and M6G plasma concentrations decreased with age, indicating improved renal excretion, as reported in other studies as well.[7 34 36 37]

In the present study, plasma concentrations of morphine and morphine metabolites were not only significantly different between neonates (group I) and the older children (groups II, III and IV), but also between infants aged 4–26 weeks (group II, median age 3 months) and 1–3 yr (group IV, median age 20 months). The major changes in morphine metabolism and elimination apparently take place in the first 3 months after birth, and only minor differences in morphine clearance are found after that age. The development of the glucuronidation capability and the renal function might have resulted in lower plasma concentrations of morphine in the older children. Clinical effects, however, may be more dependent on the concentrations in brain tissue, receptor characteristics[14] and other factors.

Table 5 Ratios of metabolites (morphine-3-glucuronide, M3G; morphine-6-glucuronide, M6G) and morphine (M) 24 h after surgery (group I 0–4 weeks, group II ⩾4–26 weeks, group III ⩾26–52 weeks, group IV ⩾1–3 yr). *P<0.003 group I *vs* groups III and IV; P=0.03 group I *vs* group II (CM and IM) (ANOVA). Values are median (interquartile range)

	Group I			Group II			Group III			Group IV		
	CM	IM	*n*	CM	IM	*n*	CM	IM	*n*	CM	IM	*n*
M3G/M ratio	5.2 (2.9–11.6)	7.0 (3.0–11.9)	28	8.6 (7.8–10.3)	9.6 (2.4–20.0)	47	8.0 (5.5–14.5)	15.7 (7.4–27.5)	27	9.1 (5.0–11.0)	16.7 (6.1–27.6)	34
M6G/M ratio	0.8* (0.5–1.7)	1.1 (0.7–1.5)	52	1.5 (1.2–2.1)	1.9 (0.5–3.8)	50	1.5 (0.9–2.3)	3.4 (1.1–5.9)	28	1.4 (1.0–2.1)	2.5 (1.3–4.6)	32
M6G/M3G ratio	0.22 (0.16–0.23)	0.17 (0.13–0.25)	30	0.18 (0.15–0.23)	0.17 (0.15–0.21)	49	0.18 (0.15–0.19)	0.19 (0.16–0.24)	27	0.18 (0.16–0.22)	0.16 (0.14–0.19)	32

CM=continuous morphine, IM=intermittent morphine.

Table 6 Data of 11 patients with respiratory insufficiency during the first 24 h after surgery

Age (days)	CM/IM	Diagnosis	Complications	Extra morphine (Y/N)	Mean dose morphine (μg kg^{-1} h^{-1})	Re-intubation? Y/N	Hr after surgery	Comments
1	IM	Exstrophy of the bladder	Apnoea	N	10	Y	6	Bryant's traction
1	IM	Jejunal atresia	Apnoea	N	10	Y	<4	30 min after morphine bolus
2	IM	Tracheo-oesophageal atresia	Respiratory obstruction	N	10	Y	21	Failed extubation
3	IM	Tracheo-oesophageal atresia	Respiratory obstruction	N	10	Y	15	Failed extubation
4	IM	Duodenal atresia	P_{CO_2} increased (8.9 and 8.3 kPa at 6 and 12 h after surgery)	N	10	N		Down's syndrome
54	CM	Neuroblastoma	Apnoea	Y	10.2	Y	6	
61	CM	Ileus	Apnoea	Y	22.2	Y	6	High pain scores; 100 μg kg^{-1}extra morphine in 3 h
78	IM	Rehbein resection	P_{CO_2} increased (8.4 kPa at 6 h after surgery)	Y	10.7	N		
90	IM	Nissen fundoplication	Inspiratory and expiratory stridor 2 h after surgery	Y	10.4	Y	< 4	
102	IM	Bilobectomy	P_{CO_2} increased (7.4 and 7.5 kPa at 6 and 12 h after surgery)	Y	11.7	N		Pneumonia
831	CM	Neuroblastoma	Apnoea	N	10	N	12	Morphine stopped at 12 h after surgery

CM=continuous morphine, IM=intermittent morphine, M=morphine.

Reported correlations between metabolite/morphine ratios and gestational age or birth weight are controversial. M3G/M and M6G/M ratios increased with increasing birth weight[37 38] and gestational age[38] (glucuronidation capability increases), which was not found by Barrett and colleagues.[39] The disparity in plasma morphine glucuronide ratios between the different studies could be a result of the varying number of patients in the individual studies, differences in gestational age and study age, in detection limits of metabolites, and in the duration of morphine infusions and the time of sampling. Because M3G and M6G have long half-lives in neonates[39] (impaired renal function), it is suggestive that in neonates the M6G/M and M3G/M ratios are increasing with increased periods of morphine infusion.

In a review examining the effects of age, renal impairment and route of administration on morphine metabolism, Faura and colleagues[7] reported a consistently high correlation between M6G and M3G, with a ratio of about 15% in neonates and children, as in adults. Across all studies, the range of the ratios of metabolites to morphine was wide. However, there was almost complete overlap between children (>1 month) and adults, but neonates (<1 month) had discernibly lower ratios for both metabolites. Although

Table 7 Overview of morphine requirements and plasma concentrations of morphine in term neonates and infants after non-cardiac surgery in earlier studies and the present study

Age	*n*	Loading dose or single dose (S) ($\mu g\ kg^{-1}$)	Dosage M infusion ($\mu g\ kg^{-1}\ h^{-1}$)	Plasma concentration morphine ($ng\ ml^{-1}$)	Comments	References
Earlier studies:						
1–7 days	4	50	7–11	18.9 (15.0–29.0) median (range)	At steady state	Lynn *et al.* [24]
31–90 days	6	50	13–19	9.1 (6.5–14.5) median (range)		Lynn *et al.* [24]
91–180 days	6	50	17–25	10.5 (7.0–22.0) median (range)		Lynn *et al.* [24]
180–380 days	10	50	25–35	10.0 (6.0–17.0) median (range)		Lynn *et al.* [24]
1–18 days	20	50	15	39.0 (23.0) mean (SD)	At steady state	Farrington *et al.* [25]
0–6 months	5	mean 150 (S)		26.2 (22.5) mean (SD)	129 min after M dose	Olkkola *et al.* [26]
2–4 years	5	150 (S)		3.8 (2.3) mean (SD)	189 min after M dose	Olkkola *et al.* [26]
Present study (CM group only)						
0–4 weeks	31	100	10.8 (mean)	22.0 (15.1–29.5) median (IQR)	At 24 h after start of M	Present study
⩾1–6 months	32	100	15.7 (mean)	7.4 (5.3–13.4) median (IQR)		
⩾6–12 months	16	100	16.7 (mean)	6.4 (4.2–9.0) median (IQR)		
⩾1–3 years	18	100	12.1 (mean)	4.8 (3.7–56) median (IQR)		

M=morphine, *n*=number of patients, IQR=interquartile range.

the number of neonates and children was small compared with that of adults (49, 90 and 1073, respectively), the M3G/M6G ratio remained constant in all subgroups (including neonates, children and adults, patients with renal impairment, and different routes of administration).

In the present study, neonates differed significantly from the older children in median M6G/M ratio (P=0.003) but there were no significant differences between the three older age groups. The M6G/M3G ratio at 24 h after i.v. morphine was not significantly different between the four age groups (0–3 yr).

Although the data are difficult to compare (median *vs* mean weighted values[7]), both studies result in similar conclusions: (i) neonates differ significantly from older patients (children and adults, respectively), having an immature morphine metabolism; (ii) children older than 4 weeks metabolize morphine like older children, as presented in our study, and like adults;[7] and (iii) the M6G/M3G ratio remains constant at all ages.

Hartley and colleagues[37] reported decreasing M6G/M3G plasma ratios, although not significantly, with increasing birth weight. This might suggest a differential development of enzymes (UGT2B7) for the formation of M3G and M6G. Recently, it was shown that UGT2B7 is responsible for the glucuronidation of morphine and is capable of catalysing the glucuronidation of both the 3- and 6-hydroxyl moieties on these molecules.[40 41] However, polymorphism in the coding sequence, as well as in the 5′-flanking region, may affect the rate of morphine glucuronidation and can result in individual differences.[42]

The SSS was developed as a measure of the severity of surgical stress.[18] Although in the present study the scores did not differ significantly between age or treatment groups, multiple regression analysis showed that they significantly influenced the dosage of morphine required. In the absence of other methods that can directly measure postoperative pain across different age groups, the SSS may help to assess the need for postoperative morphine.

Eight of the 11 children who showed respiratory insufficiency were in the IM treatment group. In most of these patients respiratory depression could not be attributed to the morphine therapy but had to be considered as a complication of their surgical operation.

In conclusion, age is the most important factor in morphine requirement and morphine metabolism. In our previous study investigating the effect of CM and IM on surgical stress responses in the same patient population, infants aged 1–3 yr in the IM group showed greater stress than those in the CM group.[17] Combining the results of both studies, we conclude that morphine given intermittently does not provide any clinical advantages and that a continuous morphine infusion is probably safer in neonates and more effective in older infants. By stratifying for age and carefully monitoring the children's behaviour, we were able to give more precise dosages for postoperative morphine after major non-cardiac surgery. We agree with the recommended dosage for continuous morphine infusions of 7 $\mu g\ kg^{-1}\ h^{-1}$ in full-term neonates.[27] However, we would advise starting with an infusion rate of 10 $\mu g\ kg^{-1}\ h^{-1}$ in infants >4 weeks of age. Differences in developmental maturation between neonates and infants indicate the need for individual drug dosages. Increase of the infusion rates should only be based on pain scoring by trained nurses, in order to prevent overdosing.

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