PAEDIATRIC PAIN MANAGEMENT:

FROM PERSONAL-BIASED TO EVIDENCE-BASED

BEHANDELING VAN PIJN BIJ JONGE KINDEREN:
VAN PERSOONLIJKE INDRUK NAAR WETENSCHAPPELIJK INZICHT

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aan Adrie
aan mijn ouders

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Chapter 1

Introduction

partly based on:

Are postoperative pain instruments useful for specific groups of vulnerable infants?
Monique van Dijk, Jeroen W.B. Peters, Nancy J. Bouwmeester, Dick Tibboel
Clin in Perinatology (2002) volume 29, issue 3 page 469-491.

1.1 Pain and pain management in neonates and infants

Development of pain pathways and mechanism

Since 1965, the most plausible theory about the mechanism of pain was proposed by Melzack and Wall.[1] They proposed that the substantia gelatinosa functioned as a gate control system that modulates the afferent stimuli before they influence the transmission cells, and that the gate control system was influenced by central neural modulators. Pain phenomena would be determined by interactions among these systems. Numerous lines of evidence suggest that even in the human foetus, pain pathways as well as cortical and subcortical centres necessary for pain perception are well developed late in gestation. The neurochemical systems now known to be associated with pain transmission and modulation are intact and functional. In adults the cutaneous flexor reflex is correlated with sensory input and corresponds with pain perception. Similar thresholds are documented in neonates, but with thresholds much lower than in adults. The thresholds are even lower in preterm neonates less than 30 weeks and increases of these thresholds are correlated with postconceptional age.[2] Probably the immaturity of the segmental control mechanisms within the spinal cord and the absence of descending inhibitory pathways cause this. During the perinatal period a number of endogenous pain control systems is developing, which means that the nociceptive input becomes under more control with increasing postnatal age. From a bio-evolutionary perspective, neonates should experience pain. At birth, the in utero protection disappears and pain perception is essential for adaptive responses to tissue damage and life threatening events, just as in adults. As such, pain can be considered as "biologically meaningful".[3]

Effects of pain stimuli

Already in 1984 Randich and Maixner[4] demonstrated that systems controlling cardiovascular function are closely coupled to systems modulating the perception of pain. Surgical stress activates neural pathways to the hypothalamic area, which stimulates the secretion of pituitary hormones.[5] The release of stress hormones: catecholamines, corticosteroids, growth hormone and glucagon, stimulates a cascade of metabolic changes leading to the breakdown of protein, fat and carbohydrate stores. Although short periods of stress can be useful as preparation to " fight or flight ", a continuing release of stress products is harmful. It can lead to a catabolic situation, preventing repair of the injured tissues, and in some patients to multi-system organ failure.[6,7] In neonates, metabolic stability is more difficult to maintain because of the greater heat loss due to a relatively greater surface area, much smaller reserves of protein, carbohydrate and fat, the

immaturity of metabolic enzymes and controlling systems, and the increased oxygen demand due to a higher metabolism. The metabolic vulnerability in neonates is associated with greater stress responses to surgery as compared with adults.[8,9] Awake circumcision,[10] awake intubation[11] and tracheal suction,[12] are procedures documented to result in large fluctuations of transcutaneous pO_2, increases in heart rate, arterial blood pressure and intracranial pressure.

Although more neonates and infants underwent major surgery during the last twenty years, as result of an increased knowledge and improved technical possibilities in paediatric surgery and anaesthesia, only a few studies investigated the effects of analgesia on surgical stress responses in this age group (Chapter 2). Anand and coworkers reported as first the effects of analgesia on surgical stress in premature neonates. Besides decreased stress responses, the most important result of adequate analgesia was the lower incidence of morbidity and mortality.[13,14] Attenuation of the deleterious effects of pathologic stress responses by the use of various anaesthetic techniques has also been well demonstrated during minor surgery and invasive procedures. The use of local anaesthetics or opioids abolished the adverse effects during lower abdominal surgery,[15] circumcision,[16] and intubation.[17] These studies had a great impact on the next generation of caregivers.

Surgical stress score

In an attempt to evaluate the magnitude of surgical stress a scoring method was developed. The so-called surgical stress score (SSS) was based on the amount of blood loss, superficial dissection and visceral trauma, the site and duration of surgery, cardiac surgical factors and associated stress factors for surgical neonates (hypothermia, prematurity, sepsis).[18] The SSS was found to predict minor, moderate and severe stress groups as measured by hormonal metabolic stress responses. Changes in plasma epinephrine, blood glucose and total gluconeogenic substrates at the end of surgery, and at 6 hrs postoperative produced the greatest discrimination between the three stress groups. Clinical outcome following surgery was also significantly different between the three stress groups as mentioned above.

Sensitization

Ongoing nociceptive stimuli, especially in preterm neonates, can result in sensitization.[19] Peptides such as Substance P (SP), and excitatory amino acids (EAA) such as glutamate and aspartate, are released by repeated stimulation of A and C fibres. Interactions of SP and EAA influence the transmission of pain stimuli from the spinal cord to the brain, which is controlled by supraspinal systems. Ongoing painful stimuli (tissue damage, repeated heel lancing in the very low preterm neonates, nerve dysfunction, surgery) or an

insufficient supraspinal inhibition, as in case of premature neonates, can activate the NMDA receptor, which results in wind up in the spinal neurones and hypersensitivity. Ultimately the wind up may end in a so-called neuropathic pain state, such as spontaneous pain, hyperalgesia to a normal pain stimulus, or allodynia, where non-painful stimuli such as touch are painful. NMDA activity can be blocked by NMDA-receptor antagonists (ketamine, dextromethorphan),[20,21] by peripheral or spinal nerve blocks with local anaesthetics and, to a lesser extent, by opioids. Low doses of morphine block the dorsal horn neuronal excitation in response to normal C fiber input, however, ten-fold higher doses of morphine are required once the reflex withdrawal is established.[22]
Hence, to guard against NMDA activity with all the consequences described earlier, nociceptive stimuli have to be blocked at an early stage. So prevention of pain is the best way of pain treatment, which can be attained by the use of pre-emptive analgesia.

Analgesia after major surgery
After major surgery pain has to be treated with opioids. This is necessary in adults, but also in neonates, infants and children.

Opioids
Opioids act differently in stressed and unstressed situations. Opioids given to unstressed subjects, stimulate secretion of corticotropin releasing factor (CRF) and increase plasma catacholamines. Noradrenergic transmission originating in the locus coeruleus is most likely to play the primary causal role in the expression of physical dependence on morphine.[23]
During pain and stress, opioids, and the endogenously released beta-endorphin, reduce the nociceptive input into the hypothalamus, lessen the CRF response and reduce the normal catecholamine rise.[24]
As a consequence, in the clinical situation, to maintain homeostasis, the severity of experienced stress is determining for the need of opioids. This finding directly challenges the previous practice of providing minimal anaesthesia for neonates based on concerns about the respiratory and hemodynamic side effects of opioids.[25,26]

How to treat pain after major surgery in neonates and infants?
The most popular opioid after major surgery is morphine. However, little is known about requirements and effects of analgesics in neonates and infants in the postoperative period. While insufficient analgesia can give rise to stress responses with an increased morbidity, as mentioned above, high doses of opioids will give an unwanted deep sedation with a possible need for prolonged mechanical ventilation and intensive care (Chapter 3).

Morphine

Morphine, an alkaloid obtained from opium, is frequently used as a postoperative analgesic drug in neonates, infants and children. Morphine is mainly metabolized by the enzyme uridine diphospho-glucuronyl transferase, type 2B7 (UDGT2B7), into the active metabolite morphine-6-glucuronide (M6G) and into morphine-3-glucuronide (M3G) [27 28]. UDGT2B7 is found in the liver, kidney, intestines and other organs. Morphine and M6G have both analgesic and respiratory depressive effects. In some studies M6G in the same doses as morphine produced even a greater degree of analgesia,[29,30] but the claim that M6G has less respiratory depression potential has not been proven.[31,32] M3G, however, does not bind to opioid receptors and may antagonize the antinociceptive effects as well as the ventilatory depression.[33] A small part of morphine, depending on age, is metabolized by sulphation or is eliminated as free, unbound morphine.[34,35] Most of the metabolites are eliminated by the kidney, a small part by biliary excretion.

Although the analgesic effect is dependent on the concentrations of morphine and M6G at the μ-receptor in the CNS, in clinical practice, morphine requirement is generally related to the plasma concentration. These concentrations, however, are not only depending on the administered dosage, but especially on pharmacokinetic factors such as administration route, clearance and volume of distribution.[34,36-46]

Age, hepatic and renal function and clinical state of the patient (cardiac function, septic condition) affect these latter two parameters. These data were investigated using a population based approach that included size as the primary covariate in an effort to disentangle age related factors from size related factors[47] (Chapter 4).

Besides pharmacokinetics, pharmacodynamics determines the effect of a drug. Maturation of the central nervous system,[48,49] earlier experiences of pain,[50] and psychological factors (surrounding, social and cultural background)[51] may all effect pharmacodynamics. Analgesic morphine plasma concentrations in neonates and older children have been reported to range from 3.8 (± 2.5) to 125 (± 9) ng/ml[34,40,52-55] This wide variation is dependent on the pain stimulus or sedation end-point, differences in pain perception and pain assessment, and the variation in clinical state of the child (severe illness, type of surgery, mechanically ventilated, tolerance, etc.). For this reason we limited our study population to neonates and infants, stratified for age, admitted to the Surgical Intensive Care Unit following major non-cardiac surgery. A subanalysis was performed in the neonates (0-28 days of age), stratified for age in ≤ 7 days and > 7 days, to provide more detailed information in this fast developing age group (Chapter 5).

Pain measurement instruments

The advanced medical technology, necessary to keep premature and severely handicapped infants alive, has led to an increasing demand for measurement methods of sustained pain in these groups of children. Improvements in paediatric surgery, anaesthesia and intensive care resulted in an increasing number of surgical procedures in non-verbal children. Evaluation of the effect of analgesics is essential in daily clinical practice and has to be performed by validated pain measurements. The choice of an instrument for measuring pain in children is strongly dependent on the child's cognitive development. It is generally accepted that self-report measures can not be obtained from children younger than 4 years of age. Observation of behaviour is, therefore, the most suitable method for evaluation of the child's pain. Another approach for measuring pain in infants consists of the registration of changes in physiological parameters, such as increments and variability in heart rate and blood pressure, lowering of respiration rate, palmar sweating, and increased levels of catecholamines. Multidimensional instruments are characterized by using both behavioural as well physiological indicators of pain. Although physiological and behavioural measures can give relevant information on the intensity of pain when self-report is not possible, these measures, taken separately, do not discriminate very well between pain and other reactions of stress, such as anxiety or hunger.[56] In addition, most physiological measures require sophisticated equipment or invasive procedures, and are therefore only applicable in medical situations in which these are used routinely, such as in intensive care environments.
An example of a multidimensional instrument is the COMFORT Scale (CS). The CS was originally designed to assess distress in infants in paediatric intensive care units. The scale consists of 6 behavioural items (alertness, calmness, respiratory response, movement, muscle tone, and facial tension) and 2 physiological items (heart rate, mean blood pressure). The raters observe the patient for two minutes. Each item can be scored on a 5-point rating scale.[57,58] In the Sophia Children's Hospital the CS was introduced to develop a validated instrument for postoperative pain measurement in non-verbal children (Chapter 6).

Evolution of pain management in the Sophia Children's Hospital

Till 1987, in the Sophia Children's Hospital, surgical neonates and infants received morphine or paracetamol for postoperative pain on an intermittent basis (rectally, intravenously or intramuscularly). Pain prescriptions were ordered as needed, and nurses had to decide by personal interpretation how often analgesics were administered. In 1987, following the Royal Children's Hospital of Melbourne, the way of morphine administration in the PICU was changed into i.v. continuous morphine infusions.[59] Unfortunately, due to the lack of validated instruments for assessment of postoperative pain in non-verbal

children, it was impossible at that time to test the difference between both ways of morphine administration. After the introduction of a validated pain score combined with an algorithm for pain management, pain management based on objective validated pain scores became daily standard care (Chapter 7).
Table 1 gives an overview of studies reporting requirements and plasma concentrations of morphine after non-cardiac surgery, with or without the use of a pain assessment scale.

Need for a study
The introduction of continuous morphine infusions about a decade ago without proper evaluation of its effects, together with the evolution of pain assessment instruments prompted us to design a study with the following research questions:

1. How reliable, valid and feasible is the multidimensional COMFORT scale to assess postoperative pain in neonates and infants < 3 years of age?
   The clinical utility and validity of the CS as postoperative pain measurement was tested comparing the old and new way of morphine administration [intravenously, as 3-hourly intermittent boluses (IM) or as continuous infusion (CM)], in four developmentally relevant age groups < 3 years of age. The Visual Analogue Scale (VAS), developed as self-report measurement,[61] was used as an observational instrument,[62] to test the concurrent validity of the COMFORT scale. The VAS scores were assigned after the 2 min of observation needed for the CS. Pain was indicated by VAS scores ≥ 4.
   The COMFORT scale was adapted for the Netherlands and its behavioural part has been proven to be a valid instrument for measurement of postoperative pain in neonates and infants after major surgery[63,64] (PhD thesis M. van Dijk).
2. Is there an improved efficacy and safety of postoperative analgesia with continuous morphine infusions compared with intermittent doses, in neonates and infants after major surgery?

1.2 Scope of this thesis

Chapter 2 reports the efficacy of continuous morphine versus intermittent morphine through hormonal-metabolic responses (plasma concentrations of epinephrine, norepinephrine, insulin, glucose, lactate), and hemodynamic responses (heart rate, mean arterial pressure) to postoperative pain in children aged 0-3 years. Safety was determined by the incidence of respiratory depression, because this is the most dangerous complication of opioid therapy.

Table 1 Overview of morphine requirements and plasma concentrations in term neonates and infants after non-cardiac surgery

Age	*n*	Loading dose or single dose (μg/kg)	Dosage M infusion (μg/kg/h)	Plasma concentration morphine (ng/ml)	Pain score	Time	Reference
Earlier studies							
1-7 days	4	50 (L)	7-11	18.9 (15.0-29.0) median (range)	Buchholz[60]	At steady state	Lynn et al.[37]
31-90 days	6	50 (L)	13-19	9.1 (6.5-14.5) median (range)	Buchholz[60]	At steady state	Lynn et al.[37]
91-180 days	6	50 (L)	17-25	10.5 (7.0-22.0) median (range)	Buchholz[60]	At steady state	Lynn et al.[37]
180-380 days	10	50 (L)	25-35	10.0 (6.0-17.0) median (range)	Buchholz[60]	At steady state	Lynn et al.[37]
1-18 days	20	50 (L)	15	39.0 (23.0) mean (SD)	Not standardized	At steady state	Farrington[46]
0 to 6 months	5	150 (S)		26.2 (22.5) mean (SD)	Not standardized	129 min after M	Olkkola[55]
2-4 years	5	150 (S)		3.8 (2.3) mean (SD)	Not standardized	189 min after M	Olkkola[55]
Present study							
0-4 weeks	31	100	10.8 (1.4) mean (SD)	22.0 (15.1-29.5) median (IQR)	CS (van Dijk)[63]	24 h after start of M	Bouwmeester et al.
4-26 weeks	32	100	15.7 (7.5) mean (SD)	7.4 (5.3-13.4) median (IQR)	CS (van Dijk)[63]	24 h after start of M	Bouwmeester et al.
26-52 weeks	16	100	16.7 (10.8) mean (SD)	6.4 (4.2-9.0) median (IQR)	CS (van Dijk)[63]	24 h after start of M	Bouwmeester et al.
1-3 years	18	100	12.1 (3.5) mean (SD)	4.8 (3.7-56) median (IQR)	CS (van Dijk)[63]	24 h after start of M	Bouwmeester et al.

M = morphine; n = number; (L) = loading dose; (S) = single dose; SD = standard deviation; IQR = interquartile range; CS = COMFORT Score.

Chapter 3 describes the effects of treatment (continuous morphine versus intermittent morphine) and the effects of age on morphine metabolism by analysis of plasma concentrations of morphine, morphine-3-glucuronide, morphine-6-glucuronide and the ratios of M3G/M, M6G/M and M6G/M3G.

Chapter 4 describes the developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. In an effort to disentangle age-related factors from size-related factors, a population-based approach was used that included size as the first covariate.

Chapter 5 describes the age-related differences in morphine requirements and metabolism in the postoperative neonate. Neonates are defined as aged < 28 postnatal days. Dosage recommendations for postoperative morphine in neonates ≤ 7 days and > 7 days of age are given. Further findings from this study suggest that neonates on mechanical ventilation have a slower morphine metabolism than non-ventilated neonates.

Chapter 6 describes the efficacy of postoperative intermittent and continuous morphine through behavioural responses (VAS and COMFORT scale) to postoperative pain in children aged 0-3 years. The repeated COMFORT "behaviour" and VAS pain scores were compared between the two treatment groups.

Chapter 7 describes the process of changing postoperative pain treatment in the surgical ICU of the Sophia Children's Hospital, from 1985 up to the present. The effects of the change from morphine as needed into morphine continuously, and the introduction of routine pain assessment with a validated pain scale, on morphine requirements and the duration of mechanical ventilation, are described in one diagnostic category of surgical neonates, i.e. neonates with oesophageal atresia with primary anastomosis.

Chapter 8 contains a general discussion and options for future pain management.

1.3 References

1. Melzack R, Wall PD. Pain mechanism: a new theory. Science 1965;150:971-978.
2. Fitzgerald M. Development of pain pathways and mechanisms. In: Anand KJS and McGrath PJ. (eds). Pain in neonates; Pain Res Clin Manag 5:19-37; Elsevier Science Publishers, Amsterdam, 1993.
3. Craig KD, Grunau RVE. Neonatal pain perception and behavioral measurement. In: Anand KJS, McGrath PJ, eds. Pain in neonates.Amsterdam: Elsevier, 1993:67-105.
4. Randich A, Maixner W. Interactions between cardiovascular and pain regulatory systems. Neurosci Biobehav Rev 1984; 8:343-367.
5. Buckingham JC. Hypothalamo-pituitary responses to trauma. Br Med Bulletin1985;41:203-211.
6. Kehlet H. Surgical stress: the role of pain and analgesia. Br J Anaesth 1989;63:189-195.
7. Frayn KN. Hormonal control of metabolism in trauma and sepsis. Clin Endocr 1986;24:577-599.
8. Anand KJS . The stress response to surgical trauma: from physiological basis to therapeutic implications. Prog Food Nutr Sci 1986;10:67-132.
9. Anand KJS. Clinical importance of pain and stress in preterm neonates. Biol Neonate 1998;73:1-9.
10. Rawlings DJ, Millar PA, Engel RR. The effect of circumcision on transcutaneous pO2 in term infants. Am J Dis Child 1980;134:676-678.
11. Raju TNK, Vidyasagar D, Torres C, Grundy D, Bennett EJ. Intracranial pressure during intubation and anesthesia in infants. J Pediatr 1980;96:860-862.
12. Hickey PR, Hansen DD, Wessel DL, Lang P, Jonas RA, Elixson EM. Blunting of stress responses in the pulmonary circulation of infants by fentanyl. Anesth Analg 1985;64:1137-1142.
13. Anand KJS, Sippell WG, Aynsley-Green A. Randomized trial of fentanyl anesthesia in preterm babies undergoing surgery: effects on the stress response. Lancet 1987;1:243-248.
14. Anand KJS, Hickey PR. Halothane-Morphine compared with high dose sufentanil for anaesthesia and postoperative analgesia in neonatal cardiac surgery. New Engl J Med 1992;326:1-9.
15. Wolf AR, Eyres RL, Laussen PC, et al. Effect of extradural analgesia on stress responses to abdominal surgery in infants. Br J Anaesth 1993;70:654-660.
16. Holve RL, Bromberger BJ, Groveman HD, Klauber MR, Dixon SD, Snyder JM. Regional anesthesia during newborn circumcision: Effect on pain response. Clin Pediatr 1983;22:813-818.
17. Friesen RH, Honda AT, Thiene RE. Changes in anterior fontanel pressure in preterm neonates during tracheal intubation. Anesth Analg 1987;66:874-878.
18. Anand KJS, Aynsley-Green A. Measuring the Severity of Surgical Stress in New-born Infants. J Pediatr Surg 1988;23:297-305.

19. Fitzgerald M, Millard C, MacIntosh N. Cutaneous hypersensitivity following peripheral tissue damage in newborn infants and its reversal with topical anaesthesia. Pain 1989;39:31-6.
20. Dickenson AH. NMDA receptor antagonists as analgesics. In: Fields HL, Liebeskind JC, eds. Progress in pain research and management, Vol 1. International Association for the Study of Pain, Seattle, 1994:173.
21. Price DD, Mao J, Mayer DJ. Central neural mechanisms of normal and abnormal pain states. In: Fields HL, Liebeskind JC, eds. Pharmacological approaches to the treatment of chronic pain: new concepts and critical issues. Progress in pain research and management, Vol 1. International Association for the Study of Pain, Seattle, 1994:61-84.
22. Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. Neurosci Lett 1986;64:221-225.
23. Narita M, Funada M, Suzuki T. Regulations of opioid dependence by opioid receptor types. Pharmacol Ther 2001;89:1-15.
24. Carr DB, Murphy MT. Operation, anesthesia, and the endorphin system. In: Napolitano LM, Chernow B, eds. Stress responses during Anesthesia (Intl Anesth Clinics, Vol. 26), Boston, Little & Brown, 1988:199.
25. Purcell-Jones G, Dormon F, Sumner E. Paediatric anaesthetist's perception of neonatal and infant pain. Pain 1988;33:181-187.
26. De Lima J, Lloyd-Thomas AR, Howard RF, Sumner E, Quinn TM. Infant and neonatal pain: anaesthetist's perceptions and prescribing patterns. BMJ 1996;313:787.
27. Coffman BL, RIOS GR, King CD, Tephly TR. Human UGT2B7 catalyzes morphine glucuronidation. Drug Metab Disp 1997;25:1-4.
28. de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Glucuronidation in humans. Pharmacogenetic and developmental aspects. Clin Pharmacokinet 1999; 36:439-52.
29. Osborne R, Joel S, Trew D, Slevin M. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. Clin Pharmacol 1990;47:12-19.
30. Stain F, Barjavel MJ, Sandouk P, Plotkine M, Scherrmann JM, Bhargava HN. Analgesic response and plasma and brain extracellular fluid pharmacokinetics of morphine and morphine-6-beta-d-glucuronide in the rat. J Pharmacol Exp Ther 1995;274:852-857.
31. Peat SJ, Hanna MH, Woodham M, Knibb AA, Ponte J. Morphine-6-glucuronide effects on ventilation in normal volunteers. Pain 1991;45:101.

32. Osborne R, Thompson P, Joel S, Trew D, Patel N, Slevin M. The analgesic activity of morphine-6-glucuronide. Br J Clin Pharmacol 1992;34:130-138.
33. Gong QL, Hedner J, Bjorkman R, Hedner T. Morphine-3-glucuronide may functionally anatagonize morphine-6-glucuronide induced antinociception and ventilatory depression in the rat. Pain 1992;48:249-255.
34. McRorie TI, Lynn AM, Nespeca MK, Opheim KE, Slattery JT. The maturation of morphine clearance and metabolism. AJDC 1992;146:972-976.
35. Yeh SY, Gorodetzky CW, Krebs HA. Isolation and identification of morphine 3- and 6-glucuronides, morphine 3, 6-diglucuronide, morphine 3-ethereal sulfate, normorphine, and normorphine 6-glucuronide as morphine metabolites in humans. J Pharm Sci 1977;66:1288-1293.
36. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. Anesthesiology 1987;66:136-139.
37. Lynn A, Nespeca MK, Bratton SL, Strauss SG, Shen DD. Clearance of morphine in postoperative infants during intravenous infusion: the influence of age and surgery. Anesth Analg 1998;86:958-963.
38. Lynn AM, Nespeca MK, Bratton SL, Shen DD. Intravenous morphine in postoperative infants: intermittent bolus dosing versus targeted continuous infusions. Pain 2000;88:89-95.
39. Choonara IA, McKay P, Hain R, Rane A. Morphine metabolism in children. Br J Clin Pharmacol 1989;28:599-604.
40. Chay PC, Duffy BJ, Walker JS. Pharmacokinetic-pharmacodynamic relationships of morphine in neonates. Clin Pharmacol Ther 1992;51:334-342.
41. Dagan O, Klein J, Bohn D, Barker G, Koren G. Morphine pharmacokinetics in children following cardiac surgery: effects of disease and inotropic support. J Card Vasc Anesth 1993;7:396-398.
42. Faura CC, Collins SL, Moore RA, McQuay HJ. Systematic review of factors affecting the ratios of morphine and its major metabolites. Pain 1998;74:43-53.
43. Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 1-Pharmacokinetics. Pediatr Anaesth 1997a;7:5-11.
44. Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 2-Clinical use. Pediatr Anaesth 1997b;7:93-101.
45. Scott CS, Riggs KW, Ling EW, et al. Morphine pharmacokinetics and pain assessment in premature newborns. J Pediatr 1999;135:423-429.
46. Farrington EA, McGuinness GA, Johnson GF, Eremberg A, Leff RD. Continuous intravenous morphine infusion in postoperative newborn infants. AJ Perinatology 1993;10:84-87.

47. Anderson BJ, McKee AD, Holford NHG. Size, myths and the clinical pharmacokinetics of analgesia in paediatric patients. Clin Pharmacokinet 1997;33:313-327.
48. Fitzgerald M. The postnatal development of cutaneous afferent fibre input and receptive field organization in the rat dorsal horn. J Physiol 1985;364:1-18.
49. Fitzgerald M, Shaw A, MacIntosh N. The postnatal development of the cutaneous flexor reflex: a comparative study in premature infants and newborn rat pups. Dev Med Child Neurol 1988;30:520-526.
50. Taddio A, Katz J, Ilersich AL, Koren G. Effect of neonatal circumcision on pain response during subsequent routine vaccination. Lancet 1997;349:599-603.
51. Bernstein BA, Pachter LM. Cultural considerations in children's pain. In: Schechter NL, Berde CB, Yaster M, eds. Pain in infants, children and adolescents, Philadelphia: Williams & Wilkins,1993;113-122.
52. Dahlstrom B, Bolme P, Feychting H, Noack G, Paalzow L. Morphine kinetics in children. Clin Pharmacol Ther 1979;26:354-365.
53. Lynn AM, Opheim KE, Tyler DC. Morphine infusion after pediatric cardiac surgery. Crit Care Med 1984;12:863-866.
54. Lynn AM, Nespeca MK, Opheim KE, Slattery JT. Respiratory effects of intravenous morphine infusions in neonates, infants and children after cardiac surgery. Anesth Analg 1993;77:695-701.
55. Olkkola KT, Maunuksela EL, Korpela R, Rosenberg PH. Kinetics and dynamics of postoperative intravenous morphine in children. Clin Pharmacol Ther 1988;44:128-136.
56. Mathews JR, McGrath PJ, Pigeon H. Assessment and measurement of pain in children. In: Schechter NL, Berde CB, Yaster M eds. Pain in infants, children, and adolescents, Philadelphia: Williams & Wilkins, 1993:97-111.
57. Ambuel B, Hamlett KW, Marx CM, Blumer JL. Assessing distress in pediatric intensive care environments: the COMFORT Scale. J Pediatric Psychol, 1992;17:95-109.
58. Marx CM, Smith PG, Lowrie LH, Hamlett KW, Ambuel B, Yamashita TS, Blumer JL. Optimal sedation of mechanically ventilated pediatric critical care patients. Crit Care Med 1994;22,163-170.
59. Beasley SW, Tibballs J. Efficacy and safety of continuous morphine infusion for postoperative analgesia in the paediatric surgical ward. Aust N Z J Surg 1987;57:233-237.
60. Buchholz M, Karl HW, Pomietto M, et al: Pain scores in infants: a modified infant pain scale versus visual analogue. J Pain Symptom Manage 15: 117-124, 1998

61. McGrath PA et al. CHEOPS: A behavioral scale for rating postoperative pain in children. In Fields HL, Dubner R, Cervero F, eds. Advances in pain research and therapy. New York Raven Press 1985:395-402.
62. Scott J, Huskisson EC. Graphic representation of pain. Pain 1976;2:175-184.
63. van Dijk M, Boer de JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 – 3 year-old infants. Pain 2000;84:367-377.
64. Van Dijk M. Pain unheard? Postoperative pain assessment in neonates and infants. Ph thesis 2001, Rotterdam.

Chapter 2

Hormonal and metabolic stress responses after major surgery in children aged 0 – 3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine

Based on:
Hormonal and metabolic stress responses after major surgery in children aged 0 – 3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine
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2. 1 Summary

Children aged 0-3 years were stratified for age and randomised to receive either continuous morphine (C.M. 10 μg kg^{-1} h^{-1}) with three-hourly placebo boluses or intermittent morphine (I.M. 30 μg kg^{-1} every 3 h) with a placebo infusion for postoperative analgesia. Plasma concentrations of epinephrine, norepinephrine, insulin, glucose and lactate were measured before and at the end of surgery and 6, 12 and 24 h after surgery. Pain was assessed by validated pain scales [the COMFORT Score and visual analogue scale (VAS)] with the availability of additional morphine doses. Minor differences occurred between the randomised treatment groups, the oldest IM group (aged 1-3 yr) having a higher blood glucose concentration ($P = 0.003$), mean arterial pressure ($P = 0.02$), and COMFORT score ($P = 0.02$) than the CM group. In the neonates, preoperative plasma concentrations of norepinephrine ($P = 0.01$) and lactate ($P < 0.001$) were significantly higher, while the postoperative plasma concentrations of epinephrine were significantly lower ($P < 0.001$) and plasma concentrations of insulin significantly higher ($P < 0.005$) than in the older age groups. Postoperative pain scores ($P < 0.003$) and morphine consumption ($P < 0.001$) were significantly lower in the neonates than in the older age groups. Our results show that continuous infusion of morphine does not provide any major advantages over intermittent morphine boluses for postoperative analgesia in neonates and infants.

2.2 Introduction

In adults, endocrine and metabolic responses to severe injury consist of a hypometabolic period, which lasts about 3 days, followed by a hypermetabolic period.[1,2] As a result of this homeostatic disturbance, cellular dehydration, capillary leakage and organ dysfunction may occur, leading to a prolonged convalescence period.[3] Although this endocrine-metabolic response can be modified by surgical anaesthesia, important reductions in stress responses depend on the analgesic method in adult patients,[4,5,6] and in children.[7] Epidural anaesthesia was more effective in reducing surgical stress during low abdominal surgery than systemic opioids.[8] Diminished stress responses and improved postoperative outcomes were noted after high-dose opioids in neonates after cardiac surgery.[9,10] More recently, the use of i.v. opioids in non-surgical, mechanically ventilated neonates resulted in reduced physiological and behavioural measurements of pain and stress[11,12] and was associated with fewer periods of hypoxaemia[13] and improved

neurological outcomes.[14] Because of the lack of randomized controlled trials in neonates and infants,[15] little is known about the alterations in hormonal-metabolic stress responses caused by postoperative analgesia or postnatal age in patients undergoing non-cardiac surgery.

This study was designed as a double-blind, randomized controlled trial to test the hypothesis that postoperative analgesia with continuous morphine infusions would provide improved analgesia with lower stress responses compared with intermittent doses. To obtain more information about physiological and behavioural responses after major surgery in young children, surgical stress was evaluated by measuring hormonal, metabolic, and haemodynamic variables and postoperative pain was assessed by behavioural responses [COMFORT and a visual analogue scale (VAS)] and by the amount of morphine used. The ontogeny of these responses is unknown because of the paucity of data beyond the neonatal age group. Therefore, we randomised the patients into four developmentally relevant age groups.[16]

2.3 Methods

The study protocol was approved by the hospital medical ethical committee, and written consent was obtained from the parents. We included children aged 0 - 3 yr, admitted to the paediatric surgical intensive care unit (PICU) after non-cardiac thoracic and abdominal surgery. Patients were excluded if they had received analgesic or sedative drugs < 6 h before surgery, if they were receiving neuromuscular blockade or if they suffered from hepatic, renal, or neurological disorders or altered muscle tone. Patients were stratified by age into four groups [group I, 0 - 4 weeks (neonates); II, 4 weeks to 26 weeks; III, 26 - 52 weeks, IV, 1 - 3 yr] and were assigned randomly to receive i.v. either continuous morphine (CM) or intermittent morphine (IM). The pharmacists prepared all study drugs, and strata-specific schedules for randomisation, and the clinical staff were blinded to the study group allocation until the data collection was complete.

Anaesthetic management was standardized. Anaesthesia was induced i.v. with thiopentone 3-5 mg kg^{-1} or by inhalation of halothane in oxygen. Fentanyl 5 µg kg^{-1} was given before orotracheal intubation, which was facilitated with atracurium 0.5 - 1 mg kg^{-1} or suxamethonium 2 mg kg^{-1}. Ventilation was controlled and anaesthesia was maintained with isoflurane 0.5 minimum alveolar concentration in 60 % nitrous oxide in oxygen or

air in oxygen. Perioperative fluids were standardized to maintain a glucose infusion rate between 4-6 mg kg^{-1} min^{-1}. Body temperature was kept within normal ranges. A peripheral artery was cannulated and the measured mean arterial blood pressure (MAP) and heart rate (HR) were used as preoperative baseline data. After the first arterial blood sample (baseline), patients received a second dose of fentanyl 5 μg kg^{-1} before surgical incision. Additional doses of fentanyl 2 μg kg^{-1} were administered when HR and/or MAP were 15 % above baseline value. At the end of surgery, the neuromuscular block was antagonized and the tracheal tube was removed. Mechanical ventilation was continued in patients who required ventilatory assistance after surgery.
Directly after surgery, all patients received an i.v. loading dose of morphine (100 μg kg^{-1}) followed by a morphine infusion of 10 μg kg^{-1} h^{-1} for children in the CM group, combined with three-hourly i.v. placebo (saline) boluses. Children in the IM group received a continuous placebo infusion (saline) combined with three-hourly i.v. doses of 30 μg kg^{-1}. The first intermittent bolus (morphine or placebo) was given 3 h after surgery. Additional analgesia was given by the nurse when there were signs of pain, indicated by a 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}could be given every 10 min if required. No other analgesic or sedative drugs were used.

Arterial blood samples were taken after induction of anaesthesia, at the end of surgery and 6, 12, and 24 h after surgery to determine plasma concentrations of epinephrine, norepinephrine, insulin, glucose and lactate. From 24 to 36 h after surgery, urine was collected for determination of the 3-methyl histidine/creatinine molar ratio (3MH/CR), a measure of protein breakdown.
After surgery, the Surgical Stress Score (SSS)[17] was computed by the surgeon and anaesthetist. Nurses performed regular assessments before surgery (baseline) and every 3 h up to 36 h after surgery. Nursing interventions included pain assessment using a VAS and the COMFORT scale,[18] blood sampling (as indicated), giving the intermittent bolus (placebo or morphine), and then nursing as needed. Thus, hormonal and metabolic stress responses were measured as plasma concentrations at time points corresponding to trough plasma concentrations in the IM group.

The SSS consists of 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.[17] The total scores in this study (excluding cardiac surgery and prematurity < 35 weeks)

ranged from 3 to 24, and were used to classify the degree of surgical stress.
The VAS, a horizontal continuous 10 cm line with the anchor points 'no pain' on the left and 'extreme pain' on the right, was used as an observational instrument. VAS scores < 4 indicate absent or mild pain and scores ≥ 4 indicate moderate to severe pain, as noted from previous studies in children.
The COMFORT scale[18,19] was originally developed and validated to assess distress in children ventilated mechanically (0-18 yr). This scale consists of six behavioural items (alertness, calmness, respiratory response, movement, muscle tone and facial tension) and two physiological items (MAP and HR). For non-ventilated children, the respiratory response item was replaced by an assessment of crying, possible scores ranging from 1 (no crying) to 5 (screaming). Total score ranges from 8 to 40. We have recently validated the COMFORT scale as a measure of postoperative pain in this age group.[20]
Plasma concentrations of epinephrine and norepinephrine were measured by HPLC using fluorimetric detection.[21] Plasma concentrations of insulin were measured using the Insulin IRMA CT kit (Medgenix). Standardized automated laboratory analysers measured plasma concentrations of glucose, lactate, total bilirubin and plasma and urinary creatinine. The concentration of urinary 3-methylhistidine was measured by ion exchange chromatography on an amino acid analyser.

In previous studies, a SD of 0.6 nmol litre^{-1} was found for epinephrine and 1.4 nmol litre^{-1} for norepinephrine.[10] To detect differences between the group values for plasma epinephrine (0.24 nmol litre^{-1}) and norepinephrine (0.56 nmol litre^{-1}) with a power of 80% at a two-sided alpha error of 0.05 would require 100 patients in each group. Repeated measurements analysis of variance (RmANOVA)[22] was used to evaluate simultaneously the effects of treatment, age groups and time after surgery. Plasma concentrations before surgery and changes from baseline values directly after surgery were compared between age groups using one-way ANOVA. Comparison with baseline values within age groups was done by the paired t-test. In these analyses, all hormonal and metabolic data had to be transformed logarithmically in order to obtain approximately normal distributions. The postoperative time points (directly after surgery and 6, 12 and 24 h after surgery) at which individual plasma concentrations were highest were compared between age groups using the Kruskal-Wallis/Mann-Whitney test. The same tests were used to compare morphine consumption between groups. Correlation coefficients given are Spearman's.
All enrolled patients were included in an intention-to-treat analysis. Nine patients dropped out during the study (five in CM, four in IM) because of the loss of arterial access (seven), the need for neuromuscular blockade (one) and one postoperative death 3 h after surgery.

2.4 Results

Table 1 shows the clinical and surgical characteristics of the enrolled patients according to their age categories and randomized treatment groups.
A total of 204 patients were enrolled: 101 in the CM group and 103 in the IM group. The randomisation schedule was stratified for age; other demographic and clinical variables were similar in the two randomised groups. Thirteen of the 35 neonates in CM (37%) were ventilated mechanically before surgery compared with six of the 33 in the IM group (18 %). This difference was not significant.

For various reasons, 23 patients needed mechanical ventilation before surgery, seven of them for acute inflammatory surgical complications.
The median doses of fentanyl for age groups I, II, III and IV were 12, 12, 17 and 15 μg kg^{-1}, respectively. Fentanyl doses did not differ significantly between the two treatment groups in any of the age groups (all $P > 0.14$). The fentanyl dose correlated significantly with the duration of surgery ($R = 0.43$, $P < 0.001$). The age groups were similar with respect to SSS.

Hormonal and metabolic stress responses
Table 2 shows the median and interquartile range of the hormonal and metabolic variables before and after surgery (average of 6, 12 and 24 h after surgery) according to age and treatment.
Overall, no significant differences in plasma concentrations were found between the randomized treatment groups (all analyses: $P \geq 0.22$). For glucose, a significant interaction was found between the effects of treatment and age ($P = 0.04$), indicating that the treatment difference was not the same in all age groups. Further analysis within each age group showed that blood glucose concentrations were lower in the CM group (16 %, $P = 0.003$) than in the IM group in the oldest age group (1-3 yr), although an opposite trend was noted amongst the neonates (CM > IM, $P = 0.07$).

Figure 1 shows the geometric mean plasma concentrations with the SE for epinephrine, norepinephrine, insulin, glucose and lactate and the insulin/glucose ratio, for all patients, according to age, and at the various time points (before and at the end of surgery and 6, 12 and 24 h after surgery).

Table 1 *Patient data [mean (range or SD)] and details of surgery. CM = continuous morphine; IM = intermittent morphine; n = number of patients. High abdominal surgery comprised diaphragmatic hernia/paresis, duodenal atresia, subtotal pancreatectomy, Nissen fundoplication, hepatic and choledochal surgery, (ad)renal surgery, stomic perforation. Superficial surgery comprised nefrectomy, ureter reimplantation, pyeloplasty,and operations for extrophy of the bladder, sacroteratoma, yolk sac tumour, pull-through, incarcerated hernia. Acute gastrointestinal surgery comprised operations for atresia, malrotation, intussusception, necrotizing enterocolitis, meconium peritonitis and perforation, and ileus surgery*

	Age group							
	I (0-4 weeks)		**II (4-26 weeks)**		**III (26-52 weeks)**		**IV (1-3 yr)**	
	CM (*n* = 35)	**IM (*n* = 33)**	**CM (*n* = 32)**	**IM (*n* = 33)**	**CM (*n* = 16)**	**IM (*n* = 15)**	**CM (*n* = 18)**	**IM (*n* = 22)**
Age (days)	8	3	97	101	267	254	632	639
(range)	(0-28)	(0-17)	(29-173)	(30-179)	(185-351)	(180-330)	(368-1070)	(393-1067)
Weight (kg)	3.1 (0.7)	2.9 (0.5)	4.9 (1.5)	4.6 (1.8)	6.9 (1.6)	7.3 (1.2)	11.1 (1.9)	11.1 (2.5)
Males/females (*n*)	21/14	19/14	20/12	22/11	9/7	9/6	9/9	10/12
Mechanical ventilation before surgery	13	6	4					
Total Surgical Stress Score	9.9 (2.8)	9.9 (2.9)	9.3 (3.3)	9.6 (2.5)	8.4 (3.1)	9.9 (2.7)	10.6 (2.9)	10.1 (3.7)
Generalized or localized infection	5	6		1			1	1
Surgical procedures								
Congenital diaphragmatic hernia	9	4			1	1	1	
Tracheo-oesophageal atresia/TOF	6	9	1	1				
Bronchopulmonary (lobectomy, pneumectomy, cyst)		1	2	1		1	5	
Cardiac (Blalock, vessel loop)			1	2				
Nissen fundoplication				2	2	2	2	4
Gastroschisis	1	1						
Acute gastrointestinal	15	15	11	5	5	2	3	2
Colonic pull-through					1			2
Closure of entero/colostoma			7	9	1	3	1	4
Rehbein's procedure	1		4	4	1	3		
Colon interposition							3	1
Urological (nefrectomy, pyeloplasty, reimplantation, bladder augmentation)		1	1	2			1	2
Miscellaneous (diaphragma paresis, tumour, teratoma, cyst, pancreatectomy, choledochal atresia)	1	2	7	7	5	3	2	7
Site of surgery								
Thoracic	5	8	6	4		2	5	1
Abdominal high/low	16/12	6/17	6/19	8/19	8/7	3/10	6/3	5/11
Thoracic combined with abdominal		2					3	2
Superficial			1	2	1		1	3

Table 2 *Hormonal and metabolic variables before and after surgery (average of 6, 12 and 24 h after surgery), according to age and treatment. All values are median interquartile range). CM = continuous morphine; IM = intermittent morphine; n = number of patients.*

	Age group															
	I (neonates, 0 – 4 weeks)				II (4 weeks - 26 weeks)				III (26 weeks – 52 weeks)				IV = 1 – 3 years			
	CM	*n*	IM	*n*	CM	*n*	IM	*n*	CM	*n*	IM	*n*	CM	*n*	IM	*n*
Epinephrine (nmol litre^{-1})																
before surgery	0.1 (0.03-0.36)	34	0.11 (0.04-0.33)	32	0.07 (0.02-0.2)	29	0.10 (0.05-0.22)	32	0.11 (0.05-0.34	16	0.16 (0.08-0.37)	15	0.19 (0.04-0.29)	18	0.10 (0.05-0.65)	21
after surgery	0.14 (0.05-0.28)	33	0.06 (0.03-0.29)	30	0.56 (0.31-0.97)	27	0.57 (0.36-0.97)	26	1.02 (0.6-1.81)	15	1.05 (0.67-1.67)	14	1.42 (0.94-2.02)	15	1.93 (1.43-2.55)	17
Norepinephrine (nmol litre^{-1})																
before surgery	1.6 (.98-3.2)	34	1.6 (0.9-2.6)	32	1.1 (0.6-0.9)	29	0.9 (0.6-1.8)	32	1.0 (0.6-1.9)	16	1.0 (0.7-1.8)	15	0.8 (0.5-1.5)	18	1.0 (0.4-2.3)	21
after surgery	2.6 (1.8-4.2)	33	2.1 (1.3-3.2)	30	2.7 (2.0-3.7)	27	2.6 (2.0-4.4)	26	2.6 (1.7-2.9)	15	2.6 (1.7-3.1)	14	2.4 (1.5-2.9)	15	2.3 (1.8-3.6)	17
Insulin (mU litre^{-1})																
before surgery	5.0 (5.0-8.0)	31	5.0 (5.0-7.5)	29	5.0 (5.0-8.0)	31	5.0 (5.0-5.8)	32	5.0 (5.0-5.0)	16	5.0 (5.0-9.0)	15	5.0 (5.0-7.0)	18	5.0 (5.0-6.0)	22
after surgery	13.8 (9.4-17.1)	32	12.0 (8.5-19.6)	28	11.0 (8.7-14.3)	27	8.3 (6.0-12.2)	25	7.0 (5.7-11.3)	15	9.7 (7.5-12.6)	14	6.7 (5.3-10.0)	15	10.0 (6.8-12.8)	17
Glucose (mmol litre^{-1})																
before surgery	5.5 (3.9-7.1)	35	5.7 (3 9-7.1)	32	5.8 (4.5-6.8)	31	5.6 (4.5-6.3)	32	4.5 (4.1-5.8)	16	5.6 (4.6-6.2)	15	4.5 (3.9-5.5)	18	4.9 (3.7-6.0)	22
after surgery	5.8 (5.2-6.7)	34	5.1 (4.5-6.7)	31	6.3 (5.1-6.5)	27	5.6 (5.1 -7.0)	25	5.8 (5.5-6.3)	15	6.3 (5.7-6.6)	14	5.9 (4.4-6.3)	15	6.7 (5.8-7.1)	18
Lactate (mmol litre^{-1})																
before surgery	1.9 (1.3-2.7)	35	2.1 (1.3-2.8)	31	1.2 (1.0-1.4)	29	1.1 (0.8-1.3)	32	1.2 (0.9-1.5)	16	1.0 (0.9-1.5)	15	1.2 (0.8-1.5)	17	1.1 (0.8-1.3)	22
after surgery	1.5 (1.2-1.8)	32	1.5 (1.2-2.2)	29	1.2 (0.8-1.4)	25	1.0 (0.8-1.3)	24	0.9 (0.8-1.0)	15	0.8 (0.8-1.0)	14	0.9 (0.8-1.0)	15	0.9 (0.7-1.0)	17
Insulin/glucose ratio (Umol^{-1})																
before surgery	1.1 (0.8-2.5)	31	1.1 (0.8-1.6)	28	1.1 (0.9-1.5)	31	1.0 (0.9-1.4)	32	1.2 (1.1-1.3)	16	1.1 (0.9-1.3)	15	1.2 (1.1-1.3)	18	1.1 (0.9-1.5)	22
after surgery	2.2 (1.8-3.0)	34	2.3 (1.7-3.1)	33	1.9 (1.6-2.5)	29	1.6 (1.1-2.0)	30	1.2 (1.0-2.1)	15	1.5 (1.3-2.1)	15	1.4 (1.1-1.7)	18	1.4 (1.0-1.9)	21

Figure 1

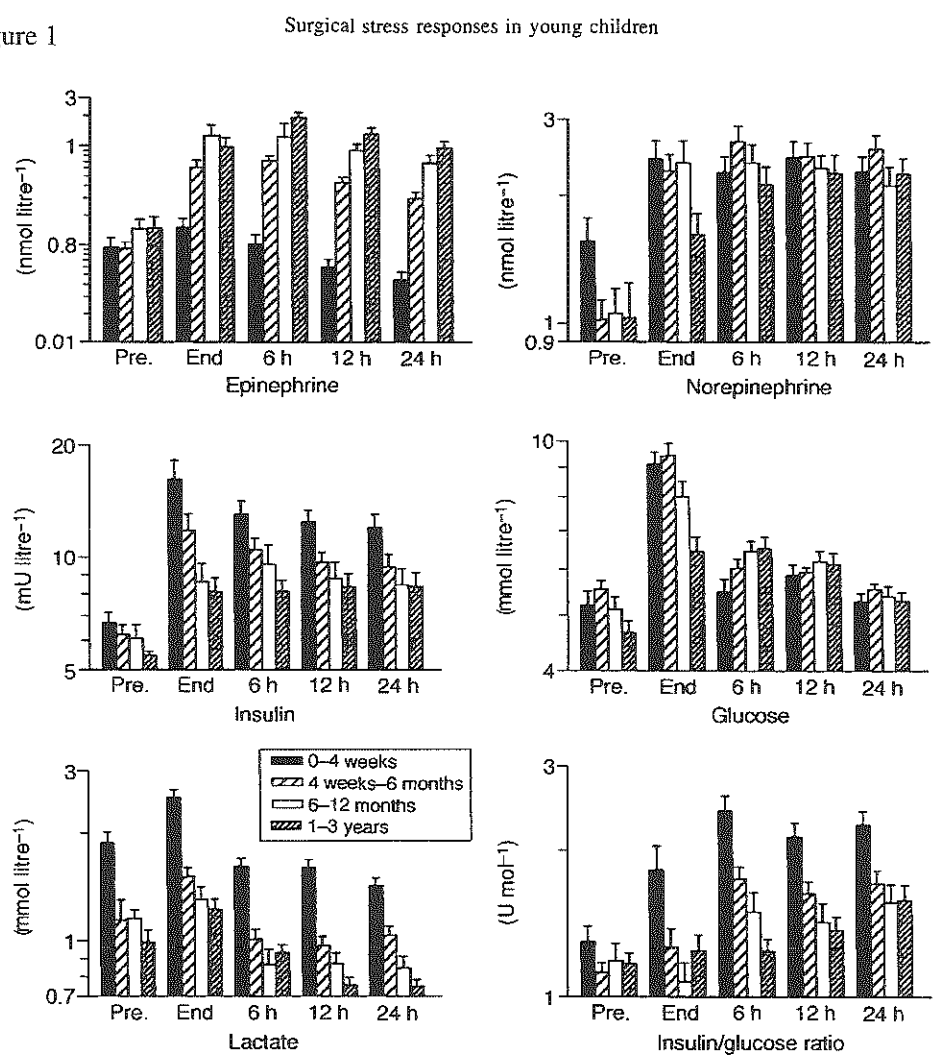

Fig 1 Plasma concentrations of epinephrine (nmol litre^{-1}), norepinephrine (nmol litre^{-1}), insulin (mU litre^{-1}), glucose (mmol litre^{-1}) and lactate (mmol litre^{-1}) and the insulin/glucose ratio (U mol^{-1}). The figure concentrates on the effects of age when the two treatment groups are combined. Data are geometric means with SE before surgery (Pre.), at the end of surgery (End) and 6, 12 and 24 h after surgery. Note the logarithmic scale of the vertical axes.

Plasma concentrations of epinephrine before surgery were not significantly different between the age groups. The mean increase in plasma epinephrine concentration directly after surgery was significantly lower in the neonatal group than in the other age groups (1.6 vs 6 - 8 times baseline value, $P < 0.001$), and no significant differences occurred between the older age groups. The mean values of the average postoperative plasma concentration of epinephrine (6, 12 and 24 h after surgery) were significantly lower in the neonatal group than in the older children (all $P < 0.001$). RmANOVA showed that postoperative decreases in plasma epinephrine differed significantly between the age groups ($P < 0.001$). In the neonates the mean plasma concentration of epinephrine had returned to the baseline value 6 h after surgery and was below the baseline value at later time points ($P < 0.05$). In the older age groups, mean values were still above baseline 24 h after surgery (all $P < 0.001$). The highest plasma concentrations were mostly found directly after surgery in age groups I and III, and 6 h after surgery in age groups II and IV. Plasma epinephrine concentrations were not significantly different with respect to spontaneous or mechanical ventilation.

Plasma norepinephrine concentrations at baseline were significantly higher in the neonates than in age group II ($P = 0.01$) and nearly so in comparison with age groups III and IV (both $P = 0.06$). The increases in plasma norepinephrine concentrations (6, 12 and 24 h after surgery) compared with baseline values were significantly smaller in the neonates than in age groups II ($P = 0.004$) and III ($P = 0.05$). The mean average plasma concentration of norepinephrine (6, 12 and 24 h after surgery) showed no significant differences between age groups or assessment times. Only for the oldest age group was there a significant increase in plasma concentrations 6 h after surgery ($P = 0.03$). No significant differences were found between age groups regarding the time at which individual patients reached the highest plasma concentration. In all age groups, plasma concentrations of norepinephrine were still significantly above baseline values 24 h after surgery (all $P < 0.001$). Neonates who were ventilated mechanically showed significantly higher plasma concentrations of norepinephrine before operation compared with the non-ventilated neonates ($P = 0.02$). This difference was not significant in the postoperative period. In patients of age group II (4 – 26 weeks) needing mechanical ventilation after surgery, there were significantly higher plasma concentrations of norepinephrine compared with the non-ventilated children of that age group ($P = 0.02$).

Plasma insulin concentrations at baseline were not significantly different between the age groups; however, directly after surgery, plasma concentrations were significantly higher

in the neonates than in age group III ($P = 0.002$), and IV ($P < 0.001$). The average plasma concentration of insulin (6, 12 and 24 h after surgery) showed a significant correlation with age ($r = -0.34$, $P = < 0.001$).

Plasma glucose concentrations before surgery were not significantly different between the age groups and they were generally highest directly after surgery in all age groups. RmANOVA of glucose plasma concentrations 6, 12 and 24 h after surgery showed a significant decrease after surgery ($P < 0.001$). At 24 h after surgery, mean plasma concentrations were not significantly different from baseline values in all age groups. The insulin/glucose ratio was not significantly different before operation, but showed significant differences after surgery between the age groups in their patterns of postoperative changes. There was a significant correlation ($r = -0.45$, $P < 0.001$) between age and insulin/glucose ratio 6, 12, and 24 h after surgery. At 24 h after surgery, the mean insulin/glucose ratio was still above baseline for all age groups.

The mean plasma concentration of lactate at baseline was significantly higher in the neonates than in the other age groups (all $P < 0.001$). Highest concentrations were found directly after surgery with no significant difference in the change from baseline values between the age groups. In the neonatal group there was a significant decrease from 6 to 24 h after surgery ($P = 0.02$). A similar effect was found in age group IV ($P < 0.001$), but there were no significant postoperative differences for age groups II and III. Mean plasma concentrations of lactate were significantly below baseline values 24 h after surgery (all $P \leq 0.001$). There was no significant difference in the urinary 3-MH/Cr ratio (from 12 to 36 h after surgery) between the randomized treatment groups or the age groups.

Plasma concentrations of epinephrine ($P = 0.01$) and norepinephrine ($P = 0.003$) were significantly higher after upper abdominal surgery than after thoracic or superficial surgery. A repeated analysis that excluded the eight patients with "superficial" surgery (Table1) gave results similar to those in Table 3. In 14 patients (11 of them neonates) hormonal and metabolic stress responses may have been influenced by acute, inflammatory surgical complications. A repeated analysis that excluded the 14 patients with "localised or generalised infection" again gave results similar to those in Table 3. Significantly higher plasma concentrations of norepinephrine occurred after blood transfusion in neonates compared with neonates without transfusion at 6 ($P = 0.01$), 12 ($P = 0.07$) and 24 h ($P = 0.03$) after surgery. These differences were not found in the other age groups.

Table 3 *Comparison between continuous morphine (CM) and intermittent morphine (IM) by RmANOVA, while controlling for age group (I, II, III and IV), sampling time (6, 12 and 24 h after surgery) and preoperative (baseline) plasma concentration. Data are the ratio of geometric means (CM/IM). *Significant differences between the age groups: I, 1.12 (P = 0.07); II, 0.99 (P = 0.75); III, 0.96 (P = 0.57); IV, 0.84 (P = 0.003).*

Variable	Ratio (CM/IM)	95% CL	P
Epinephrine	1.08	0.81-1.44	0.59
Norepinephrine	1.05	0.91-1.20	0.51
Insulin	0.92	0.81-1.05	0.22
Glucose	0.98*	0.95-1.04	0.52
Insulin/glucose ratio	0.97	0.86-1.08	0.55
Lactate	0.98	0.90-1.07	0.67

Blood pressure and heart rate

RmANOVA showed that postoperative increases in MAP (3 - 36 h after surgery) from baseline values depended on age. Significantly greater increases in the IM group compared with the CM group were found in age group III [12.0 (SD 5.8) mm Hg, P = 0.04] and within age group IV [10.6 (4.4) mm Hg, P = 0.02], but no significant differences were found in the other age groups.

In the neonates, mean HR at baseline was significantly higher in the CM than in the IM group (P = 0.03). Increases in HR at the end of surgery or postoperatively were not significantly different between the two treatment groups. However, the change from baseline HR increased significantly with age (P = 0.002), with maximum values recorded 6 h after surgery for all age groups.

Pain assessment

Postoperative pain scores, morphine consumption during the first 24 h after surgery and the number of patients needing postoperative mechanical ventilation during > 36 h after surgery are shown in Table 4.

Mean VAS scores (3 - 36 h after surgery) were significantly different between the age groups but not between the CM and IM groups. VAS scores generally declined with time after surgery. More than 24 h after surgery, the mean VAS was still significantly higher in age group II than in each of the other age groups (all P < 0.04).

The mean VAS scores were significantly lower in the neonates (1.3) than in the three older age groups (2.4, 2.1, and 1.8 respectively) (all P < 0.003) and in group IV compared with group II (P < 0.001). VAS scores of ≥ 4 occurred less frequently in neonates than in the older age groups (P < 0.002) and in group IV compared with age group II (P = 0.004).

The occurrence of VAS ≥ 4 was correlated significantly with plasma concentrations of norepinephrine, but only in age groups III and IV at 6 h after surgery (both $P < 0.05$). The mean COMFORT score (3 - 36 h after surgery) was significantly different between CM and IM only in age group IV (18.8 and 20.8, respectively), ($P = 0.02$). Overall the mean COMFORT score was significantly ($P < 0.001$) lower in the neonates (17.4) than in the older age groups (21.4, 20.6 and 19.8 respectively). Generally, the plasma concentrations of epinephrine and norepinephrine were weakly correlated with COMFORT scores at the various time points.
Morphine consumption (excluding the loading dose) during the first 24 h after surgery was significantly different between the age groups, but not between the CM and IM groups. The morphine consumption during the first 24 h after surgery was significantly lower in the neonatal group than in the age groups II, III and IV, (all $P < 0.001$), and significantly higher in group II versus IV ($P = 0.035$).

2.5 Discussion

We present the first randomized, placebo-controlled trial that includes a double-blind assessment of the clinical and physiological effects of continuous vs intermittent morphine for postoperative analgesia in neonates and older infants. In addition, we report important differences between the different age groups that will allow deeper understanding of the ontogeny of hormonal-metabolic stress responses in early life. Although the post-neonatal period is associated with major changes in the regulation of the hypothalamic-pituitary-adrenal axis and the hypothalamic sympathetic outflows (via the posterior hypothalamic nuclei and locus coeruleus), the effect of these developmental events on the neuroendocrine responses to surgical stress remains unclear.

On the basis of these data, we can reject our primary hypothesis that continuous infusions of morphine postoperatively produce improved postoperative analgesia and lower hormonal-metabolic responses. Although supplementary doses of morphine were used to treat clinical signs of distress after surgery, standard criteria were used for these treatments in the CM and IM groups. Clinical bias was eliminated by a double-blind study design and total morphine consumption was similar in the two randomized groups. The additional morphine doses were considered to be necessary for the patient's comfort and for ethical reasons. In infants aged 1-3 yr, greater degrees of stress were noted in the IM group than in the CM group, as noted by significant increases in postoperative

hyperglycaemia, mean arterial pressure and clinical assessment by the COMFORT score. Because these measurements were performed at the time of trough morphine concentrations for the IM group, these differences may have been caused by the relatively great plasma clearance of morphine in this age group.[23-25] Thus, it is likely that the longer duration of opioid effect after intermittent morphine boluses in the younger age groups resulted in clinical and physiological effects that were similar to those of a continuous infusion.

Similar clinical trials in adult patients have reported conflicting results, suggesting superior[26] equivocal[27] or inferior[28] clinical effects of continuous i.v. infusions vs intermittent doses of morphine for postoperative analgesia. To our knowledge, a similar clinical trial has not been reported in paediatric patients, although several studies comparing i.v. with epidural morphine analgesia have been reported.[29]
These data indicate that the pattern of surgical stress responses differs between neonates (postnatal age 0 - 4 weeks) and older age groups. Robust developmental differences were found for the postoperative changes in hormonal-metabolic variables (plasma epinephrine, norepinephrine, insulin and lactate), cardiovascular responses (MAP and HR), behavioural variables used for pain assessment (VAS and COMFORT scores), and postoperative morphine consumption.

Compared to previous data,[30] the magnitude of postoperative epinephrine responses was reduced in these neonates because of the effective anaesthetic and analgesic regimens used in the present study, although the brief duration of this response was similar to those in previous data.[30] Neonates with complex congenital heart defects were able to mount greater epinephrine responses,[10] suggesting that neonates are capable of increasing their production of epinephrine depending on the level of surgical stress. Decreased plasma concentrations of epinephrine at the end of surgery and decreased postoperative VAS and COMFORT scores in the neonates compared with older infants suggest that the doses used for fentanyl anaesthesia during surgery and postoperative morphine analgesia were inadequate for the older infants.[31] This is further corroborated by the greater amounts of additional postoperative morphine required by the older infants than by the neonates. These findings can be explained by developmental differences in pharmacokinetic and pharmacodynamic factors between neonates and older infants. In studies comparing the effect of i.v. opioids (fentanyl at a mean dose of 1.3 $\mu g\ kg^{-1}$ and morphine to a maximum of 0.2 $mg\ kg^{-1}$) with spinal and extradural analgesia during major surgery in infants (0 - 4 yr), all methods gave adequate postoperative analgesia, but more effective suppression of

epinephrine and norepinephrine was found in the spinal and extradural groups.[8] In the present study, the mean plasma concentrations of epinephrine and norepinephrine were similar to those of the spinal and extradural groups, suggesting that the fentanyl doses were adequate even for high abdominal and thoracic surgery. Most full-term infants older than 4 weeks did not require mechanical ventilation, because they had opioid-induced ventilatory depression.

In contrast with the neonates, the older age groups had plasma concentrations of epinephrine that remained increased during the first 24 h after surgery, which might have been a result of additional stress factors operative in older infants, such as their emotional reactions to a strange environment, hunger, and separation anxiety. Alternatively, greater catecholamine responses may have resulted from direct or reflex stimulation of the efferent nerves supplying the adrenal glands during upper abdominal surgery.[32]
The significantly higher plasma concentrations of nor-epinephrine at baseline in the ventilated than in the non-ventilated neonates might be explained by the withdrawal of sedative and analgesic drugs before surgery (according to the study protocol) in a limited number of patients.
Preoperative neonatal plasma concentrations of lactate were comparable with those in previous studies.[10] Baseline values of the present study are not quite comparable with published results[8,10] because the first blood sampling in the present study occurred after the administration of fentanyl anaesthesia, whereas in the other studies baseline samples were drawn before analgesia.
Neonates had lower pain scores and needed less morphine than older children, probably because of the increased morphine metabolism more than 4 weeks after birth, resulting from closure of the ductus venosus and maturation of hepatic enzymes.[33,34]
We found no consistent correlation of physiological signals of acute pain (plasma concentration of epinephrine and norepinephrine) with behavioural pain scores (VAS and COMFORT scale).

The results of the present study allow us to draw important clinical and physiological conclusions. We can resolve the clinical controversy regarding continuous vs intermittent morphine analgesia. We have shown that neonates and infants up to 1 yr of age can be given intermittent morphine doses, thereby avoiding the excessive fluid intake and the need of infusion equipment. Older infants (1-3 yr) may require either a continuous infusion or more frequent dosing regimens (every 1-2 h) or judicious increases in the intermittent doses used for postoperative morphine analgesia.

Table 4 *Postoperative pain scores [mean (SD)], morphine consumption in the first 24 h after surgery (excluding loading dose), [median (interquartile range)], and number of patients ventilated mechanically > 36 h after surgery. The range of the visual analogue scale (VAS) is 1 – 10 and that of the COMFORT score is 3 – 24. * Average of values 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36 h after surgery. CM = continuous morphine; IM = intermittent morphine; n = number of patients.*

	Age group															
	I = Neonates (0 - 4 weeks)				**II = 4 -26 weeks**				**III = 26 - 52 weeks**				**IV = 1 - 3 years**			
	CM	***n***	**IM**	***n***	**CM**	***n***	**IM**	***n***	**CM**	***n***	**IM**	***n***	**CM**	***n***	**IM**	***n***
VAS score *	1.3 (0.8)	34	1.3 (0.5)	32	2.6 (0.8)	28	2.3 (0.9)	29	2.0 (0.8)	15	2.1 (0.8)	14	1.5 (1.2)	16	2.1 (1.2)	20
COMFORT score *	17.4 (2.9)	31	17.3 (2.3)	28	21.8 (2.0)	26	21.0 (3.1)	27	20.2 (3.1)	15	21.2 (3.1)	12	18.7 (3.1)	15	2.1 (2.6)	17
Morphine ($\mu g\ kg^{-1}\ h^{-1}$)	10.0 (10.0-11.3)	34	10.0 (10.0-10.5)	33	12.3 (11.2-17.8)	29	11.6 (10.2-14.8)	30	11.7 (10.4-14.9)	15	12.1 (10.2-15.2)	15	10.9 (10.2-11.5)	17	11.0 (10.0-15.4)	21
Mechanical ventilation > 36 hours after surgery		26		15		4		7		0		1		2		2

In addition, we have documented significant differences in hormonal and metabolic stress responses, physiological variables, behavioural responses and morphine consumption between neonates and older infants. These differences may result from the developmental changes in opioid pharmacology that occur in early infancy. Either neonates are unable to mount robust behavioural responses to postoperative pain or they may need less morphine for satisfactory behavioural pain scores. It is also evident that neonates need analgesia and/or sedation during mechanical ventilation in order to control catecholamine responses. In the different age groups between 4 weeks and 3 yr, we found similar patterns of hormonal-metabolic responses, behavioural responses and postoperative morphine consumption (although minor differences were found between infants aged 4-26 weeks and 1-3 yr).

We speculate that combined therapy with different classes of analgesic and sedative drugs will provide more effective control of physiological and behavioural responses, especially in children 1-3 yr of age, who may have a high level of anxiety in the PICU. Further studies are needed to establish the efficacy and safety of such combinations. We strongly support the recent editorial calling for more randomized clinical trials to investigate analgesic regimens in young children, due to the absence of validated clinical protocols for infants undergoing surgery.[15] Not only will these studies provide a scientific framework for the postoperative management of neonates and young infants, but they may also provide clues about the development of pain and stress-responsive systems in the developing brain.

2.6 Acknowledgements

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2.7 References

1. Cuthbertson DP. Post-shock metabolic response. Lancet 1942; i:433-7
2. Frayn KN. Hormonal control of metabolism in trauma and sepsis. Clin Endocrinol 1986;24:577-99
3. Hill AG, Hill GL. Metabolic response to severe injury. Br J Surg 1998;85:884-90
4. Kehlet H. Surgical stress: the role of pain and analgesia. Br J Anaesth 1989;63:189-95
5. Kehlet H. Modification of responses to surgery by neural blockade: clinical implications. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade, 2nd Edn. Philadelphia: J.B. Lippincot Company, 1988;145-88
6. Kehlet H. The stress response to surgery: release mechanisms and the modifying effect of pain relief. Acta Chir Scand Suppl 1988;550 (Suppl):22-8
7. Anand KJS, Ward-Platt MP. Neonatal and pediatric stress responses to anesthesia and operation. Int Anesthesiol Clin 1988;26:218-25
8. Wolf AR, Eyres RL, Laussen PC, et al. Effect of extradural analgesia on stress responses to abdominal surgery in infants. Br J Anaesth 1993;70:654-60
9. Anand KJS, Sippell WG, Aynsley-Green A. Randomized trial of fentanyl anesthesia in preterm babies undergoing surgery: effects on the stress response. Lancet 1987;31:243-8
10. Anand KJS, Hickey PR. Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med 1992;326:1-9
11. Guinsburg R, Kopelman BI, Anand KJS, de Almeida MF, Peres C de A, Miyoshi MH. Physiological, hormonal, and behavioral responses to a single dose in intubated and ventilated preterm neonates. J Pediatr 1998;132:954-9
12. Orsini AJ, Leff KH, Costarino A, Dettorre MD, Stefano JL. Routine use of fentanyl infusions for pain and stress reduction in infants with respiratory distress syndrome. J Pediatr 1996;129:140-5
13. Quinn MW, Wild J, Dean HG, et al. Randomized double-blind controlled trial of effect of morphine on catecholamine concentrations in ventilated pre-term babies. Lancet 1993;342:324-7
14. Pokela ML. Pain relief can reduce hypoxemia in distressed neonates during routine treatment procedures. Pediatrics 1994;93:379-83
15. Choonara I. Why do babies cry? BMJ 1999;319:1381
16. Bouwmeester NJ, Hop WCJ, Tibboel D. Metabolic stress responses in postoperative children aged 0-3 years (abstract). Paed Anaesth 2000;10:690-1
17. Anand KJS, Aynsley-Green A. Measuring the severity of surgical stress in newborn infants. J Pediatr Surg 1988;23:297-305

18. Ambuel B, Hamlett KW, Marx CM, et al. Assessing distress in pediatric intensive care environments: The COMFORT Scale. J Pediatr Psychol 1992;17:95-109
19. Marx CM, Smith PG, Lowrie LH, et al. Optimal sedation of mechanically ventilated pediatric critical care patients. Crit Care Med 1994;22:163-70
20. van Dijk M, Boer de JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 – 3 year-old infants. Pain 2000;84:367-77
21. van der Hoorn FA, Boomsma F, Man in 't Veld AJ, Schalekamp MA. Determination of catecholamines in human plasma by high-performance liquid chromatography: comparison between a new method with fluorescence detection and an established method with electrochemical detection. J Chromatogr 1989;487:17-28
22. Berkely. BMPD Statistical Software Manual, Module 5V. University of California Press.1990;1207-44
23. Hunt A, Joel S, Dick G, Goldman A. Population pharmacokinetics of oral morphine and its glucuronides in children receiving morphine as immediate-release liquid or sustained-release tablets for cancer pain. J Pediatr 1999;135:47-55
24. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. Clin Pharmacokinet 1996;31:423-43
25. Lynn A, Nespeca MK, Bratton SL, Strauss SG, Shen DD. Clearance of morphine in postoperative infants during intravenous infusion: the influence of age and surgery. Anesth Analg 1998;86:958-63
26. Rutter PC, Murphy F, Dudley HA. Morphine: controlled trial of different methods of administration for postoperative pain relief. Br Med J 1980;280:12-3
27. Cuschieri RJ, Morran CG, Howie JC, McArdle CS. Postoperative pain and pulmonary complications: comparison of three analgesic regimens. Br J Surg 1985;72:495-8
28. Marshall H, Porteous C, McMillan I, MacPherson SG, Nimmo WS. Relief of pain by infusion of morphine after operation: does tolerance develop? Br Med J (Clin Res Ed) 1985;291:19-21
29. Malviya S, Pandit VA, Merkel S et al. A comparison of continuous epidural infusion and intermittent intravenous bolus doses of morphine in children undergoing selective dorsal rhizotomy. Reg Anesth Pain Med 1999;24:438-43
30. Anand KJS, Brown MJ, Bloom SR, Aynsley-Green A. Studies on the hormonal regulation of fuel metabolism in the human newborn infant undergoing anaesthesia and surgery. Horm Res 1985;22:115-28
31. Yaster M. The dose response of fentanyl in neonatal anesthesia. Anesthesiology 1987;66:433-5

32. Engquist A, Brandt MR, Fernandes A, Kehlet H. The blocking effect of epidural analgesia on the adrenocortical and hyperglycemic responses to surgery. Acta Anaesthesiol Scand 1977;21:330-5
33. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. Anesthesiology 1987;66:136-9
34. Greeley WJ, Bruijn de NP. Changes in sufentanil pharmacokinetics within the neonatal period. Anesth Analg 1988;67:86-90

Chapter 3

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

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

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

Design
Randomized double-blind study

Setting
Paediatric Surgical Intensive Care Unit

Methods
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), following abdominal or thoracic surgery, received morphine 100 $\mu g\ kg^{-1}$ after surgery, and were randomly assigned to either continuous morphine (CM, 10 $\mu g\ kg^{-1}h^{-1}$) or intermittent morphine boluses (IM, 30 $\mu g\ kg^{-1}$ every 3h). Pain was measured with the COMFORT behavioural scale and the Visual Analogue Scale. Additional morphine was administered on guidance of the pain scores. Morphine (M), morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) plasma concentrations were determined 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 as 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 M, M3G and M6G (all $P < 0.001$), and significantly lower M6G/M ratio ($P < 0.03$) than the older groups. The M6G/M3G ratio was similar in all age groups.

Conclusion
Neonates require a narrower therapeutic window for postoperative morphine analgesia than older age groups, with no differences in the safety or effectiveness of intermittent doses compared to 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 $\mu g\ kg^{-1}h^{-1}$ at plasma concentrations of < 15 ng ml^{-1}.

3.2 Introduction

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, which are affected by the age, hepatic function, renal function and clinical condition of these patients.[6-9] As a result of these factors, morphine pharmacokinetic studies have reported a noticeable variability between individual 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 gender,[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. In the same patient population, we have recently reported the effects of morphine administration on their hormonal and metabolic stress responses following major surgery.[17]

3.3 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 to 3

years, 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 prior to surgery, or suffered from hepatic, renal or neurologic disorders. Patients were stratified into four age groups: I) 0 - 4 weeks, II) 4 to 26 weeks, III) 26 to 52 weeks, IV) 1 - 3 years. They were randomly assigned to receive either intravenous continuous morphine (CM) or intermittent morphine (IM). The pharmacist prepared all study drugs and strata-specific schedules for randomisation. For each age group the boxes with study drugs were numbered consecutively and used in sequence. Each included patient received a study number, consisting of a number of the age group (I to IV) and a sequence number (1 to 68). Anaesthetic management was standardized in all patients. Anaesthesia was induced with i.v. thiopentone 3 - 5 mg kg^{-1} or, when i.v. induction was impossible, by inhalation of halothane in oxygen (< 5 % of the patients). After the insertion of an i.v. line, the anaesthetic procedure was similar for all patients. Fentanyl 5 $\mu g\ kg^{-1}$ was given before orotracheal intubation, which was facilitated with atracurium 0.5 - 1 mg kg^{-1} or suxamethonium 2 mg kg^{-1}. Ventilation was controlled and anaesthesia was maintained with isoflurane 0.5 minimum alveolar concentration (MAC) in 60 % nitrous oxide in oxygen or air in oxygen. Perioperative fluids were standardized to maintain a glucose infusion rate between 4 - 6 mg $kg^{-1}\ min^{-1}$. Body temperature was kept within normal ranges. A peripheral artery was cannulated and the measured mean arterial blood pressure (MAP) and heart rate (HR) data served as preoperative baseline data. Patients received a second dose of fentanyl 5 $\mu g\ kg^{-1}$ before surgical incision and additional doses of fentanyl 2 $\mu g\ kg^{-1}$ when HR and/or MAP were 15 % above baseline value. At the end of surgery, the neuromuscular block was antagonized and the tracheal tube was 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) to classify the degree of surgical stress.[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 intravenous loading dose of morphine hydrochloride (100 $\mu g\ kg^{-1}$ in 2 min), followed by a morphine infusion of 10 $\mu g\ kg^{-1}\ h^{-1}$ for children in the CM group, combined with three-hourly intravenous placebo (saline) boluses. Children in the IM group received three-hourly intravenous morphine doses of 30 $\mu g\ kg^{-1}$, 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 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] of which total scores could range from 6 to 30, and the Visual Analogue Scale (VAS), ranging from 0 to10. The modified CS counts six behavioural items: alertness, calmness, respiratory response (for mechanically ventilated children) or crying (for the non-ventilated children), movement, muscle tone, and facial tension.[20] VAS scores were taken after the 2-minute observation periods needed for the CS. Additional analgesia was given when there were signs of pain, indicated by VAS scores ≥ 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 $\mu g\ kg^{-1}$ 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 to determine blood gas values and plasma concentrations of M, M3G and M6G. Respiratory depression was defined by the presence of apnoea or arterial $PaCO_2$ values ≥ 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

Sample preparation

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 (C6H6, Baker, cat.nr 7212-01). The extraction column was conditioned with two column volumes of methanol, two column volumes of water and 1 ml of 500 mM diammonium sulphate (pH = 9.3). The serum (0.6 ml) was diluted with 0.6 ml 500 mM diammonium sulphate (pH = 9.3) before it was brought on top of the extraction column. It was washed with 2 ml of 50 mM diammonium sulphate (pH = 9.3) after which it was allowed to dry for 15 seconds. The elution was carried out with 0.5 ml 0.01 M KH_2PO_4 buffer, pH = 2.1,

containing 11 % acetonnitrile. From this elute 50 µl was injected on the analytical column.

Chromatography

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 = 210nm (Separations, HI-Ambacht, the Netherlands), in sequence with an ESA electrochemical detector (ESA, Kratos, Rotterdam; present: Interscience, Breda, 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 oxidised 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 0.4V, while the detector 1 potential was 0.3V. This minimizes interfering peaks because only compounds with an oxidation potential from 0.3 to 0.4V are recorded. Chromatographic separations were achieved using a Cp-Sper C8 column (250 x 4.6 mm) (Chrompack, Bergen op Zoom, the Netherlands). The mobile phase was a 0.01 M KH_2PO_4 buffer, pH = 2.1, containing 11 % acetonnitrile and 0.4 g/l heptane sulphonic acid.

Recovery and reproducibility

For the measurement of M3G, M6G and morphine, the calibration samples contained all three compounds. In serum all calibration graphs (containing 6 data points) were linear: for M3G the concentrations ranged from 25 - 580 ng/ml (r = 0.9992); for M6G from 5 - 100 ng/ml (r = 0.9982) and for M, from 5 - 90 ng/ml (r = 0.9963). The quantitation limit was 5 ng/ml for M and M6G and 25 ng/ml for M3G. However, in individual samples, the chromatogram allowed for a lower threshold. Using these values yes or no should have affected the mean plasma concentrations. 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 were less than 10 % for all compounds and the accuracy was about 5 %.[22,23]

Standardized automated laboratory analysers measured plasma concentrations of bilirubin and creatinine.

Statistical analysis

Relations between age and the studied plasma concentrations (M, M3G and M6G) were investigated using ANOVA. We applied multiple regression analysis to determine the effects of the factors 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 distributions. 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 due to prior 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, n = 1), and another patient required neuromuscular blockade after surgery (hemi-hepatectomy n = 1). 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 (alpha = 0.01) with a power greater than 80 %.

3.4 Results

Table 1 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).

Table 1 Patients data and details of surgery in 197 patients.

	I (neonates, 0-4 weeks)		II (4-26 weeks)		III (26-52 weeks)		IV (1-3 years)	
	CM	IM	CM	IM	CM	IM	CM	IM
(*n*)	31	32	32	33	16	14	18	21
Age (days)	4	2	90	95	273	267	613	574
(range)	(0-28)	(0-17)	(29-173)	(30-179)	(185-351)	(187-330)	(368-1070)	(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 ($\mu mol\ l^{-1}$)	46 (22)	47 (25)	26 (18)	23 (14)	31 (36)	54 (45)	28 (36)	27 (16)
Plasma total bilirubin ($\mu mol\ l^{-1}$)	91 (67)	108 (56)	23 (39)	35 (55)	15 (31)	7 (3)	6 (2)	7 (3)
Plasma bilirubin glucuronide ($\mu mol\ l^{-1}$)	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 >24h post 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)
Type of 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. Age (days): median (range); (n) number of patients; other values are mean (SD).

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 Surgical Stress Scores.

Morphine requirements

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 2 shows the need for extra morphine as percentage of patients and the total requirement of morphine kg^{-1} h^{-1} (excluding the loading dose) in the four age groups. Only 38 % of neonates (age group I) required additional morphine, a significantly lower percentage than in all older age groups. More infants aged 4 to 26 weeks (91 % of group II) required additional morphine than the children aged 1 to 3 years (72 % of group IV).

Table 2 Morphine requirements for 24 hours after surgery

Age group	I (0-4 weeks) ($n = 63$)	II (4–26 weeks) ($n = 65$)	III (26–52 weeks) ($n = 30$)	IV (1-3 yr) ($n = 39$)
No. of patients with extra morphine (%) *	24 (38)	59 (91)	26 (87)	28 (72)
§Morphine maintenance dose $\mu g\ kg^{-1}hr^{-1}$#	10.0 (10.0-10.7)	12.3 (10.6-16.6)	11.9 (10.4-15.3)	10.9 (10.0-14.3)

Values are percentages, or median (interquartile range); (n) number of patients.
**Age group I versus groups II, III and IV ($P < 0.001$); II versus IV ($P = 0.011$) (X^2 –test).*
 # Age group I versus groups II, III and IV ($P < 0.001$) ANOVA. § Excluding the loading dose of 100 $\mu g\ kg^{-1}$.

Additional morphine

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 age 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 group. 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.

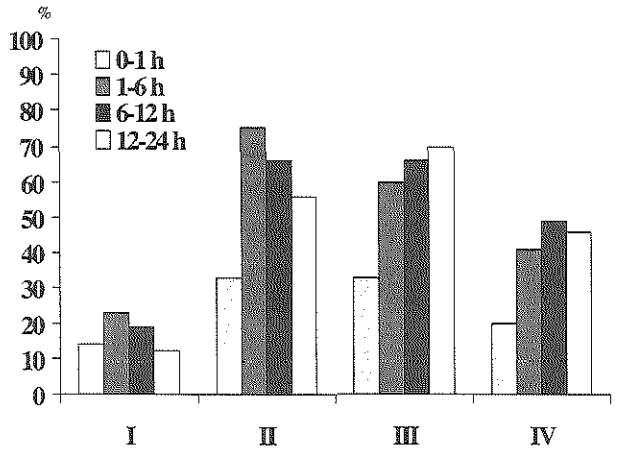

Fig. 1 *Percentages of patients in all age groups (group I. 0-4 weeks, II. 4-26 weeks, III. 26-52 weeks, IV.1-3 yr) needing additional morphine during the first 24 h after surgery (0-1 h, 1-6 h, 6-12 h, 12-24 h).*

Morphine dosage kg^{-1}

The age group and type of morphine administration significantly affected the required morphine dosage kg^{-1} day^{-1}. 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 amount of 30 μg kg^{-1} in the CM group, the treatment groups did no longer differ from one another. Age group I needed significantly less morphine kg^{-1} than the other age groups (ANOVA, $P < 0.001$) (Table 2).

Morphine plasma concentrations

Analysis of morphine plasma concentrations at 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. The plasma concentrations at 12 and 24 h after surgery were no longer dependent on type of treatment.

Table 3 Plasma concentrations of morphine, M3G and M6G at 6, 12 and 24 h after surgery, according to age and treatment group

		Age Groups															
		I (neonates, 0-4 weeks)				**II (4 –26 weeks)**				**III (26-52 weeks)**				**IV (1-3 yr)**			
CP ($ng.ml^{-1}$)	time after surgery (h)	**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	13.42† (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; CP = concentration plasma; M3G = morphine-3-glucuronide; M6G = morphine-6-glucuronide; n = number of patients. Data are median (interquartile range).

**Age group I higher than all other age groups (CM and IM) (P < 0.001); † II higher than IV (CM and IM) (P < 0.001), # CM higher than IM in all age groups (P < 0.007); § I higher than III and IV (CM and IM) (P < 0.003) (ANOVA)*

Table 3 gives the plasma concentrations of morphine and its metabolites M3G and M6G, and the differences between age and treatment groups at 6, 12 and 24 h after surgery.

Plasma levels were significantly higher in age group I than in the other groups, and in age group II versus group IV (Table 3). ANOVA showed that morphine plasma concentrations were significantly affected by the total morphine dose administered ($P < 0.001$). Plasma morphine levels in the CM neonatal group (at 12 and 24 h after surgery) were significantly correlated with plasma creatinine levels ($r = 0.5$, $P = 0.01$; $r = 0.4$, $P = 0.04$, respectively), and with plasma bilirubin levels ($r = 0.6$, $P = 0.001$).

Morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) concentrations
Difficulties in detection of M3G plasma concentrations in the neonatal group, because of disturbing spikes, resulted in many missing values ($n = 32$) for M3G in this age group. ANOVA of M3G and M6G plasma concentrations revealed that the age group and the administered dosage of morphine kg^{-1} significantly affected these plasma levels (both $P < 0.001$).

Although plasma concentrations of M3G and M6G were higher in CM than in IM, this difference was only significant for M3G at 6 h after surgery. M3G and M6G plasma concentrations were significantly higher in age group I than in the other age groups and in group II versus group IV at 12 and 24 h after surgery (all $P < 0.001$) (Table 3). 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 2abc shows the median plasma concentrations of M, M3G and M6G, in the four age groups for CM and IM at 6, 12 and 24 h after surgery.

M3G/M and M6G/M ratios
Table 4 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 only significant differences between age groups, not between the different treatments. The M6G/M ratio was lower in age group I than in all other age groups (Table 4).

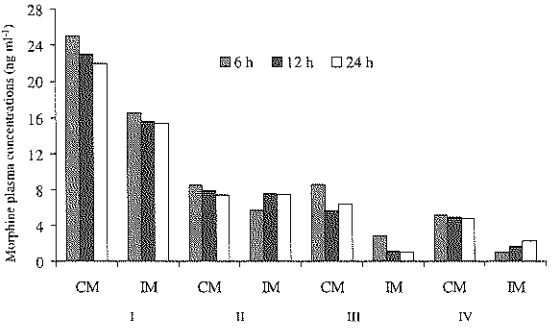

Fig 2a *Morphine plasma concentrations (median) in all age groups (group I. 0 - 4 weeks, II. 4 - 26 weeks, III. 26 - 52 weeks, IV. 1 - 3 yr) at 6, 12 and 24 h after surgery. CM = continuous morphine, IM = intermittent morphine.*

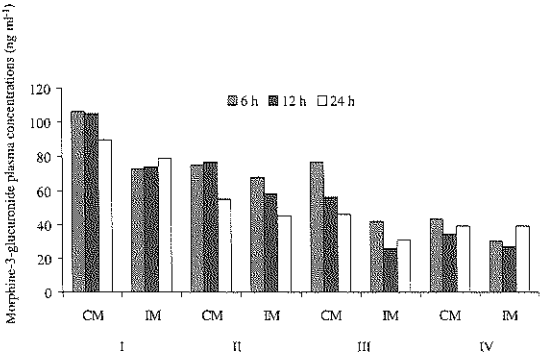

Fig. 2b *Morphine-3-glucuronide (M-6-G) plasma concentrations (median) in all age groups (group I. 0 - 4 weeks, II. 4 - 26 weeks, III. 26 - 52 weeks, IV. 1 - 3 yr) at 6, 12 and 24 h after surgery. CM = continuous morphine, IM = intermittent morphine.*

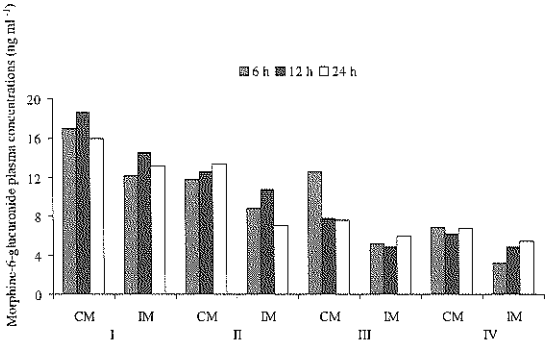

Fig. 2c *Morphine-6-glucuronide (M-6-G) plasma concentrations (median) in all age groups (group I. 0 - 4 weeks, II. 4 - 26 weeks, III. 26 - 52 weeks, IV. 1 - 3 yr) at 6, 12 and 24 h after surgery. CM = continuous morphine, IM = intermittent morphine*

Table 4 Morphine and morphine metabolite ratios at 24 h after surgery

	Age groups										
	I (0-4 weeks)			II (4-26 weeks)			III (26-52 weeks)			IV (1-3 yr)		
	CM	IM	*n*	CM	IM	*n*	CM	IM	*n*	CM	IM	*n*
M3G/M ratio	5.2	7.0	28	8.6	9.6	47	8.0	15.7	27	9.1	16.7	34
	(2.9-11.6)	(3.0-11.9)		(7.8-10.3)	(2.4-20.0)		(5.5-14.5)	(7.4-27.5)		(5.0-11.0)	(6.1-27.6)	
M6G/M ratio	0.8*	1.1	52	1.5	1.9	50	1.5	3.4	28	1.4	2.5	32
	(0.5-1.7)	(0.7-1.5)		(1.2-2.1)	(0.5-3.8)		(0.9-2.3)	(1.1-5.9)		(1.0-2.1)	(1.3-4.6)	
M6G/M3G	0.22	0.17	30	0.18	0.17	49	0.18	0.19	27	0.18	0.16	32
ratio	(0.16-0.23)	(0.13-0.25)		(0.15-0.23)	(0.15-0.21)		(0.15-0.19)	(0.16-0.24)		(0.16-0.22)	(0.14-0.19)	

M = morphine; M3G= morphine-3-glucuronide; M6G = morphine-6-glucuronide; CM = continuous morphine, IM = intermittent morphine
Values are median (interquartile range); n = number of patients.
** Age group I versus groups III and IV ($P < 0.003$), group I versus II ($P = 0.03$), (CM and IM); ANOVA.*

Table 5 Data of 11 patients with respiratory insufficiency during the first 24 h after surgery

Age (days)	CM/IM	Diagnosis	Complications	Extra M Yes/No	Mean dose M ($\mu g\ kg^{-1}\ h^{-1}$)	Re-intubation Yes/No	Hours 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 M 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	$pCO_2\uparrow$ (8.9 and 8.3 kPa at 6 and 12 h post surgery)	N	10	N		Downs syndrome
54	CM	Neuroblastoma	Apnoea	Y	10.2	Y	6	
61	CM	Ileus	Apnoea	Y	22.2	Y	6	High pain scores; 100 $\mu g\ kg^{-1}$ extra M in 3 h
78	IM	Rehbein resection	$pCO_2\uparrow$ (8.4 kPa at 6 h post surgery)	Y	10.7	N		
90	IM	Nissen fundoplication	In- and expiratory stridor 2 h post surgery	Y	10.4	Y	< 4	
102	IM	Bilobectomy	$pCO_2\uparrow$ (7.4 and 7.5 kPa at 6and 12 h post surgery)	Y	11.7	N		Pneumonia
831	CM	Neuroblastoma	Apnoea	N	10	N	12	M stopped at 12 h post surgery

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

Table 6 Overview of morphine requirements and plasma concentrations of morphine in 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[25]
0 to 6 months	5	mean 150 (S)		26.2 (22.5) mean (SD)	129 min after M dose	Olkkola[26]
2-4 years	5	150 (S)		3.8 (2.3) mean (SD)	189 min after M dose	Olkkola[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	
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; SD = standard deviation; IQR = interquartile range.

M6G/M3G-ratio

Neither age group nor treatment at any time point had any significant effect on the M6G/M3G ratio (Table 4).

Adverse effects

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

Table 6 gives an overview of studies reporting requirements and plasma concentrations of morphine after non-cardiac surgery, including the present data.[24-26]

3.5 Discussion

In this clinical study we investigated a) the effects of various variables on the morphine dose required in infants, and b) 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 $\mu g\ kg^{-1}\ h^{-1}$ 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 through the minimal dose of 10 $\mu g\ kg^{-1}\ h^{-1}$ (concentration median 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 $\mu g\ kg^{-1}\ h^{-1}$. Even with the additional morphine, the required dose was lower than the recommended dosage of 20 $\mu g\ kg^{-1}\ h^{-1}$. [27-31] Remarkably, of the age groups older than 4 weeks, children aged 1 to 3 years 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 6). 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 > 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 CS and VAS scores postoperatively. It seems that plasma concentrations as high as 15 ng ml^{-1} are not necessary for adequate postoperative analgesia in infants > 4 weeks. Although at the time of surgery all patients had been without morphine therapy > 6 h , plasma morphine was still detectable in five neonates. This would indicate that clearance in this age group is low (approx. 9 ml kg^{-1} min^{-1}).[9] Morphine plasma 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 in a nurse-controlled way, based on observational pain scores, resulted in similar plasma concentrations in CM and IM from 12 h after surgery. In the CM group we report median concentrations that decreased from 7.4 to 6.4 to 4.8 ng ml^{-1} with increasing age. These data are consistent with an increase in plasma clearance over the age range investigated.

Plasma concentrations of morphine which should produce effective analgesia in neonates and older children have been reported to range from 3.8 (± 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, mechanically 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 metabolised in the liver into M3G and M6G by urinediphosphate glucuronosyl transferase (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 two years. Using the ¾ power model adult levels of clearance were reached at an earlier age, between 2 and 6 months.[35]

High morphine plasma levels and low M3G- and M6G-morphine 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, signifying that they were able to glucuronidate morphine. Nevertheless, hepatic induction of these enzyme systems cannot be ruled out. The high plasma levels of morphine

metabolites in the neonates were due to a low renal function, 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 by the active metabolite M6G. While the M3G/M and M6G/M ratios increased with advancing age, indicating improved morphine metabolism, the M3G and M6G plasma concentrations decreased with advancing 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 (age group I) and the older children (age groups II, II and IV), but also between infants aged 4 to 26 weeks (group II, median age 3 months) and 1 to 3 years (group IV, median age 20 months). The major changes in morphine metabolism and elimination apparently take place in the first 3 months after birth, 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 levels 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.

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 et al.[39] The disparity in plasma morphine glucuronide ratios between the different studies could be due to 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 et al. reported a consistently high correlation between M6G and M3G, with a ratio of about 15 % as well in neonates and children, as in adults.[7] 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 of both metabolites to morphine. Although the number of neonates and children was small compared with that of adults (49, 90 and 1073, respectively), the ratio M3G/M6G remained constant in all subgroups analyzed

(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), without significant differences between the three older age groups. The M6G/M3G ratio at 24 h after intravenous morphine was not significantly different between the four different age groups from 0 to 3 years.
Although the data are difficult to compare (median versus mean weighted values) both latter studies result in similar conclusions, i.e. A) neonates differ significantly from older patients (children and adults, respectively), having an immature morphine metabolism, B) children > 1 month metabolize morphine like older children, as presented in our study, and like adults,[7] and C) the M6G/M3G ratio remains constant at all ages.
Hartley reported decreasing M6G/M3G plasma ratios, although not significantly, with increasing birth weight.[37] The latter might suggest a differential development of enzymes (UDGT) for the formation of M3G and M6G.
Recently it was shown that Uridine 5'-diphosphate-glucuronyltransferase-2B7 (UGT2B7) is responsible for the glucuronidation of morphine and is capable of catalyzing 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 significantly differ 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 belonged to 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.

3.6 Conclusions

Age is the most important factor in morphine dosage 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 fullterm neonates.[27] However, we would advise to start with an infusion rate of 15 $\mu g\ kg^{-1}\ h^{-1}$ 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 with its associated risks.

3.7 Acknowledgements

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3.8 References

1. Campbell NN, Reynolds GJ, Perkins G. Postoperative analgesia in neonates: an Australia-wide survey. Anaesthesia & Intensive Care 1989; 17:487-91.
2. Farrington EA, McGuinness GA, Johnson GF, Erenberg A, Leff RD. Continuous intravenous morphine infusion in postoperative newborn infants. American Journal of Perinatology 1993; 10:84-7.
3. Haberkern CM, Lynn AM, Geiduschek JM, Nespeca MK, Jacobson LE, Bratton SL, Pomietto M. Epidural and intravenous bolus morphine for postoperative analgesia in infants. Canadian Journal of Anaesthesia 1996; 43:1203-10.
4. Johnston CC, Collinge JM, Henderson SJ, Anand KJS. A cross-sectional survey of pain and pharmacological analgesia in Canadian neonatal intensive care units. Clinical Journal of Pain 1997; 13:308-12.
5. Rees EP, Tholl DA. Morphine use and adverse effects in a neonatal intensive care unit. CMAJ (Canadian Medical Association Journal) 1994; 150: 499-504.
6. Lynn A, Nespeca MK, Bratton SL, Strauss SG, Shen DD. Clearance of morphine in postoperative infants during intravenous infusion: the influence of age and surgery. Anesth Analg 1998; 86:958-63.
7. Faura CC, Collins SL, Moore RA, McQuay HJ. Systematic review of factors affecting the ratios of morphine and its major metabolites. Pain 1998; 74: 43-53.
8. Dagan O, Klein J, Bohn D, Barker G, Koren G. Morphine pharmacokinetics in children following cardiac surgery: effects of disease and inotropic support. J Card Vasc Anesth 1993; 7:396-98.
9. Scott CS, Riggs KW, Ling EW, Fitzgerald CE, Hill ML, Grunau RVE, Solimano A, Craig KD. Morphine pharmacokinetics and pain assessment in premature newborns. J Pediatr 1999; 135:423-9.
10. Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 1-Pharmacokinetics. Pediatr Anaesth 1997; 7:5-11.
11. Guinsburg R, de Araujo Peres C, Branco de Almeida MF, de Cassia Xavier Balda R, Cassia Berenguel R, Tonelotto J, Kopelman BI. Differences in pain expression between male and female newborn infants. Pain 2000; 85;127-33.
12. Kinney HC, Ottoson CK, White WF. Three-dimensional distribution of 3H-naloxone binding to opiate receptors in the human fetal and infant brainstem. J Comparative Neurology 1990; 291:55-78.
13. Marsh DF, Hatch DJ, Fitzgerald M. Opioid systems and the newborn. Br J Anaesth 1997; 79:787-95.
14. Rahman W, Dashwood MR, Fitzgerald M, Aynsley-Green A, Dickenson AH. Postnatal development of multiple opioid receptors in the spinal cord and development of spinal morphine analgesia. Brain Research. Developmental Brain Research 1998; 108:239-54.

15. Grunau RE, Oberlander TF, Whitfield MF, Fitzgerald C, Lee SK. Demographic and therapeutic determinants of pain reactivity in very low birth neonates at 32 weeks' postconceptional age. Pediatrics 2001; 107:105-112.
16. Bernstein BA, Pachter LM. Cultural considerations in children's pain. In: Schechter NL, Berde CB, Yaster M, eds. Pain in infants, children and adolescents. Philadelphia: Williams & Wilkins, 1993;113-122.
17. Bouwmeester NJ, Anand KJS, Dijk van M, Hop WCJ, Boomsma F, Tibboel D. Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine. Br J Anaesth 2001; 87:390-9.
18. Anand KJS, Aynsley-Green A. Measuring the severity of surgical stress in newborn infants. J Pediatr Surg 1988; 23:297-305.
19. Ambuel B, Hamlett KW, Marx CM, Blumer JL. Assessing distress in pediatric intensive care environments: The COMFORT Scale. J Pediatr Psychol 1992; 17 :95-109.
20. Dijk van M, Boer de JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 – 3 year-old infants. Pain 2000; 84:367-77.
21. Lynn AM, Nespeca MK, Opheim KE, Slattery JT. Respiratory effects of intravenous morphine infusions in neonates, infants and children after cardiac surgery. Anesth Analg 1993; 77:695-701.
22. Verwey-van Wissen CP, Koopman-Kimenai PM, Vree TB. Direct determination of codeine, norcodeine, morphine and normorphine with their corresponding O-glucuronide conjugates by high-performance liquid chromatography with electrochemical detection. J Chromatogr 1991; 570:309-320.
23. Kimenai PM. High performance liquid chromatography of morphine and its conjugated metabolites: morphine-3-glucuronide and morphine-6-glucuronide. In: Clinical pharmacokinetics of nicomorphine. Metabolic conversion: an important aspect of drug action. Nijmegen: Katholic University, 1996;40-46.
24. Lynn A, Nespeca MK, Bratton SL, Strauss SG, Shen DD. Clearance of morphine in postoperative infants during intravenous infusion: the influence of age and surgery. Anesth Analg 1998; 86:958-63.
25. Farrington EA, McGuinness GA, Johnson GF, Eremberg A, Leff RD. Continuous intravenous morphine infusion in postoperative newborn infants. AJ Perinatology 1993; 10:84-7.
26. Olkkola KT, Maunuksela EL, Korpela R, Rosenberg PH. Kinetics and dynamics of postoperative intravenous morphine in children. Clin Pharmacol Ther 1988; 44:128-36.
27. Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 2-Clinical use. Pediatr Anaesth 1997; 7:93-101.

28. Hendrickson M, Myre L, Johnson DG, Matlak ME, Black RE, Sullivan JJ. Postoperative analgesia in children: a prospective study of intermittent intramuscular injection versus continuous intravenous infusion of morphine. J Ped Surg 1990; 25:185-91.
29. Bray RJ. Postoperative analgesia provided by morphine infusion in children. Anaesthesia 1983; 38:1075-8.
30. Beasley SW, Tibballs J. Efficacy and safety of continuous morphine infusion for postoperative analgesia in the paediatric surgical ward. Aust N Z J Surg 1987; 57:233-7.
31. Lynn AM, Nespeca MK, Bratton SL, Shen DD. Intravenous morphine in postoperative infants: intermittent bolus dosing versus targeted continuous infusions. Pain 2000; 88:89-95.
32. Dahlstrom B, Bolme P, Feychting H, Noack G, Paalzow L. Morphine kinetics in children. Clin Pharmacol Ther 1979; 26: 354-65.
33. Chay PC, Duffy BJ, Walker JS. Pharmacokinetic-pharmacodynamic relationships of morphine in neonates. Clin Pharmacol Ther 1992; 51: 334-342.
34. McRorie TI, Lynn AM, Nespeca MK, Opheim KE, Slattery JT. The maturation of morphine clearance and metabolism. AJDC 1992; 146: 972-976.
35. Anderson BJ, McKee AD, Holford NHG. Size, myths and the clinical pharmacokinetics of analgesia in paediatric patients. Clin Pharmacokinet 1997; 33: 313-327.
36. Choonara IA, McKay P, Hain R, Rane A. Morphine metabolism in children. Br J Clin Pharmacol 1989; 28: 599-604.
37. Hartley R, Green M, Quinn MW, Rushforth JA, Levene MI. Development of morphine glucuronidation in premature neonates. Biol Neonate 1994; 66: 1-9.
38. Saarenmaa E, Neuvonen PJ, Rosenberg P, Fellman V. Morphine clearance and effects in newborn infants in relation to gestational age. Clin Pharmacol Ther 2000; 68:160-166.
39. Barrett DA, Barker DP, Rutter N, Pawula M, Shaw PN. Morphine, morphine-6-glucuronide and morphine-3-glucuronide pharmacokinetics in newborn infants receiving diamorphine infusions. Br J Clin Pharmacol 1996; 41:531-537.
40. Coffman BL, King CD, Rios GR, Tephly TR. The glucuronidation of opioids, other xenobiotics, and androgens by human UGT2B7Y(268) and UGT2B7H(268). Drug Metab Dispos 1998; 26:73-77.
41. de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Glucuronidation in Humans. Pharmacogenetic and Developmental aspects. Clin Pharmacokinet 1999; 36:439-452.
42. Carrier JS, Turgeon D, Journault K, Hum DW, Bélanger A. Isolation and Characterization of the Human UGT2B7 Gene. Biochemical and Biophysical Research Communications 2000; 272, 616-621.

Chapter 4

Developmental pharmacokinetics of morphine and metabolites in neonates, infants and young children

Based on:

Developmental pharmacokinetics of morphine and metabolites in neonates, infants and young children

Nancy J. Bouwmeester, Brian J. Anderson, Dick Tibboel, Nicholas H.G. Holford.

Submitted.

4.1 Abstract

Background
Data concerning metabolism of morphine and its metabolites in young children are scant. Previous studies have not differentiated the effects of size from those related to age during infancy.

Methods
Postoperative children 0 - 3 years were given an intravenous loading dose of morphine hydrochloride (100 μg/kg in 2 min) followed by either an intravenous morphine infusion of 10 μg/kg/h (n = 92) or 3-hourly intravenous morphine boluses 30 μg/kg (n = 92). Additional morphine (5 μg/kg) every 10 min was given if the Visual Analogue Pain Scale (VAS, 0 - 10) score was ≥ 4. Serum (0.6 ml) was sampled within 5 min of the loading dose and at 6, 12 and 24 h for morphine, morphine-3-glucuronide (M3G) and morphine–6-glucuronide (M6G). The formation clearances of morphine base to its glucuronide metabolites as well as metabolite elimination clearances were estimated using non-linear mixed effects models.

Results
Population parameter estimates and their variability (%) for a one compartment, first order elimination model were as follows: volume of distribution 115 l (54), formation clearance to M3G 24.3 (91) l/h, formation clearance to M6G 2.9 (87) l/h, elimination clearance of M3G 7.2 (65) l/h, elimination clearance of M6G 5.0 (76) l/h; standardized to a 70 kg person using allometric '¼ power' models. Clearance by other routes contributed 50% of total body clearance. The volume of distribution increased exponentially with a maturation half-life of 2 weeks from 72 l/70kg at birth; formation clearance to M3G and M6G increased with maturation half-life of 79 days from 5.2 and 0.6 l/h/70kg respectively at birth. Serum bilirubin concentration was inversely related to metabolite formation. Metabolite clearance increased with age (maturation half-life 131 days) with a time course similar to that described for glomerular filtration rate in infants.

Conclusion
M3G is the predominant metabolite of morphine in young children and total body morphine clearance is 87 % that of older children at 6 months. A mean steady-state serum concentration of 20 ng/ml can be achieved in children after non-cardiac surgery in an intensive care unit with a morphine hydrochloride infusion of 8.5 μg/kg/h at birth (term

neonates), 15 μg/kg/h at 1 month, 22 μg/kg/h at 3 months, 27 μg/kg/h at 12 months postnatal age and 25 μg/kg/h for 1 - 3 year old children.

4.2 Introduction

Morphine is largely metabolized by uridine 5'-diphosphate glucuronosyltransferase UGT2B7 to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).[1] In vitro studies using liver microsomes from fetuses aged 15 - 27 weeks indicated that morphine glucuronidation was approximately 10 – 20 % of that seen with adult microsomes.[2,3] Morphine glucuronidation has been demonstrated in premature infants as young as 24 weeks. Morphine clearance is reported as 23.6 (S.D. 8.5) ml/min/kg in infants and children greater than 11 days old.[4] Lynn et al[5] report clearances (ml/min/kg) greater than those of adults at 3 months of age. In a systematic review of morphine metabolism Faura et al[6] conclude that children older than 1 month metabolize morphine like adults. The use of the per kilogram size model (ml/min/kg) has confused interpretation of morphine developmental pharmacokinetics; an overestimation occurs as size decreases.[7] Anderson et al[8] corrected available clearance data from different age groups using a ¾ power allometric size model to demonstrate that adult values for clearance are reached at about 6 months.
We had the opportunity to examine morphine and metabolite serum concentrations in children 0 - 3 years old given either intermittent boluses or morphine infusion.[9] These data were investigated using a population based approach that included size as the primary covariate in an effort to disentangle age related factors from size related factors.

4.3 Methods

Patients and methods
The study was approved by the hospital medical ethical committee and written consent obtained from the parents of studied children. Children aged 0 to 3 years, admitted to the paediatric surgical intensive care unit following non-cardiac thoracic and abdominal surgery were considered for enrolment. Patients were excluded if they had received morphine within 6 h before surgery, or if they suffered from hepatic, renal or neurological disorders. Patients were randomly assigned to receive either intravenous morphine hydrochloride infusion or intermittent morphine hydrochloride boluses. The pharmacists

randomised and prepared all study drugs. Clinical staff were blinded to the study group allocation.
At the end of surgery, mechanical ventilation was continued in patients who required ventilatory assistance after surgery. Directly after surgery all patients were given an intravenous loading dose of morphine hydrochloride (100 μg/kg over 2 min), followed by either a morphine infusion of 10 μg/kg/h combined with three-hourly intravenous placebo (saline) boluses or a continuous placebo infusion (saline) combined with three-hourly intravenous morphine hydrochloride boluses of 30 μg/kg. Additional morphine (5 μg/kg every 10 min) was given if the Visual Analogue Pain Scale (VAS, 0 - 10) scores were ≥ 4. No other analgesic or sedative drugs were used.
Arterial blood samples (1.4 ml) were taken after induction of anaesthesia (baseline), at the end of surgery, and at 6, 12, and 24 h after surgery to determine serum concentrations of morphine, M3G and M6G.

Pain was assessed 3 hourly by nurses trained in the use of the behavioural part of the COMFORT Score[10] and the VAS (0 - 10). The VAS was measured after the 2 minutes of observation needed for the COMFORT Score. Nursing interventions included pain assessment, blood sampling and administration of intermittent bolus (placebo or morphine) medication.

Morphine and metabolite assay

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 (C6H6, Baker, cat.nr 7212-01). The extraction column was conditioned with two column volumes of methanol, two column volumes of water and 1 ml of 500 mM diammonium sulphate (pH = 9.3). The serum (0.6 ml) was diluted with 0.6 ml 500 mM diammonium sulphate (pH = 9.3) before it was brought on top of the extraction column. It was washed with 2 ml of 50 mM diammonium sulphate (pH = 9.3) after which it was allowed to dry for 15 seconds. The elution was carried out with 0.5 ml 0.01 M KH_2PO_4 buffer, pH = 2.1, containing 11 % acetonnitrile. From this elute 50 μl was injected on 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 = 210nm (Separations, HI-Ambacht, the Netherlands), in sequence with an ESA electrochemical detector (ESA, Kratos, Rotterdam; present: Interscience, Breda, 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 oxidised 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 0.4V, while the detector 1 potential was 0.3V. This minimises interfering peaks because only compounds with an oxidation potential from 0.3 to 0.4V are recorded. Chromatographic separations were achieved using a Cp-Sper C8 column (250 x 4.6 mm) (Chrompack, Bergen op Zoom, the Netherlands). The mobile phase was a 0.01 M KH_2PO_4 buffer, pH = 2.1, containing 11 % acetonnitrile and 0.4 g/l heptane sulphonic acid.

In serum all calibration graphs (containing 6 data points) were linear: for M3G the concentrations ranged from 25-580 ng/ml (r = 0.9992); for M6G from 5 - 100 ng/ml (r = 0.9982) and for M, from 5 -90 ng/ml (r = 0.9963). On average, the quantitation limit was 5 ng/ml for M and M6G and 25 ng/ml for M3G. However, in individual samples, the chromatogram allowed for a lower threshold. In this concentration range, the intra-day precision was less than 10 % for all compounds and the accuracy was about 5%.[11,12] Standardised automated laboratory analysers measured serum concentrations of bilirubin and creatinine.
Morphine hydrochloride dose, and M3G and M6G concentrations were converted to anhydrous morphine base equivalents using a molecular weight of 285 for morphine, 322 for morphine hydrochloride and 461 for the two glucuronide metabolites.

Modelling

Population parameter estimates

Population parameter estimates were obtained using a non-linear mixed effects model. This model accounts for population parameter variability (between and within subjects) and residual variability (random effects) as well as parameter differences predicted by covariates (fixed effects). The population parameter variability in model parameters was modelled by a proportional variance model. The covariance between clearance, distribution volume and absorption half-life was incorporated into the model. A proportional term characterised the residual unknown variability for morphine. An additive and a proportional term characterised the residual unknown variability for M3G and M6G concentrations. The population mean parameters, between subject variance and residual variances were estimated using NONMEM version V release 1.1.[13] Estimation used the first order conditional estimate method with the interaction option and ADVAN 6 with Tol = 5. Convergence criterion was 3 significant digits. A Compaq Digital Fortran

Version 6.5 compiler with Intel Celeron 333 MHz CPU (Intel Corp., Santa Clara, CA) under MS Windows 1998 (Microsoft Corp., Seattle, WA) was used to compile NONMEM.

Differential equations were used to describe the pharmacokinetics of morphine and its metabolites.

$$CLT = CL2M3G + CL2M6G + CLEX$$

$$dCS/dt = (RATEIN - CS \times CLT) / V$$

$$dM3G/dt = (CL2M3G \times CS - CLM3G \times CM3G) / V3M$$

$$dM6G/dt = (CL2M6G \times CS - CLM6G \times CM6G) / V6M$$

The model is shown in Figure 1. CLT is total body clearance, V is the volume of distribution for morphine, CS is morphine serum concentration, CL2M3G is formation clearance to M3G, CL2M6G is formation clearance to M6G, CLM3G is the elimination clearance of M3G, CLM6G is the elimination clearance of M6G, VM is the volume of distribution of glucuronide metabolites, CLEX is unaccounted clearance, RATEIN is the morphine infusion rate.

The metabolite volumes of distribution (V3M, V6M) can not be identified with the current study design and were fixed at 23 and 30 l/70kg, based on a studies by Penson et al[14] and Hanna et al[15] in adults.

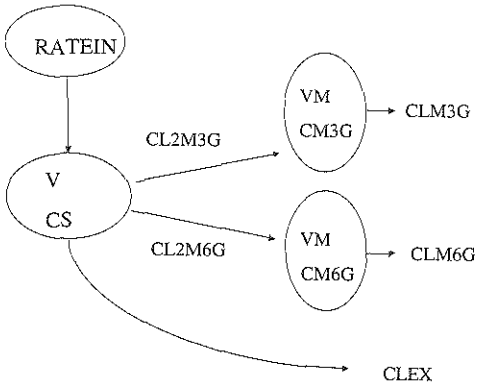

Figure 1 *Pharmacokinetic Model. CLT is total body clearance, V is the volume of distribution for morphine, CS is morphine serum concentration, CL2M3G is the formation clearance to M3G, CL2M6G is the formation clearance to M6G, CLM3G is the elimination clearance of M3G, CLM6G is the elimination clearance of M6G, VM is the volume of distribution of glucuronide metabolites, CLEX is unaccounted clearance, RATEIN is the morphine infusion rate.*

Covariate Analysis

The parameter values were standardized for a body weight of 70-kg using an allometric model[7,16]

$$P_i = P_{std} \times (W_i / W_{std})^{PWR}$$

where P_i is the parameter in the ith individual, W_i is the weight in the ith individual and P_{std} is the parameter in an individual with a weight W_{std} of 70 kg. The PWR exponent was 0.75 for clearance and 1 for distribution volumes.[16-19]

Exponential functions were applied to allow for age-related changes for the formation of metabolites (CL2M3G, CL2M6G), clearance of metabolites, unaccounted clearance and morphine volume of distribution (see Table 3b). e.g.

$$CL2M3G = (CL2M3Gstd \times (Wt/70)^{0.75}) \times (1 - \beta cl \times EXP(-PNA\ in\ days \times Ln(2)/Tcl))\ \text{l/h}$$

$$CLM3G = (CLM3Gstd \times (Wt/70)^{0.75}) \times (1 - \beta rf \times EXP(-PNA\ in\ days \times Ln(2)/Trf))\ \text{l/h}$$

$$CLEX = (CLEXstd \times (Wt/70)^{0.75}) \times (1 - \beta ex \times EXP(-PNA\ in\ days \times Ln(2)/Tex))\ \text{l/h}$$

$$V = (Vstd \times (Wt/70)) \times (1 - \beta vol \times EXP(-PNA\ in\ days \times Ln(2)/Tvol))\ \text{l}$$

βcl, βrf, βex and βvol are parameters estimating the fraction below CL2M3G, CLM3G, CLEX and V respectively at birth; Tcl, Trf, Tex and Tvol describe the maturation half-lives of the age-related changes of CL2M3G, CLM3G, CLEX and V.

The effect of altered renal function on CLM3G & CLM6G was modelled using an estimate of renal function in children older than one week of age. Renal function was standardised to a 40-year-old adult male with a creatinine clearance of 6 l/h and a creatinine of 85.947 mcmol/l.[20] This empirical model used age (PNA) as a covariate to predict creatinine production rate with scaling constant (Kage) for age e.g.

$$CLM3G = CLM3Gstd \times (Wt/70)^{0.75} \times 85.947/creatinine \times EXP(Kage \times PNA/365-40)$$

Serum bilirubin (mcmol/l) was used as a marker of hepatic function and its effect on CL2M3G & CL2M6G was modelled with an exponential function with a scaling constant (Kbili) e.g.

$$CL2M3G = CL2M3Gstd \times (Wt/70)^{0.75} \times EXP(bilirubin \times Kbili)$$

The quality of fit of the pharmacokinetic model to the data was assessed by visual examination of plots of observed versus predicted concentrations. Models were nested and an improvement in the objective function was referred to the Chi-squared distribution to assess significance e.g. an objective function change (OBJ) of 3.84 is significant at $\alpha = 0.05$.

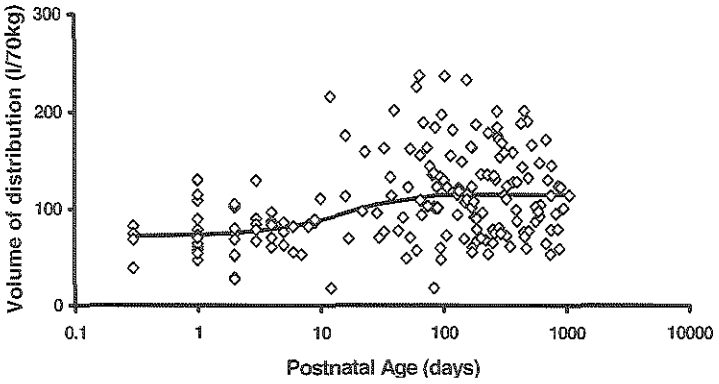

Figure 2 *Volume of distribution change with postnatal age. Individual predicted volumes, standardised to a 70-kg person, from the NONMEM post hoc step, are plotted against age. The solid line represents the non-linear relation between volume of distribution and age.*

4.4 Results

The analysis comprised 184 subjects (1856 observations). The number of children given intermittent bolus and those given morphine infusion were the same ($n = 92$). There were 106 boys and 78 girls. Mean (range) age and weight of the patients were 195 (0 - 1070) days and 5.9 (1.9 - 16.8) kg. Parameter estimates, standardised to a 70-kg, 40 year old person are shown in Table 1a. Metabolism by routes other than M3G and M6G was undetectable. Covariate analysis estimates are shown in table 1b. The covariance of the pharmacokinetic parameters, expressed as the correlation of population parameter variability was low (table 2). Table 3a shows metabolite formation and clearance estimate changes with age.

The volume of distribution of morphine increased exponentially with a maturation half-life of 2 weeks from 72 l/70kg at birth (figure 2); formation clearance to M3G (figure 3a) and M6G (figure 3b) increased with a maturation half-life of 78.7 days from 5.8 and 0.6 l/h/70kg at birth to predicted values of 25 and 3 l/h/70kg at 3 years respectively. At 6 months formation clearances were 87 % of those predicted in children at 3 years. Formation maturation of both metabolites was the same. The objective function was not improved by using individual maturation parameters for each metabolite. Serum bilirubin concentration was inversely related to metabolite formation clearances (figure 4).

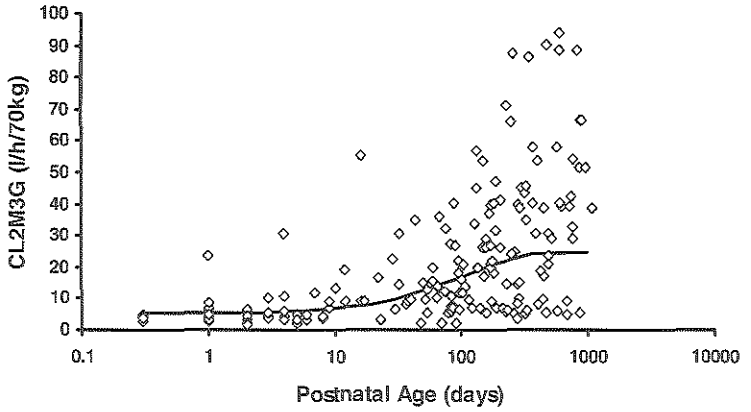

Figure 3a *Individual predicted formation clearances to M3G, standardised to a 70-kg person, from the NONMEM post hoc step, are plotted against age. The solid line represents the non-linear relation between clearance and age.*

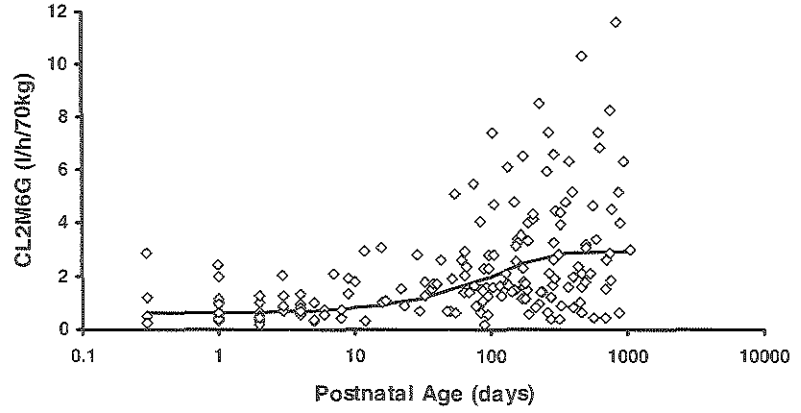

Figure 3b *Individual predicted formation clearances to M6G, standardised to a 70-kg person, from the NONMEM post hoc step, are plotted against age.*

Table 1a Pharmacokinetic parameter estimates. These estimates are standardised to a 70-kg person using an allometric size model; %CV is the coefficient of variation for the population parameter estimate.

Parameter	Estimate	CV %
CLT	52.3	-
CL2M3G	24.3	91
CL2M6G	2.9	87
CLM3G	7.2	65
CLM6G	5.0	76
CLEX	25.1	95
V	115	54
V3M	23 fixed	-
V6M	30 fixed	-
Err morphine (proportional)	0.38	
Err M3G (additive) ng/ml	3.4	
Err M3G (proportional)	0.36	
Err M6G (additive) ng/ml	0.46	
Err M6G (proportional)	0.30	

CLT = population estimate for CL (l/h//70kg) in children, V is the volume of distribution for morphine (l/70kg), CL2M3G is formation clearance to M3G (L/h/70kg), CL2M6G is formation clearance to M6G (l/h/70kg), CLM3G is the clearance of M3G (l/h/70kg), CLM6G is the clearance of M6G (l/h/70kg), CLEX is unaccounted clearance, Err is the residual error. The metabolite volumes of distribution (V3M, V6M) can not be identified with the current study design and were fixed at 23 and 30 l/70kg, based on a studies by Penson et al[14] and Hanna et al[15] in adults.

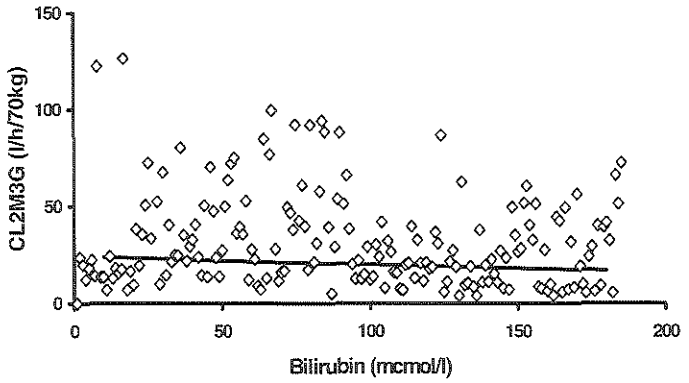

Figure 4 *Individual a posteriori Bayesian estimates for CL2M3G corrected for size and age plotted against serum bilirubin. Formation clearance decreases as serum bilirubin increases.*

Table 1b Covariate Models and Estimates for Pooled Population Parameters

Parameter	Estimate
βvol	0.381
Tvol	13.5 days
βcl	0.793
Tcl	78.7 days
βrf	0.789
Trf	131 days
βex	0.739
Tex	55.9 days
Kage	0.0128
Kbili	-0.00195

a) Volume of distribution

$V = (Vstd \times (Wt/70)) \times (1 + \beta vol \times EXP(-PNA\ in\ days \times Ln(2)/Tvol))$ *l*

βvol is a parameter estimating the fraction below V at birth, Tcl describes the maturation half-life of the age-related change for V. PNA is postnatal age.

b) Formation clearance

$CL2M3G = (CL2M3Gstd \times (Wt/70)^{0.75}) \times (1 - \beta cl \times EXP(-PNA\ in\ days \times Ln(2)/Tcl))$ *L/h*

$CL2M6G = (CL2M6Gstd \times (Wt/70)^{0.75}) \times (1 - \beta cl \times EXP(-PNA\ in\ days \times Ln(2)/Tcl))$ *L/h*

βcl is a parameter estimating the fraction below CL2M3G and CL2M6G at birth, Tcl describes the maturation half-life of the age-related change for CLM3G and CL2M6G.

c) Metabolite clearance

$CLM3G = (CLM3Gstd \times (Wt/70)^{0.75}) \times (1 - \beta rf \times EXP(-PNA\ in\ days \times Ln(2)/Trf))$ *l/h*

$CLM6G = (CLM6Gstd \times (Wt/70)^{0.75}) \times (1 - \beta rf \times EXP(-PNA\ in\ days \times Ln(2)/Trf))$ *l/h*

$CLEX = (CLEXstd \times (Wt/70)^{0.75}) \times (1 - \beta ex \times EXP(-PNA\ in\ days \times Ln(2)/Tex))$ *l/h*

βrf and βex are parameters estimating the fraction below CLM3G, CLM6G and CLEX at birth, Trf and Tex describe the maturation half-life of the age-related change for CLM3G, CLM6G and CLEX.

d) Creatinine clearance[40] in children older than one week of age. Creatinine clearance was standardised to a 40 year old person and centred about 85.947 mcmol/l. This empirical model used age (PNA) as a covariate to predict creatinine production rate with scaling constant (Kage) e.g.

$CLM3G = CLM3Gstd \times (Wt/70)^{0.75} \times 85.947/creatinine \times EXP(Kage \times PNA/365-40)$

e) Relationship of bilirubin to CL2M3G & CL2M6G

$CL2M3G = CL2M3Gstd \times (Wt/70)^{0.75} \times EXP(bilirubin \times Kbili)$

Kbili is a scaling factor

Metabolite elimination clearance of M3G and M6G increased with a maturation half-life of 131 days from 1.53 and 1.1 l/h/70kg at birth to predicted values of 7.2 and 5 l/h/70kg at 3 years respectively (figure 5a & b). This maturation curve closely approximated that described for the maturation of glomerular filtration rate in infants. The effect of altered renal function on M3G elimination clearance is shown in figure 6. This effect appears minimal.

Table 2 Correlation of population pharmacokinetic parameter variability

	CL2M3G	CL2M6G	CLM3G	CLM6G	V
CL2M3G	1				
CL2M6G	0.65	1			
CLM3G	0.73	0.40	1		
CLM6G	0.388	0.76	0.64	1	
V	0.003	0.09	-0.21	-0.08	1

Figures 7a, b & c demonstrate the quality of fit for pharmacokinetic data over the study time. The individual Bayesian predictions for serum concentration of morphine, M3G and M6G are compared to those observed. These predictions are based on maximum a posteriori Bayesian estimates of the parameters for each specific individual using their observed data. The fit is poorest for the prediction of serum metabolite concentration after the initial loading dose of morphine. The weighted residuals (WRES) for each subject with values for each subject joined by vertical bars are shown in Figure 8. This plot gives a good indication of which patient's data deviated in a particular direction.

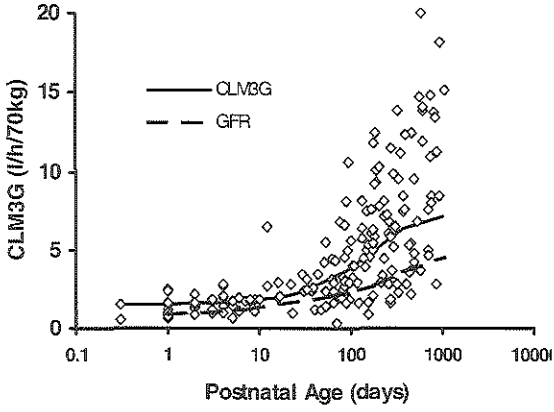

figure 5a

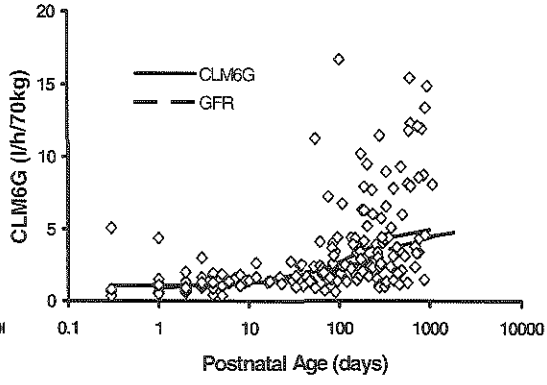

figure 5b

Figure 5 *Individual a posteriori Bayesian estimates of CLM3G (A) are plotted against postnatal age. The dashed line represents the maturation of glomerular filtration rate (ml/min/1.73m^2), scaled to overlie CLM3G maturation (data from Bergstein[39]). It closely approximates that of predicted CLM3G maturation. Individual a posteriori Bayesian estimates of CLM6G (B) are plotted against postnatal age.*

Table 3a Morphine base parameter estimate changes with age estimated in this current study

Age days	V l/70kg	CL2M6G l/h/70kg	CL2M3G l/h/70kg	CLM3G l/h/70kg	CLM6G l/h/70kg	CLEX l/h/70kg	CLT base l/h/70kg
0	71.9	0.6	5.2	1.5	1.1	6.6	12.4
7	84.4	0.8	6.3	1.7	1.2	8.1	15.2
30	105.6	1.2	9.7	2.4	1.6	12.3	23.2
90	114.6	1.9	15.9	3.7	2.5	19	36.8
180	115	2.5	20.8	5	3.5	23.1	46.4
365	115	2	24	6.4	4.4	24.9	51.8
1000	115	3	24.8	7.2	5	25.1	52.9

Table 3b Morphine clearance changes with post conception age. Data taken from Scott et al.[24]

PCA Weeks	Weight Kg	Clearance ml/min/kg	CLT std (CV%) l/h/70kg
24-27	1.1	2.27	3.378 (47)
28-31	1.4	3.21	5.07 (49)
32-35	2.2	4.51	7.98 (44)
36-39	3.6	7.8	15.6 (32)

Table 3c Morphine sulphate clearance changes with postnatal age in term neonates. Data taken from Lynn et al[5] and McRorie et al.[27] *Weights are estimates only

Age Days	Weight * Kg	Clearance ml/min/kg	CLT std l/h/70kg	Weight Kg	Clearance ml/min/kg	CLT std l/h/70kg
	Lynn et al			McRorie et al		
0-7	3	9.8	18.7 (12.0-30.6)	3.2	5.5	10.6 (6.2-16.3)
8-30	4	13.3	27.3	3.9	7.4	15.1 (6.9-38.4)
31-90	5.6	23.9	53.4 (37.3-74.4)	4.3	10.5	22.0 (20.5-42.0)
91-180	7.5	32.3	77.6 (44.5-125.2)	5.1	13.9	30.3 (18.2-52.6)
181-365	8.5	38.1	94.5 (44.6-172.1)	7.2	21.7	51.6 (13.7-68.0)
Adult[4]	70	22	92.4 (CV% 38)			

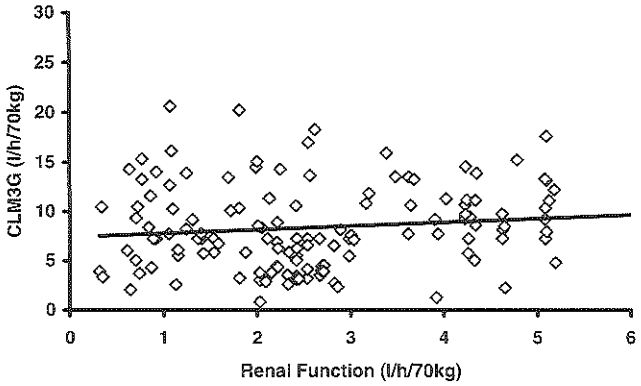

Figure 6 *The relationship of renal function to metabolite elimination clearance of M3G, corrected for size and age.*

4.5 Discussion

Size has considerable impact on the estimation and interpretation of pharmacokinetic parameters in children[7,8,21] and has been unaccounted for in paediatric morphine pharmacokinetic studies.[5,22-27] The impact of size is demonstrated in table 3b & 3c, where reported clearance estimates, standardised to a 70-kg person with an allometric "¾ power model", show that clearance is similar to adults within 6 - 12 months. Size was the primary covariate used in our analysis of the effects of age and weight. This deliberate choice was based on known biological principles. A great many physiological, structural and time related variables scale predictably within and between species with weight exponents of 0.75, 1 and 0.25 respectively.[17] We have used these "1/4 power models" in this current study rather than centred weight, or some other function of weight, because the "1/4 power models" have sound biological principles. West et al[18,19] have used fractal geometry to mathematically explain this phenomenon. The ¾ power law for metabolic rates was derived from a general model that describes how essential materials are transported through space-filled fractal networks of branching tubes.[18,19] These design principles are independent of detailed dynamics and explicit models and should apply to virtually all organisms. By choosing weight as the primary covariate, the secondary effects of age could be investigated. We had no prior biological model for the effect of age on clearance or apparent volume, but assumed first order processes, which are common in biology.

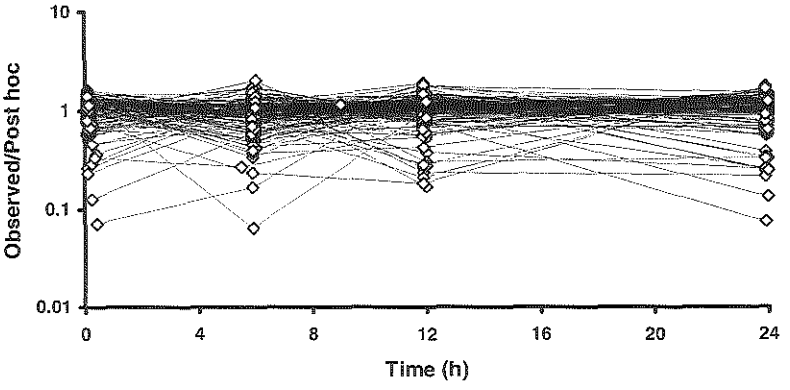

figure 7a

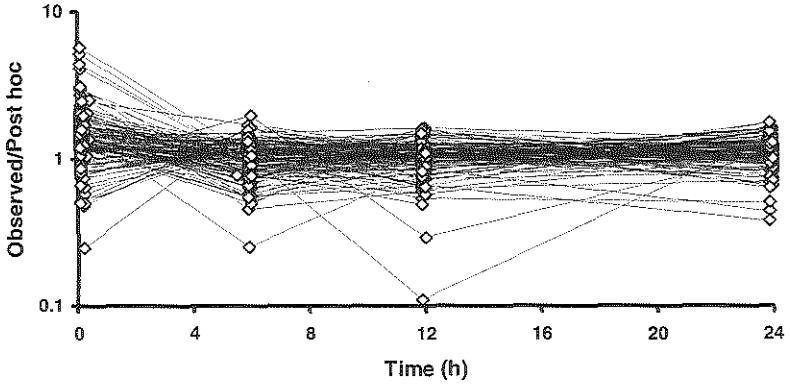

figure 7b

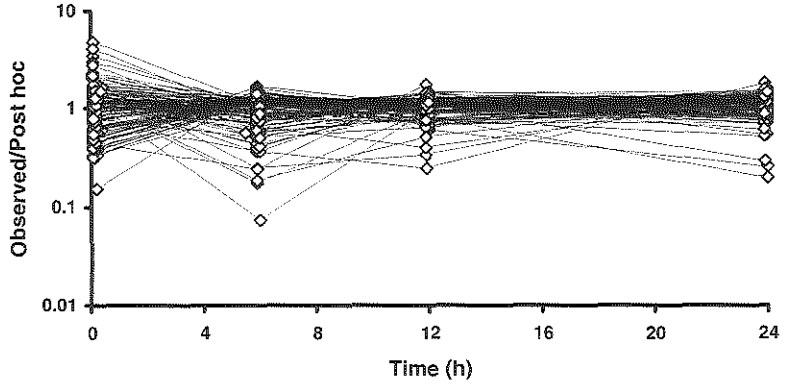

figure 7c

Figure 7 *Figures 7a, b & c demonstrate the quality of fit for pharmacokinetic data over the study time period – a line connects each subject's data. The individual a posteriori Bayesian predictions for serum concentration of morphine (A), M3G (B) and M6G (C) are compared to those observed. These predictions are based on maximum a posteriori Bayesian estimates of the parameters for each specific individual using their observed data.*

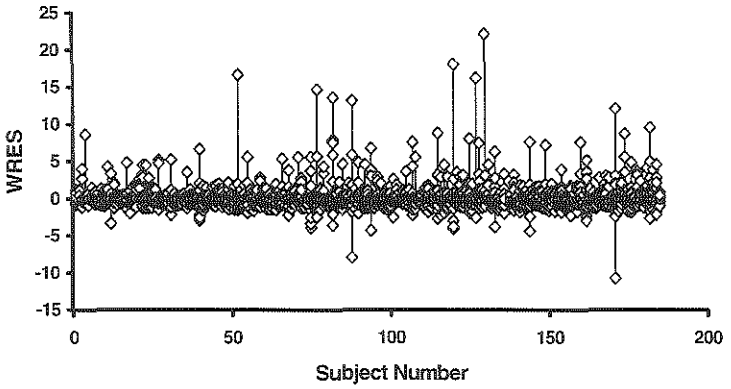

Figure 8. *The weighted residuals (WRES) for each subject with values for each subject joined by vertical bars are shown.*

The predominant metabolite was M3G. Formation clearance to M3G and M6G increased with maturation half-life of 79 days from 5.2 and 0.6 l/h/70kg at birth to predicted adult values of 25 and 3 l/h/70kg respectively. The total body clearance (CLT) was 87 % that of older children by 6 months and 98 % that predicted in adults by 1 year. Morphine HCl CLT and its rate of maturation fall between those described by McRorie et al[27] and those described by Lynn et al[25] or Hunt et al,[28] when their estimates are standardised to a 70-kg person with a ¾ power model (table 3c). Our estimates are for the anhydrous morphine base rather than sulphate or hydrochloride salts and were determined using a population-based analysis. Differences may be related the population studied and the nature of the illness within that population.[5] McRorie[27] and Lynn[25] determined clearance after infusion by dividing infusion rate in those patients whom achieved steady state concentration. Patients who did not achieve steady-state concentrations were excluded and it is unclear from their papers if the morphine salt used in the infusion and measured concentrations of morphine were corrected for molecular weight.

There are few data concerning morphine metabolite formation or elimination clearance in neonates and children. Barrett et al[29] studied the pharmacokinetics of morphine, M6G and M3G in 19 ventilated new-born infants (24 - 41 weeks gestation) who were given diamorphine infusions. The authors made the assumption that 55 % of administered morphine is converted to M3G and 10 % to M6G, based on adult literature.[30] The CLT reported by Barrett et al[29] (4.6 ml/min/kg, 7.2 l/h/70kg) is similar to that observed in the study by Scott et al in premature neonates[24] (Table 3b) and the CL2M3G (2.5 ml/min/kg, 4.0 l/h/70kg) is similar to that in our current study. We estimate a formation clearance contribution of 42 % for M3G in infants rather than 55 % in adults. Similarly, the

CL2M6G (0.46 ml/min/kg, 0.72 l/h/70kg) is smaller than expected (0.63 l/h/70kg) because of the smaller contribution from this metabolite (5 % vs. 10 %). CLT observed in our current study in term neonates is 50 % greater than that described by others in premature neonates[23,24] (4.6 ml/min/kg, 7.2 l/h/70kg), consistent with intrauterine development of glucuronidation.[1]

The volume of distribution increased exponentially with a maturation half-life of 2 weeks from 72 l/70kg at birth to 115 (CV 54 %) l/70kg at 6 months. Kart et al,[4] in a literature review, were unable to discern age related changes in volume of distribution. However, the methods used in the literature to determine volume of distribution vary greatly and it is difficult to compare estimates. Individual studies such as that by Pokela et al[31] report similar age-related changes to ours. The volume of distribution increased from 91 (S.D. 28) l/70kg in neonates 1 - 4 days old, 126 (S.D. 56) l/70kg at 8 - 60 days and 168 (S.D. 105) l/70kg at 61 - 180 days of age.

The metabolite volumes of distribution in neonates and children are unknown. Penson et al[14] report a volume of distribution for M3G (V3M) of 23.1 l/70kg in adults. Adult estimates for the volume of distribution for M6G (V6M) are from 8.4 to 30 l/70kg.[15,32-34] V6M is believed to be greater than V3M because of higher lipophilicity at physiological pH;[35] consequently a V6M of 30 l/70kg was empirically chosen. The goodness of fit was poorest for the prediction of serum metabolite concentration after the initial loading dose of morphine (figure 7) and may be attributable to fixing VM at a set value with no associated variability. The CLM3G of 7.2 (CV 65 %) l/h/70kg is similar to that described by Penson[32] (10.1, SD 2.9 l/h/70kg) in adults. Both M6G formation and clearance is reduced compared to adults. Penson[14] and Lotsch[34] report a CLM6G of 9.4, SD 2.8 l/h/70kg and 9.24, SD 1.68 l/h/70kg respectively. These data suggest that both CL2M6G and CLM6G increase out of early childhood to approach those of adults.

The morphine metabolites M3G and M6G are water-soluble compounds, enabling renal excretion. The time course of metabolite elimination clearance follows that of glomerular filtration rate (GFR), although clearance of M3G is greater (see figure 5). This may be attributable to renal tubular secretion[30,36,37] and non-renal elimination.[30,38] Glomerular filtration rate (GFR) changes are usually referenced to body surface area in children,[39] a model that approximates the "3/4 power model" but uses 2/3 as the weight exponent. Attempts to use the Cockcroff and Gault models[40] to predict creatinine production rate failed. An empirical formula based on age to predict creatinine production was used. Creatinine production increased with age (Kage 0.0128) as opposed to adults in whom production decreases with age (Kage –0.014).[40] The increase in children is assumed to be a consequence of increasing muscle bulk with age as opposed to the decrease in muscle

bulk that occurs with age in adults. The maturation of GFR is determined by inulin clearance, but is commonly estimated by creatinine clearance. However, creatinine clearance (CrCl) may result in overestimation as GFR declines because of tubular secretion, changes in metabolic state altering creatinine production, and measurement errors at low concentrations significantly altering CrCl estimation. We demonstrated minimal effect attributable to altered renal function (based on creatinine production) because maturation of metabolite elimination clearance, which mirrored GFR maturation, was already accounted for.

Serum bilirubin was used as a marker of hepatic function. This is a crude marker of hepatic function because serum concentrations are dependent on both formation and clearance of bilirubin. Bilirubin is metabolised in the liver by another glucuronosyltransferase, UGT1A1, and does not compete for the same metabolic pathway as morphine.[1] Activity of this enzyme also increases immediately after birth, reaching adult values around 3 to 6 months.[41] It was possible to relate bilirubin (ΔOBJ 50) to metabolite formation. Clearance was reduced from 24 l/h/70kg when serum bilirubin is 5 mcmol/l to 17 l/h/70kg when bilirubin is 180 mcmol/l.
Routes other than glucuronidation clear morphine in humans. Renal clearance of unmetabolised morphine contributes 19 % of CLT in infants younger than 3 months, 13 % in older infants and 11 % in adults.[27] Sulphate metabolism for morphine is believed to be similar to that for acetaminophen and contributes approximately 6 l/h/70kg, a clearance that is the same for neonates and adults.[27,42] Faecal excretion and normorphine formation contribute minimally. We were unable to quantify these other routes in this current study and these clearances were accounted for by the CLEX parameter. CLEX contributed 47 % of CLT at 3 years while CL2M3G contributed 42% and CL2M6G 6 %, suggesting there is further gradual maturation of glucuronidation during childhood or adolescence before adult ratios of 35 %, 55 % and 10 % respectively are reached.

4.6 Acknowledgements

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4.7 References

1. de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Glucuronidation in humans. Pharmacogenetic and developmental aspects. Clin Pharmacokinet 1999; 36:439-52.
2. Pacifici GM, Sawe J, Kager L, Rane A. Morphine glucuronidation in human fetal and adult liver. Eur J Clin Pharmacol 1982; 22:553-8.
3. Pacifici GM, Franchi M, Giuliani L, Rane A. Development of the glucuronyltransferase and sulphotransferase towards 2-naphthol in human fetus. Dev Pharmacol Ther 1989; 14:108-14.
4. Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 1--Pharmacokinetics. Paediatr Anaesth 1997; 7:5-11.
5. Lynn A, Nespeca MK, Bratton SL, Strauss SG, Shen DD. Clearance of morphine in postoperative infants during intravenous infusion: the influence of age and surgery. Anesth Analg 1998; 86:958-63.
6. Faura CC, Collins SL, Moore RA, McQuay HJ. Systematic review of factors affecting the ratios of morphine and its major metabolites. Pain 1998; 74:43-53.
7. Holford NHG. A size standard for pharmacokinetics. Clin Pharmacokinet 1996; 30:329-332.
8. Anderson BJ, McKee AD, Holford NH. Size, myths and the clinical pharmacokinetics of analgesia in paediatric patients. Clin Pharmacokinet 1997; 33:313-27.
9. Bouwmeester NJ, Anand KJ, van Dijk M, Hop WC, Boomsma F, Tibboel D. Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine. Br J Anaesth 2001; 87:390-9.
10. van Dijk M, de Boer JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. Pain 2000; 84:367-77.
11. Kimenai PM. Clinical pharmacokinetics of nicomorphine. Metabolic conversion: an important aspect of drug action. Clinical Pharmacology. Nijmegen: Katholic University, 1996.
12. Verwey-van Wissen CP, Koopman-Kimenai PM, Vree TB. Direct determination of codeine, norcodeine, morphine and normorphine with their corresponding O-glucuronide conjugates by high-performance liquid chromatography with electrochemical detection. J Chromotogr 1991; 570:309-20.
13. Beal SL, Sheiner LB, Boeckmann A. Nonmem User's Guide. San Francisco: Division of Pharmacology, University of California, 1999.
14. Penson RT, Joel SP, Clark S, Gloyne A, Slevin ML. Limited phase I study of morphine-3-glucuronide. J Pharm Sci 2001; 90:1810-6.
15. Hanna MH, Peat SJ, Knibb AA, Fung C. Disposition of morphine-6-glucuronide and morphine in healthy volunteers. Br J Anaesth 1991; 66:103-7.

16. Karalis V, Macheras P. Drug disposition viewed in terms of the fractal volume of distribution. Pharm Res 2002; 19:696-703.
17. Peters HP. Chpt 4. Physiological correlates of size. In: Beck E, Birks HJB, Conner EF, eds. The Ecological Implications of Body Size. Cambridge: Cambridge University Press, 1983:48-53.
18. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. Science 1997; 276:122-6.
19. West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science 1999; 284:1677-9.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41.
21. Anderson BJ, Meakin GH. Scaling for size: some implications for paediatric anaesthesia dosing. Paediatr Anaesth 2002; 12:205-19.
22. Chay PC, Duffy BJ, Walker JS. Pharmacokinetic-pharmacodynamic relationships of morphine in neonates. Clin Pharmacol Ther 1992; 51:334-42.
23. Hartley R, Green M, Quinn M, Levene MI. Pharmacokinetics of morphine infusion in premature neonates. Arch Dis Child 1993; 69:55-8.
24. Scott CS, Riggs KW, Ling EW, et al. Morphine pharmacokinetics and pain assessment in premature newborns. J Pediatr 1999; 135:423-9.
25. Lynn AM, Nespeca MK, Bratton SL, Shen DD. Intravenous morphine in postoperative infants: intermittent bolus dosing versus targeted continuous infusions. Pain 2000; 88:89-95.
26. Choonara IA, McKay P, Hain R, Rane A. Morphine metabolism in children. Br J Clin Pharmacol 1989; 28:599-604.
27. McRorie TI, Lynn AM, Nespeca MK, Opheim KE, Slattery JT. The maturation of morphine clearance and metabolism [published erratum appears in Am J Dis Child 1992 Nov;146(11):1305]. Am J Dis Child 1992; 146:972-6.
28. Hunt A, Joel S, Dick G, Goldman A. Population pharmacokinetics of oral morphine and its glucuronides in children receiving morphine as immediate-release liquid or sustained-release tablets for cancer pain. J Pediatr 1999; 135:47-55.
29. Barrett DA, Barker DP, Rutter N, Pawula M, Shaw PN. Morphine, morphine-6-glucuronide and morphine-3-glucuronide pharmacokinetics in newborn infants receiving diamorphine infusions. Br J Clin Pharmacol 1996; 41:531-7.
30. Hasselstrom J, Sawe J. Morphine pharmacokinetics and metabolism in humans. Enterohepatic cycling and relative contribution of metabolites to active opioid concentrations. Clin Pharmacokinet 1993; 24:344-54.

31. Pokela ML, Olkkola KT, Seppala T, Koivisto M. Age-related morphine kinetics in infants. Dev Pharmacol Ther 1993; 20:26-34.
32. Penson RT, Joel SP, Roberts M, Gloyne A, Beckwith S, Slevin ML. The bioavailability and pharmacokinetics of subcutaneous, nebulized and oral morphine-6-glucuronide. Br J Clin Pharmacol 2002; 53:347-54.
33. Osborne R, Thompson P, Joel S, Trew D, Patel N, Slevin M. The analgesic activity of morphine-6-glucuronide. Br J Clin Pharmacol 1992; 34:130-8.
34. Lotsch J, Weiss M, Kobal G, Geisslinger G. Pharmacokinetics of morphine-6-glucuronide and its formation from morphine after intravenous administration. Clin Pharmacol Ther 1998; 63:629-39.
35. Carrupt PA, Testa B, Bechalany A, el Tayar N, Descas P, Perrissoud D. Morphine 6-glucuronide and morphine 3-glucuronide as molecular chameleons with unexpected lipophilicity. J Med Chem 1991; 34:1272-5.
36. Somogyi AA, Nation RL, Olweny C, et al. Plasma concentrations and renal clearance of morphine, morphine-3-glucuronide and morphine-6-glucuronide in cancer patients receiving morphine. Clin Pharmacokinet 1993; 24:413-20.
37. Van Crugten JT, Sallustio BC, Nation RL, Somogyi AA. Renal tubular transport of morphine, morphine-6-glucuronide, and morphine-3-glucuronide in the isolated perfused rat kidney. Drug Metab Dispos 1991; 19:1087-92.
38. Milne RW, McLean CF, Mather LE, et al. Influence of renal failure on the disposition of morphine, morphine-3-glucuronide and morphine-6-glucuronide in sheep during intravenous infusion with morphine. J Pharmacol Exp Ther 1997; 282:779-86.
39. Bergstein JM. Introduction to glomerular diseases. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson Textbook of Pediatrics. Philadelphia: W.B. Saunders Co, 2000:1574-1575.
40. Bjornsson TD. Use of serum creatinine concentrations to determine renal function. Clin Pharmacokinet 1979; 4:200-22.
41. Onishi S, Kawade N, Itoh S, Isobe K, Sugiyama S. Postnatal development of uridine diphosphate glucuronyltransferase activity towards bilirubin and 2-aminophenol in human liver. Biochem J 1979; 184:705-7.
42. van der Marel CD, van Lingen RA, Pluim MA, et al. Analgesic efficacy of rectal versus oral acetaminophen in children after major craniofacial surgery. Clin Pharmacol Ther 2001; 70:82-90.

Chapter 5

Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism

Based on:
Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism
Nancy J. Bouwmeester, Wim C.J. Hop, Monique van Dijk, Kanwal.J.S. Anand, John N. van den Anker, Dick Tibboel.
Submitted.

5.1 Abstract

Objective
To investigate age-related differences in morphine requirements and metabolism in full term neonates following major surgery.

Design
Randomized double-blind study

Setting
Paediatric Surgical Intensive Care Unit

Patients and Interventions
Sixty-eight neonates (52 aged ≤ 7 days, 16 aged > 7 days) following abdominal or thoracic surgery, received morphine 100 μg/kg after surgery, and were randomly assigned to either continuous morphine (CM, 10 μg/kg/h) or intermittent morphine boluses (IM, 30 μg/kg/3 h). Pain was measured with the COMFORT behavioural scale and the Visual Analogue Scale. Additional morphine was administered on guidance of the pain scores. Morphine (M) and morphine-6-glucuronide (M6G) plasma concentrations were determined before, directly after, and at 6, 12 and 24 h after surgery.

Results
Neonates aged ≤ 7 days differed significantly from neonates > 7 days in morphine requirement [median 10 vs. 10.8 μg/kg/h, ($P < 0.001$)], morphine plasma concentration [23.0 vs. 15.3 ng/ml, ($P = 0.027$)], and M6G/M ratio [0.6 vs. 1.5, ($P = 0.018$)]. Pain scores did not differ between age groups or morphine treatment groups.
Neonates who were mechanically ventilated > 24 h ($n = 37$) had significantly higher morphine plasma concentrations than the spontaneously breathing neonates ($n = 15$) at 12 and 24 h after surgery (29.1 vs. 13.1 ng/ml and 26.9 vs. 12.0 ng/ml, respectively; both $P < 0.001$).
Morphine plasma concentrations were not correlated with effective analgesia or respiratory depression. Five neonates showed respiratory insufficiency, all on IM, however the difference between CM and IM was not significant.

Conclusion
Neonates aged ≤ 7 days require significantly less morphine postoperatively than older neonates do. Mechanical ventilation decreases morphine metabolism and clearance. Both intravenous morphine regimens (CM and IM) were equally effective and safe.

5.2 Introduction

Although health care professionals become increasingly alert to pain management in neonates and infants,[1-6] adequate treatment of continuing pain is not guaranteed. We still do not know which morphine doses will provide sufficient analgesia after major surgery in newborn infants. Physiological alterations starting from birth, with improving hepatic and renal clearing capacity and changing volume of distribution, are likely to influence the efficacy and safety of morphine in the vulnerable neonate.[7-11]
Previously we investigated in infants of different ages (0-3 yr) the effects of two morphine administration regimens (continuous versus intermittent intravenously) on hormonal and metabolic stress responses and morphine requirement after major non-cardiac surgery.[12] We concluded that age was the most important variable, because significant differences were found between neonates and older infants. Within the age groups, differences between the two methods of morphine administration were found only in the older age groups.

In the present study we investigated the effect of developmental maturation on morphine metabolism in full term neonates after thoracic or abdominal surgery. We distinguished between neonates aged ≤ 7 days and > 7 days, because hepatic and renal physiology change prominently in the first week after birth. The analysis included a) age-related aspects, i.e. analgesia, morphine (M) need, morphine and morphine-6-glucuronide (M6G) concentrations; and b) effects of other clinical factors, i.e. apnoea, mechanical ventilation, intermittent versus continuous morphine.

5.3 Materials and methods

Sixty-eight neonates aged 0 to 4 weeks (gestational age 35–42 weeks and body weight ≥ 1500 grams), admitted to the surgical intensive care unit following thoracic or abdominal surgery, were enrolled in this study. Neonates with neurological, renal, or hepatic

dysfunction, or with opioid therapy less than 6 h prior to surgery were excluded. The study protocol was approved by the Medical Ethics Committee of the Erasmus MC Rotterdam. Patients were enrolled only after informed consent had been obtained from the parents.

Anaesthetic management was completely standardized. Anaesthesia was induced intravenously with thiopentone 3 - 5 mg/kg or by inhalation with halothane in oxygen. Fentanyl 5 μg/kg was given before orotracheal intubation, which was facilitated with atracurium 0.5 - 1 mg/kg or suxamethonium 2 mg/kg. Ventilation was controlled and anaesthesia was maintained with isoflurane 0.5 minimum alveolar concentration in 60% nitrous oxide in oxygen or air in oxygen. Perioperative fluids were standardized to maintain a glucose infusion rate between 4 - 6 mg/kg/min; body temperature was kept within normal ranges. A peripheral artery was cannulated, and the measured mean arterial blood pressure (MAP) and heart rate (HR) data served as preoperative baseline values. Patients received a second dose of fentanyl 5 μg/kg before surgical incision. Additional doses of fentanyl 2 μg/kg were administered when HR and/or MAP were 15% above baseline value. At the end of surgery, the neuromuscular block was antagonized and the tracheal tube was removed. Mechanical ventilation was continued in patients who required ventilatory support.

The anaesthetist then computed the Surgical Stress Score (SSS) to classify the degree of surgical stress.[13] 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.

All neonates received a dose of morphine hydrochloride 100 μg/kg at the end of surgery and were randomly allocated to equivalent doses of continuous morphine infusions (CM, 10 μg/kg/h) or intermittent morphine boluses (IM, 30 μg/kg/3h), given intravenously. Pain was assessed by trained nurses before surgery and every 3 h for 24 h after surgery using the validated behavioural COMFORT scale (CS), (total scores range from 6 to 30) and the Visual Analogue Scale (VAS), ranging from 0 to10. Recently the behavioural part of the CS (further referred to as behavioural CS) has been proven to be a reliable and valid instrument to assess postoperative pain in neonates and infants aged 0-3 years[14 15]. The behavioural CS includes six behavioural items: alertness, calmness, respiratory response for ventilated or crying for non-ventilated children, physical movement, muscle tone, and facial tension. VAS scores were assigned after every 2-minute observation period in which the behavioural CS was scored. VAS scores ≥ 4 are supposed to reflect

moderate to severe pain. Every time the nurse scored a VAS ≥ 4, the child was given an additional 5 μg/kg dose of morphine, repeated every 10 minutes when required. Respiratory insufficiency was defined by the presence of apnoea or arterial PaCO2 values ≥ 7.3 kPa in spontaneously breathing neonates.[16]

Arterial blood samples were taken after induction of anaesthesia (baseline), directly after surgery, and at 6, 12, and 24 h postoperatively to determine blood gas values and plasma concentrations of M and M6G.
Blood was sampled before an intermittent bolus was given; thus, plasma concentrations in the IM group were measured at time points corresponding with trough plasma morphine concentrations.
Standardized automated laboratory analysers measured plasma total bilirubin and creatinine concentrations. Plasma levels of M and M6G were measured by high-performance liquid chromatography (HPLC).[17] In serum all calibration graphs were linear: for M the concentrations ranged from 5 - 90 ng/ml and for M6G from 5 - 100 ng/ml. The quantitation limit was 5 ng/ml for M and M6G. However, in individual samples, the chromatogram allowed for a lower threshold. In this concentration range, the intra- and inter-day coefficients of variation were less than 10 % for all compounds and the accuracy was about 5 %, implying a high degree of precision.

Statistical Analysis
In order to be able to analyse the effects of age, we distinguished between neonates aged ≤ 7 days and > 7 days. The relations between the need for extra morphine (yes/no) and various factors in the univariate analysis were analysed using Fisher's exact test; multivariate analysis was done using logistic regression. Correlation coefficients are Spearman's rho. Other tests used are given in the text. P =0.05 (two-sided) was considered the limit of significance.

5.4 Results

We included sixty-eight patients, of whom 52 were aged ≤ 7 days, and 16 > 7 days). Table 1 gives their clinical and surgical characteristics. Apart from the age-related differences in weight, heart rate (HR), mean arterial blood pressure (MAP), and the plasma concentrations of creatinine and bilirubin, the two age groups showed no significant differences.

Table 1 Patient characteristics and details of surgery

	Age ≤ 7 days *n* = 52	**Age > 7 days** *n* = 16
Postnatal age in days (range)	2 (0-7)	14 (8-28)
Gestational age in weeks	38.2 (36.1-42.1)	39.2 (37.3-40.1)
Study weight in kg	2.8 (2.4-3.3)	3.4 (3.1-3.9)
Birth weight in kg	2.9 (2.4-3.4)	3.2 (3.0-3.5)
No. of boys/girls	31/21	9/7
No. of patients receiving CM/IM	24/28	11/5
Mean Arterial Blood Pressure baseline (mmHg)	50 (44-56)	58 (52-66)
Heart Rate baseline (b/min)	136 (125-144)	147 (133-158)
Plasma total bilirubin (μmol/l)	110 (57-142)	38 (15-78)
Plasma bilirubin glucuronide (μmol/l)	6.0 (5.0-7.0)	6.0 (4.0-13.0)
Plasma creatinine (μmol/l)	46 (34-66)	24 (16-39)
No. requiring preoperative mechanical ventilation (%)	14 (26%)	5 (31%)
No. requiring postoperative mechanical ventilation during >24 h (%)	30 (57%)	7 (43%)
Surgical Stress Score	9.0 (8.0-11.8)	11.0 (8.0-13)
Surgical procedures (n)		
Congenital diaphragmatic hernia	10	4
Tracheo-oesophageal atresia	13	1
Bronchopulmonary (lobectomy)		1
Gastroschisis	2	
Intestinal atresia/malrotation/colonic "pull through"	17	5
Septic gastro-intestinal [a]	7	4
Exstrophy of the bladder	1	
Miscellaneous [b]	2	1

Values are median (interquartile range) unless stated otherwise. CM = Continuous Morphine; IM = Intermittent Morphine; n = number of patients.
[a] *intussusception, necrotizing enterocolitis, meconium peritonitis, perforation, ileus. (teratoma,*
[b] *pancreatectomy, Hirschsprung's disease, closure d. omphalo-mesentericus.*

Morphine

Six patients, all on mechanical ventilation (5 aged ≤ 7 days, 1 aged > 7 days), were excluded from morphine analysis, five because of detectable plasma morphine levels at baseline [congenital diaphragmatic hernia (n = 4), meconium peritonitis (n = 1)], and one because of loss of the arterial line at the end of surgery (n = 1).

The factors postnatal age, gestational age, sex, body weight, plasma concentration of creatinine and total bilirubin, preoperative and postoperative mechanical ventilation, SSS, and morphine treatment (CM or IM), were investigated for their relationship with the need for additional morphine (yes or no) during the first 24 h after surgery.

Table 2 Morphine data at 24 h after surgery, according to treatment and age

	CM (n = 30)		IM (n = 32) #	
	Age ≤ 7 days (n = 20)	**Age > 7 days (n = 10)**	**Age ≤ 7 days (n = 27)**	**Age > 7 days (n = 5)**
Extra morphine (n)				
Yes	5	8	8	2
No	15	2	19	3
M requirement (μg/kg/h)	10.0 (10.0-10.2)*	10.8 (10.2-11.9)	10.0 (10.0-10.4)	10.0 (10.0-11.2)
n	20	10	27	5
M in plasma (ng/ml)	23.0 (17.1-32.0)†	15.3 (7.7-22.6)	15.4 (11.4-19.7)	8.2
n	19	10	23	2
M6G in plasma (ng/ml)	16.4 (12.1-20.0)	15.8 (13.3-28.2)	13.5 (10.6-19.2)	7.6
n	19	10	24	2
M6G/M ratio	0.6 (0.5-1.3)‡	1.5 (1.0 –2.6)	1.1 (0.7-1.5)	4.3
n	18	10	21	2

CM = Continuous Morphine; IM = Intermittent Morphine; M = Morphine M6G = morphine-6-glucuronide; n = number of patients. # Note: trough values in the IM group.
*In CM: *Lower in neonates ≤7 days vs. >7 days (P < 0.001); † higher in neonates ≤7 days vs. >7 days (P = 0.027); ‡Lower in neonates ≤7 days vs. >7 days (P = 0.018) (Mann-Whitney test). Values are number or median (interquartile range).*

In multivariate logistic analysis, only age [13/47 ≤ 7 days (27%) vs. 10/15 > 7 days (66 %); P = 0.006], and preoperative mechanical ventilation [1/13 ventilated (7 %) vs. 22/48 non-ventilated (46 %); P = 0.014] were significant predictors of the need for additional morphine. Postoperative mechanical ventilation did not significantly influence the need for extra morphine.

Table 2 lists for each age group the morphine requirement and the plasma concentrations of M and M6G in CM and IM at 24 h after surgery.

Morphine requirement (related to body weight) was significantly lower in the younger neonates on CM (P < 0.001, Mann Whitney U test).

Morphine plasma concentrations

Median plasma concentrations of morphine at 24 h after surgery were significantly higher in neonates aged ≤ 7 days as compared with the older neonates in the CM group (P = 0.027) (Table 2). There were no significant differences in plasma morphine levels between neonates with or without extra morphine at any time point.

Figure 1 shows the plasma concentrations according to age (≤ 7 days and > 7 days) and treatment (CM and IM), at 6 h (left panel) and 12 h (right panel) after surgery.

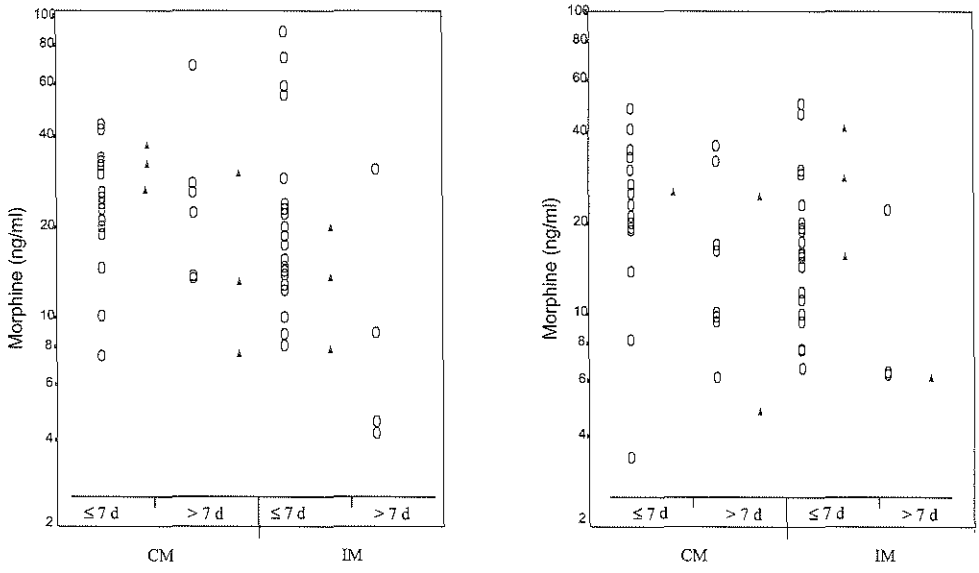

Fig. 1 *Morphine plasma concentrations at 6 hours (left panel) and 12 hours (right panel) after surgery, according to age (≤7 days or > 7 days of age) and treatment group [continuous morphine (CM) or intermittent morphine (IM)]. Plasma levels of patients who did not need extra morphine during next period (6-12 h at the left and 12-24 h at the right) are indicated by circles. Plasma levels of patients who did need extra morphine during next period are marked with triangles.*

Morphine plasma concentrations varied widely and were not indicative for additional morphine need in the postoperative period following these measured values.
Neonates who were mechanically ventilated for longer than 24 h postoperatively ($n = 37$) had significantly higher morphine plasma concentrations than the non-ventilated patients ($n = 15$) at 12 and 24 h after surgery (29.1 vs. 13.1 ng/ml and 26.9 vs. 12.0 ng/ml, respectively; both $P < 0.001$). This difference in morphine plasma levels was not related to age or treatment regimen (CM vs. IM). Morphine requirements did not significantly differ between ventilated and non-ventilated neonates.

Table 3 Physiological responses and pain scores during the first 24 hours after surgery

Age	n	HR	MAP	CS	VAS	VAS ≥4 (%)
≤ 7days	49	137* (13)	49* (7)	12.6 (2.6)	1.3 (0.7)	5.1
>7days	16	151 (12)	58 (9)	13.3 (2.1)	1.7 (0.7)	7.8

HR = Heart rate (b/min); MAP = Mean arterial blood pressure (mmHg); CS = COMFORT behavioural Score; VAS = Visual Analogue Score (means of measurements at 3, 6, 9, 12, 15, 18, 21 and 24 h after surgery); VAS ≥4, as percentage of total VAS scores during 24 h; n = number of patients.
**HR and MAP lower in neonates aged ≤7 vs. > 7 days (P < 0.001) (Mann-Whitney test). Values are mean (SD)*

Morphine-6-glucuronide plasma concentrations

M6G was detectable in the plasma of all neonates from 6 h after surgery. M6G plasma concentrations did not significantly differ between the younger and older neonates.
The median M6G/M ratio was significantly lower in the younger neonates at 6, 12 and 24 h after surgery (all P < 0.04) (Table 2).Although the plasma concentrations of M6G did not significantly differ between ventilated and non-ventilated neonates, the M6G/M ratio was significantly lower in postoperative mechanically ventilated neonates at 12 h and 24 h postoperatively (0.7 vs. 1.6 and 0.7 vs. 1.4, respectively; both P < 0.02). The M6G/M ratios in neonates ventilated for less than 24 hours (n = 10) were in between those of the ventilated and non-ventilated neonates.

Physiological and behavioural responses

Table 3 gives the mean values (SD) of HR, MAP and pain scores for the first 24 h postoperatively. Hemodynamic data could not be analysed in 3/68 neonates due to loss of the arterial line during the study.
In multiple regression analysis mean HR was significantly higher with higher age and body weight (both P < 0.05).
MAP was only dependent on age and was significantly lower in neonates aged ≤ 7 days, even after adjusting for baseline values (P < 0.001).
Mean COMFORT and VAS scores correlated significantly with each other (r = 0.7; P < 0.001). Pain scores did not significantly differ between neonates aged ≤ 7 and > 7 days or between different morphine treatment. Frequencies of VAS scores ≥ 4 (indicating pain) ranged from 0 to 3, and were not related to age, plasma concentrations of morphine or M6G, specific diagnoses, or type of surgery performed.

Respiratory depression

The number of spontaneously breathing neonates increased from 15 at 6 h (9 aged ≤ 7 days, 6 aged > 7 days) to 22 at 24 h postoperatively (14 ≤ 7 days, 8 > 7 days). Only one of them (duodenal atresia) showed increased PaCO2 levels amounting to 8.9, associated with high morphine (trough) concentrations of 55 ng/ml at 6 after surgery. Four others (morphine trough plasma levels varying from 8 to 23.9 ng/ml) required intubation and mechanical ventilation: failed extubation after repair of oesophageal atresia (n=2); apnoea after repair of exstrophy of the bladder (n = 1) and after jejunal atresia (n = 1). All these five neonates were on IM and aged ≤ 7 days; none of them had received additional morphine in the postoperative period. Although the four infants who needed reintubation were on IM, the difference between CM and IM was not significant (P > 0.1). Remarkably, two other young neonates on IM with morphine trough plasma levels of 29 and 59 ng/ml, respectively, at 6 h postoperative, did not manifest either hypercarbia or hypoventilation.

Other adverse effects

Hypotension related to the administration of morphine was not observed. Urinary retention could not be monitored because most of the neonates had a urinary catheter in. As all had undergone major abdominal or thoracic surgery, it could not be established whether either surgery or morphine therapy had altered gut motility.

5.5 Discussion

This randomized, controlled trial aimed at evaluating the effects of age on morphine metabolism in full term newborns. After surgery, neonates aged ≤ 7 days required fewer additional morphine doses, maintained higher plasma morphine levels, and converted less morphine to M6G (lower M6G/M ratios) than older neonates. The higher morphine plasma concentrations might, in part, result from a smaller volume of distribution at this age. While a meta-analysis showed that the morphine volume of distribution is not dependent on age,[18] in other studies the volume of distribution tended to be somewhat smaller in neonates aged ≤ 7 days compared with older infants, but this difference was not statistically significant.[7,10] A morphine loading dose of 50 μg/kg does probably suffice for neonates aged ≤ 7 days, whereas 100 μg/kg is mostly necessary for older infants. From a meta-analysis, an initial morphine infusion of 7 μg/kg/h was calculated to be sufficient for postoperative pain treatment in full term neonates.[18] An adjustment was

suggested with regard to cardiac and non-cardiac surgery (5 μg/kg/h and 10 - 15 μg/kg/h, respectively).[19] In our study, only 27 % of the neonates ≤ 7 days of age required extra morphine compared with 66 % of those > 7 days, suggesting that postoperative pain in some of the younger neonates could have been adequately treated with less morphine than the minimal dose used.

Findings from our study suggest that concentrations between 15 and 20 ng/ml are effective in postoperative neonates up to 4 weeks of age. However, as documented earlier, morphine plasma concentrations ranged widely, and no significant correlation was found between plasma levels and the need for extra morphine during the following hours. In a study comparing the effects of IM versus CM in non-ventilated infants (including 14 neonates < 1 month of age) 7 % of the infusion group had respiratory problems even when adjusted to a target morphine plasma concentration of 20 ng/ml.[20] Although in the present study median morphine plasma concentrations were higher in neonates ≤ 7 days, none of the spontaneously breathing neonates in the CM group had respiratory problems. Five neonates, all on IM, showed respiratory depression. In only one of them this could be attributed to the morphine therapy, because periods of apnoea started 30 min after a morphine bolus dose. In the others the respiratory problems largely resulted from surgical complications. This suggests that morphine plasma concentrations alone are not necessarily indicative of ventilatory depression.

In the present study, mechanical ventilation was associated with higher plasma morphine levels, similar plasma M6G levels and lower M6G/M ratios. In five neonates, who were on ventilation preoperatively and had been without morphine therapy > 6 h, morphine was still detectable at the time of surgery. Data on the clinical consequences of mechanical ventilation on portal hemodynamics and renal function are conflicting.[21,22] However, although morphine metabolism is more dependent on the glucuronidation capability, a slower morphine metabolism and a longer elimination time may be the result of a decreased hepatic and renal perfusion due to positive endexpiratory pressure (PEEP). A decreased M6G production, combined with a reduced renal clearance, can explain the similar M6G plasma concentrations and higher morphine in mechanically ventilated neonates. Bearing in mind the individual variability of morphine clearance, at this young age, a 6-hour period is apparently too short to effectively clear plasma of morphine,[10] especially under conditions of mechanical ventilation. This phenomenon can also explain why neonates who had been mechanically ventilated before surgery needed less morphine after surgery.

Postoperative ventilation did not influence the need for additional morphine. However, in spite of the non-significant differences in morphine requirements between postoperatively ventilated and non-ventilated neonates, the mechanically ventilated neonates proved to have higher plasma concentrations of morphine.
The clinical effect of morphine also relies on the formation of its active metabolite M6G. Morphine is largely metabolized by the age-dependent isoform Uridine 5'-Diphophate Glucuronosyltransferase (UGT)-2B7 to M6G and M3G.[23] In this study the M6G/M ratio was significantly lower in the neonates aged ≤ 7 days, probably as a result of the low UGT activity at this age.
Remarkably, the hemodynamic variables (HR and MAP) showed no significant correlation with pain scores. This questions the reliability of HR and MAP as parameters for pain measurement in this age group.[24]

5.6 Conclusions

In conclusion, findings from the present study suggest that in neonates > 7 days of age a morphine dosage of 10 μg/kg/h is sufficient for postoperative analgesia after non-cardiac major surgery. Hepatic and renal disturbances, however, may require adjusted dosages. For neonates ≤ 7 days of age an initial morphine infusion of 5-10 μg/kg/h is suggested, after a loading dose of 50 μg/kg. Further research into morphine requirements in this age group is needed. Morphine plasma concentrations varied widely. We found no consistency between morphine plasma levels and analgesia, or between plasma levels and respiratory depression. In neonates on mechanical ventilation, morphine plasma concentrations increased with unchanged M6G plasma levels, probably owing to a decreased hepatic and renal function. Although in the present study the CM and IM groups showed no significant differences in safety, the intermittent morphine regimen did not provide any advantage. Morphine given as a continuous infusion is more feasible and might be regarded as safer in neonates.
Further findings from this study suggest that neonates on mechanical ventilation have a slower morphine metabolism than spontaneously breathing neonates. Behavioural observation can be used as indication for tapering off the morphine infusion, thus preventing overdosing with its associated risks.

5.7 Acknowledgements

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5. 8 References

1. Choonara I (1999) Why do babies cry. BMJ 319:1381
2. Lima de J, Lloyd-Thomas AR, Howars RF, Sumner E, Quinn TM (1996) Infant and neonatal pain anaesthetists' perceptions and prescribing patterns. BMJ 313:787
3. Anand KJS (2001) Consensus statement for the prevention and management of pain in the newborn. Arch Pediatr Adolesc Med 155:173-180
4. Anand KJS, Sippell WG, Aynsley-Green A (1987) Randomized trial of fentanyl anesthesia in preterm babies undergoing surgery: effects on the stress response. Lancet1:243-48
5. Fitzgerald M, Millard C, McIntosh N (1989) Cutaneous hypersensitivity following peripheral tissue damage in newborn infants and its reversal with topical anesthesia. Pain 39:31-6
6. Anand KJS, Scalzo FM (2000) Can adverse neonatal experiences alter brain development and subsequent behavior? Biol Neonate 77:69-82
7. Lynn AM, Slattery JT (1987) Morphine pharmacokinetics in early infancy. Anesthesiology 66:136-9
8. Choonara IA, McKay P, Hain R, Rane A (1989) Morphine metabolism in children. Br J Clin Pharmacol 28:599-604
9. McRorie TI, Lynn AM, Nespeca MK, Opheim KE, Slattery JT (1992) The maturation of morphine clearance and metabolism. AJDC 146:972-6
10. Pokela ML, Olkkola KT, Seppälä T, Koivisto M (1993) Age-related morphine kinetics in infants. Dev Pharmacol Ther 20:26-34
11. Faura CC, Collins SL, Moore RA, McQuay HJ (1998) Systematic review of factors affecting the ratios of morphine and its major metabolites. Pain 74:43-53
12. Bouwmeester NJ, Anand KJS, Dijk van M, Hop WCJ, Boomsma F, Tibboel D (2001) Hormonal and metabolic stress responses after major surgery in children aged 0 – 3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine. BJA 87:390-9
13. Anand KJS, Aynsley-Green A (1988) Measuring the severity of surgical stress in newborn infants. J Pediatr Surg 23:297-305
14. Ambuel B, HamLett KW, Marx CM, Blumer JL (1992) Assessing distress in paediatric intensive care environments: the COMFORT scale. J Pediatr Psychol 17:95-109
15. Dijk van M, Boer de JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ (2000) The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0–3 year-old infants. Pain 84:367-77
16. Lynn AM, Nespeca MK, Opheim KE, Slattery JT (1993) Respiratory effects of intravenous morphine infusions in neonates, infants, and children after cardiac surgery. Anesth Analg 77:695-701

17. Verwey-van Wissen CP, Koopman-Kimenai PM, Vree TB (1991) Direct determination of codeine, norcodeine, morphine and normorphine with their corresponding O-glucuronide conjugates by high-performance liquid chromatography with electrochemical detection. J Chromatogr 570:309-20
18. Kart T, Christrup LL, Rasmussen M (1997) Recommended use of morphine in neonates, infants and children based on a literature review: Part 2-Clinical use. Pediatr Anaesth 7:93-101
19. Lynn AM, Nespeca MK, Bratton SL, Strauss SG, Shen DD (1998) Clearance of morphine in postoperative infants during intravenous infusions: the influence of age and surgery. Anesth Analg 86:958-63
20. Lynn AM, Nespeca MK, Bratton SL, Shen DD (2000) Intravenous morphine in postoperative infants: intermittent dosing versus targeted continuous infusions. Pain 88:89-95
21. Richard C, Berdeaux A, Delion F, Riou B, Rimailho A, Giudicelli JF, Auzepy P (1986) Effect of mechanical ventilation on hepatic drug pharmacokinetics. Chest 90:837-41
22. Mutlu GM, Mutlu EA, Factor P (2001) GI Complications in patients receiving mechanical ventilation. Chest 119:1222-41
23. Coffman B, Rios GR, King CD, Tephly TR (1997) Human UGT2B7 catalyzes morphine glucuronidation. Drug Metab Dispos 25:1-4
24. van Dijk M, Boer de JB, Koot HM, Duivenvoorden HJ, Passchier J, Bouwmeester N, Tibboel D (2001) The association between physiological and behavioral pain measures in 0- to 3-year old infants after major surgery. J Pain Symptom Manage 22:600-9

Chapter 6

Efficacy of continuous versus intermittent morphine administration after major surgery in 0 to 3-year-old infants; a double-blind randomized controlled trial

Based on:
Efficacy of continuous versus intermittent morphine administration after major surgery in 0 to 3 year-old infants; a double-blind randomized controlled trial
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6.1 Summary

A randomized double-blind clinical trial compared the efficacy of 10 μg/kg/h morphine continuous intravenous infusion (CM) with that of 30 μg/kg morphine (IM) every 3 h after major abdominal or thoracic surgery, in 181 infants aged 0 - 3 years. Efficacy was assessed by the caregiving nurses with the COMFORT 'behaviour' and a visual analogue scale (VAS) for pain, every 3 h in the first 24 hours after surgery. Random regression modeling was used to simultaneously estimate the effect of randomized group assignment, actual morphine dose (protocol dosage plus extra morphine when required), age category, surgical stress, and the time-varying covariate mechanical ventilation on COMFORT 'behaviour' and the observational VAS rated pain, respectively. Overall, no statistical differences were found between CM and IM morphine administration in reducing postoperative pain. A significant interaction effect of condition with age category showed that the CM assignment was favorable for the oldest age category (1 - 3 years old). The greatest differences in pain response and actual morphine dose were between neonates and infants aged 1 - 6 months, with lower pain response in neonates who were on average satisfied with the protocol dosage of 10 μg/kg/h. Surgical stress and mechanical ventilation were not related to postoperative pain or morphine doses, leaving the inter-individual differences in pain response and morphine requirement largely unexplained.

6.2 Introduction

Reports on pediatric postoperative pain advocate good pain management comprising both pain assessment by validated instruments and adequate analgesic treatment (Berde, 1989; Beyer and Bournaki, 1989; Cohen, 1993; Glass, 1998; Goddard and Pickup, 1996; Morton, 1997). To accomplish this, more evidence-based knowledge about postoperative pain and related issues in pediatric samples is needed (McGrath, 1998; McIntosh, 1997).

One area of research examines the psychometric properties of (newly developed) postoperative pain instruments (Boelen et al., 1999; Buchholz et al., 1998; Buttner and Finke, 2000; Gilbert et al., 1999; McGrath et al., 1985; Merkel et al., 1997; Tarbell et al., 1992; van Dijk et al., 2000). These studies suggest that behavioural pain measures are the preferred substitute measures when self-report is not possible, as is the case in preverbal infants. Another area of research describes the efficacy and safety of analgesic treatments

after surgery in infants. After major surgery, opioids (especially morphine) are the most frequently employed analgesics. The efficacy and safety of intravenous (i.v.) continuous morphine after major surgery in children was examined in three studies. (Beasley and Tibbals, 1987) found that 20 - 25 μg/kg/h morphine was effective after major surgery in 121 non-ventilated children 0 to > 14 years of age. Millar et al. (1987) concluded that 14 - 21 μg/kg/h morphine was effective in 85 % of 20 children, 3 months to 12 years of age. Finally, Esmail et al. (1999) evaluated the efficacy of morphine after major surgery in 110 non-ventilated children aged 3 months to 16-year-old children, with infusion rates ranging from 10 to 40 μg/kg/h; the 65.5 % inadequate analgesia in the latter study was related to the lower infusion rates. In all three studies, pain was the major outcome variable, assessed by either the visual analogue scale (VAS) or graphic rating scale (GRS) (Scott and Huskisson, 1976) in the studies of Beasley and Tibbals (1987) and Millar et al. (1987), and age-appropriate validated pain instruments in the study of Esmail et al. (1999). Clinical signs of ventilatory depression, a safety outcome of major importance, were not observed in these latter studies. All three studies have some methodological drawbacks. Firstly, they include children of all ages, making it difficult to establish age-related differences in pain and morphine requirement. Secondly, because of a lack of standardized protocols, the rationale for varying doses remained unclear. Thirdly, because ventilated infants were excluded, neonates were underrepresented in these studies, which is unfortunate because, nowadays, infants with congenital anomalies are often operated on at an early age (Jona, 1998).

Studies comparing different routes of administration in pediatric samples, reported that i.v. morphine administration gives better pain relief than intramuscular morphine injections (Bray, 1983; Hendrickson et al., 1990). In addition, needle pain and fear for needles make intramuscular injections an undesirable route of administration (Hendrickson et al., 1990).

To our knowledge, there are no double-blind randomized clinical trials which have compared the efficacy of i.v. morphine administration and that of intermittent i.v. morphine administration in both neonates and infants. Besides comparing the efficacy of these two modes of administration, it is of clinical importance to examine patient or procedural characteristics that might explain individual differences. First, there may be large age-related differences in response to standardized levels of morphine. Second, the efficacy of morphine after major surgery is often determined without considering

differences in surgical procedures. One study described slower morphine clearance after cardiac than after non-cardiac surgery in neonates and infants (Lynn et al., 1998), which may imply that smaller morphine doses may be required in cardiac surgery. Although there are no objective measures to determine the painfulness of a surgical procedure, there is a measure developed for assessing the severity of surgical stress (SSS) in neonates (Anand and Aynsley-Green, 1988). To date, the relationship between postoperative pain and surgical stress has not been explored. Third, the effects of mechanical ventilation on postoperative pain assessment are unknown.

This study addressed the postoperative analgesic efficacy of two modes of morphine administration, i.e. equal doses of morphine either through continuous i.v. infusion or through i.v. bolus injections every 3 h following major abdominal or thoracic surgery. In addition, we examined the impact of age, severity of stress, and mechanical ventilation on the individual pain responses.

6.3 Methods

Patients

Between March 1995 and September 1998 a total of 204 children aged 0 - 3 years, admitted for major abdominal or thoracic surgery to the Sophia Children's Hospital Rotterdam, entered the study after informed consent of the parents was obtained.
Included were: neonates (≥ 35 weeks gestation and bodyweight ≥ 1500 g) and infants aged up to 3 years.
Exclusion criteria were: use of analgesic or sedative co-medication (e.g. acetaminophen or midazolam) influencing the measured amount or potency of morphine, use of neuromuscular blockers, hepatic or renal dysfunction, seriously compromised neurological status, or altered muscle tone.
The Medical Ethical Committee of the Hospital approved the study.

6.4 Assessment instruments

COMFORT scale

Pain was assessed with the behavioural part of the COMFORT scale (further referred to as

COMFORT 'behaviour'). This scale has proved a reliable and valid instrument to assess postoperative pain in 158 neonates and infants, using trained nurses as observers (van Dijk et al., 2000). Prior to this study, 39 nurses were trained to assess the COMFORT scale and VAS. The linearly weighted Cohen's kappa, as a measure for the interrater reliability, ranged from 0.54 to 0.93 for the individual COMFORT items. The COMFORT 'behaviour' score encompasses six behaviour items: alertness, calmness, muscle tone, movement, facial tension, and either respiratory response (for ventilated children) or crying (for non-ventilated children), all of them with response categories ranging from 1 (low distress/no pain) to 5 (high distress/pain). The total score thus ranges from 6 to 30.

Visual Analogue Scale

In addition, the nurses completed an observational VAS for a clinical rating of pain in each child. The VAS is a horizontal continuous 10-cm line with the anchors 'no pain' on the left side and 'extreme pain' on the right side. The score ranges from 0 to 10 (Lawrence et al., 1993; McGrath et al., 1985; Taddio et al., 1995; Tarbell et al., 1992).

Surgical Stress Score

The SSS (Anand and Aynsley-Green, 1988) was developed to assess the severity of surgical stress in neonates and includes the following items: amount of blood loss (score range 0 - 3); site of surgery (score range 0 - 2); amount of superficial trauma (score range 1 - 3); extent of visceral trauma (score range 1 - 4); duration of surgery (score range 1 - 5); associated stress factors: a) hypothermia (score range 0 - 3), b) infection (score range 0 - 3). The items prematurity and cardiac surgery were not applicable in our study and therefore the score could range from 3 to 22. These items are clearly described in the scoring list; information needed for scoring of the SSS is obtained from the surgical and anesthesia records. The SSS was scored jointly by the attending anesthesiologist and surgeon immediately after surgery in accordance with the original description of the SSS (Anand and Aynsley-Green, 1988).

Design

A randomized double-blind clinical trial was carried out to compare the efficacy of i.v. continuous morphine (CM) and i.v. intermittent morphine (IM) after major abdominal or thoracic surgery in infants aged 0 - 3 years. Patients were stratified into four developmentally relevant age categories: neonates (≥ 35 weeks gestation and weight

≥ 1500 grams), younger infants (1 - 6 months), older infants (7 - 12 months) and toddlers (1 - 3 years). Infants within these age categories were randomly assigned to CM or IM administration. The hospital pharmacist prepared the study drugs; the randomization schedule was known to the pharmacist only and retained until the end of the trial.
Pain was assessed prior to surgery, after return to the Pediatric Surgical Intensive Care unit (PSICU), and every 3 h during the first 36 h postoperative. Pain assessment, blood sampling, administration of the morphine or placebo bolus and handling of the child was consistently done in this order.

Procedure
Anaesthetic management was standardized. Perioperative fluids were standardized to maintain a glucose infusion rate between 4 and 6 mg/kg/min; body temperature was kept within normal ranges. A peripheral artery was cannulated and the measured mean arterial blood pressure (MAP) and heart rate (HR) data were used as peroperative baseline values. After the first arterial blood sample (baseline), patients received a second dose of 5 μg /kg of fentanyl before surgical incision. Additional doses of 2 μg /kg of fentanyl were administered when HR and/or MAP were 15 % above baseline value. The mechanical ventilation was continued in patients who required ventilatory assistance after surgery. At the end of surgery, all patients were given an i.v. loading dose of 100 μg/kg morphine. Protocol morphine dosage, following the loading dose, was administered in the following way. The CM group started with a morphine infusion of 10 μg/kg/h, combined with a i.v. placebo bolus (saline) every 3 h. The IM group received a continuous placebo infusion (saline), combined with a i.v. morphine bolus of 30 μg/kg every 3h. The first intermittent bolus (morphine or placebo) was given 3 h after surgery. Morphine boluses were administered within the span of approximately 30 s. When children were considered to be in pain, an observational VAS pain was scored after which additional morphine could be given according to the following decision rules.
The first hour after surgery when VAS ≥ 4: 30 μg/kg morphine (= approximately one-third of the loading dose), to be repeated when VAS remained ≥ 4 every 15 min. More than 1 h after surgery and VAS ≥ 4: 5 μg/kg morphine may be given, to be repeated every 10 min. If this did not result in adequate pain control, the anesthesiologist was consulted for additional analgesic treatment.
Mechanical ventilation was continued after surgery in neonates < 37 weeks postconceptional and after repair of esophageal atresia or congenital diaphragmatic hernia.

In older age categories, postoperative ventilation was applied depending on the surgical procedure.

Statistical analysis

The outcome variables COMFORT 'behaviour' and observational VAS rated pain were skewed to the right and logtransformed (base 10) to achieve normality. Actual morphine dose was highly skewed to the right and therefore divided into three categories (1= 10 μg/kg/h, 2 = >10 to ≥ 15 μg/kg/h and 3 = > 15 μg/kg/h).

Random regression modeling, using SAS 6.12 for Windows, was used to simultaneously estimate the effect of randomized group assignment, actual morphine dose (protocol dosage plus extra morphine when required), age category, SSS and the time-varying covariate mechanical ventilation on COMFORT 'behaviour' and observational VAS rated pain, respectively. Random regression modeling has many advantages: it allows for missing data and an unequal number of data for each subject, and for the inclusion of fixed and time-varying covariates. Furthermore, a realistic covariance structure (as opposed to compound symmetry or independence between repeated measures) can be implemented (Gibbons et al., 1993).

6.5 Results

Initially, 204 infants were allocated to this trial. However, five were lost to follow up; one infant died within the first hours after surgery due to irreversible pulmonary hypertension, three patients had a failing arterial line, and one patient experienced clinical signs of ventilatory depression. In addition, 18 patients were excluded because they did not comply with the inclusion criteria: three required muscle relaxants, seven received midazolam, four received acetaminophen or diclophenac, and four received both midazolam and acetaminophen.

Table 1 gives the background characteristics of the sample (n = 181) and the excluded cases (n = 23)

The excluded infants did not significantly differ with regard to background characteristics, except age. This is primarily due to the low number of excluded neonates.

Furthermore, the surgical stress score tended to be higher for the excluded infants. The two randomized groups were comparable with respect to age and gender.

Table 1 Background characteristics of the original sample and the group completing the trial

	Completed trial (n = 181)		Excluded cases (n = 23)[a]		P
	n	Percentage	n	Percentage	
Randomized group assignment					
Continuous morphine	88	49	13	56.5	
Intermittent morphine	93	51	10	43.5	0.47
Age categories					
Neonates	65	36	1	4	
1 – 6 months	54	30	13	56	0.01[b]
6 – 12 months	27	15	4	17	
1 – 3 years	35	19	5	22	
Age in days					
Median (IQR)	84 (5-279)		163 (61-301)		0.05
Gender					
Boys	104	57.5	15	65	
Girls	77	42.5	8	35	0.48
Location of surgery[c]					
Superficial	12	7	1	4	
Low abdominal	86	48	5	22	
High abdominal	53	29	9	39	0.07[b]
Thoracic	24	13	7	31	
Thoracic + abdominal	6	3	1	4	
Mechanical ventilation Postoperative					
Yes	75	41	10	43	
No	106	59	12	57	0.72
Severity of surgical stress					
Median (IQR)	9 (8-11)		11 (9-13)		0.06

[a] *Lost to follow-up: n = 1 deceased within 3 h after surgery, n = 3 failing arterial line, n = 1 ventilatoy depression; excluded because of non-compliance with criteria: n = 7 received midazolam, n = 4 received acetaminophen or diclofenac, n = 4 received both midazolam and acetaminophen, n = 3 requiring muscle relaxants.*

[b] *Exact test.*

[c] *Superficial surgery: comprised nephrectomy, ureter reimplantation, pyeloplasty, exstrophy of the bladder, sacroteratoma, yolk sac tumor, pull-through, incarcerated hernia. Low abdominal: Rehbein resection, closure entero/colostoma, gastrointestinal operations such as for atresia, intussusception, malrotation, necrotizing enterocolitis, and meconium peritonitis. High abdominal:comprised diaphragmatic hernia/paresis, duodenal atresia, subtotal pancreatectomy, Nissen fundoplication, hepatic and choledochal surgery, (ad)renal surgery, stomic perforation. Thoracic surgery: Tracheo-oesophageal atresia, lobectomy, pneumectomy, Blalock and vessel loop. Thoracic + abdominal : Colon interposition, operation for oesophageal/anal atresia.*

Table 2 shows the summary statistics for pain assessments, morphine dosage and postoperative mechanical ventilation for the two randomized groups.

Table 2 Data on pain assessment, morphine dosage and mechanical ventilation after surgery, in the two randomized group assignments: CM (n = 88) and IM (n = 93)[a]

	CM	IM	P
Pain assessment[b]			
Observational VAS			
Median (IQR)	1.9 (1.1 – 2.8)	1.8 (1.2 – 2.6)	0.84
Maximum VAS			
Median (IQR)	4.9 (2.4 –6.2)	4.6 (2.8 – 6.6)	0.25
COMFORT 'behaviour)			
Median (IQR)	14.3 (12.2 – 16.1)	14.2 (12.4 – 16.3)	0.97
Morphine dosage[c]			
Actual morphine dosage (μg/kg/h)			
Median (IQR)	10.8 (10 – 12.2)	10.4 (10 – 12.5)	0.59
Actual morphine dosage (number of patients)			
10 μg/kg/h	26 (30 %)	36 (39 %)	
>10 μg/kg/h	62 (70 %)	57 (61 %)	0.26
Mechanical ventilation			
Yes	38 (43 %)	37 (40 %)	
No	50 (57 %)	56 (60 %)	0.64

[a] *CM = continuous morphine , IM = intermittent morphine; IQR = Interquartile range*
[b] *Assessed nine times in the first 24 h.*
[c] *Maximum dosage 36.9 in the CM assignment, 26.7 in the IM assignment.*

In the CM assignment, 26 of the infants (29 %) were without pain with the 10 μg/kg/h morphine as opposed to 36 (39 %) in the IM assignment (Fig. 1). This difference was not statistically significant. ($\chi 2_{\text{Yates' corrected}} = 1.31$, P = 0.26, two-sided). Extra boluses of morphine, according to the decision rules of the protocol, were given once or more, to 119 infants (66 % of the sample). Of these, 39 infants received extra morphine within the first hour after surgery, which consisted of one-third of the loading dosage. Within the first 6 hours after surgery 92 infants received extra morphine. Another 20 infants received their first extra bolus between 6 and 12 h after surgery. Only seven children received a first extra bolus of morphine12 h after surgery.

The effects of the predictor variables on COMFORT 'behaviour' and observational VAS rated pain as outcome variables are given in Tables 3 and Table 4, respectively. Both models incorporated random intercepts and random slopes.

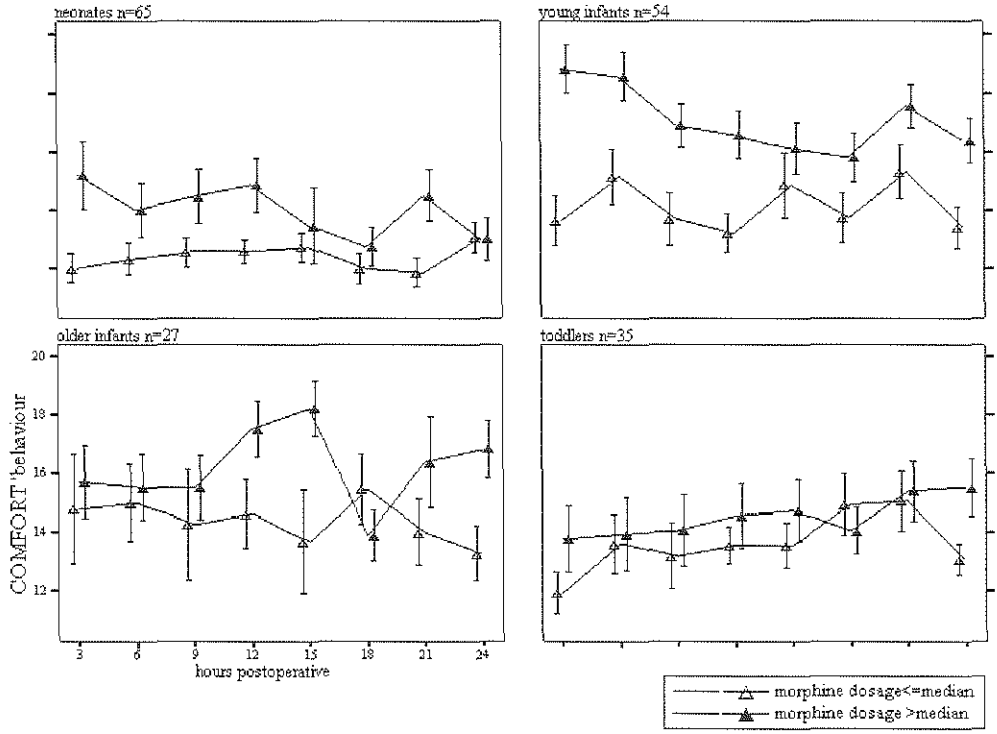

Fig. 1 Mean and SE of COMFORT 'behaviour' scores for the four age groups split by median morphine dosage: 77 % of the neonates (50 of 65) had morphine dosage <=median, 30 % of young infants (16 of 54), 33 % of the older infants (9 of 27) and 46 % of the toddlers (16 of 35).

The randomized group assignment did not have differential effects on the repeated COMFORT 'behaviour' or observational VAS rated pain scores. However, actual morphine dose was significantly related to observational VAS rated pain, after observing that the
> 15 µg/kg/h category had significantly higher VAS scores than the two lower dosage morphine categories. Age category significantly predicted both outcome variables, indicating that the 1 - 6 months infants had significantly higher pain scores than the neonates. The interaction between age categories and randomized group assignment was significant for observational VAS rated pain behaviour. This was explained by the difference between neonates and toddlers, with the CM condition being more favorable than the IM condition for the toddlers, but not for the neonates.

Table 3 Predictability of COMFORT 'behaviour' (n=181)[a]

Outcome variable : COMFORT 'behaviour'				
	ß	**SE of ß**	**t**	**P**
Morphine condition	0.015	0.04	0.36	0.72
Morphine dosage[b]				
10 µg/kg/h	-0.06	0.03	-1.89	0.06
>10 to ≤ 15 µg/kg/h	-0.01	0.03	-0.22	0.82
Age category[c]				
1 - 6 months	*0.09*	*0.03*	*3.85*	*0.0001*
6 - 12 months	0.05	0.03	1.82	0.07
1 - 3 years	-0.01	0.03	-0.29	0.77
Morphine condition * age category				
Condition * 1 - 6 months	-0.04	0.03	-1.27	0.20
Condition * 6 - 12 months	0.004	0.04	0.11	0.91
Condition * 1 - 3 years	0.05	0.03	1.48	0.14
Morphine condition * morphine dosage				
Condition * 10 µg/kg/h	0.001	0.04	0.02	0.99
Condition * >10 µg/kg/h	-0.005	0.04	-0.14	0.89
Linear time trend	0.001	0.001	0.09	0.93
Surgical Stress Score	-0.003	0.002	-1.49	0.14
Mechanical ventilation	-0.003	0.01	-0.24	0.81

[a] *Random regression modelling for repeated measurements.*
[b] *Morphine dosage category: 1 = 10 µg/kg/h and 2 = >10 to ≤ 15 µg/kg/h compared to 3 = > 15 µg/kg/h (reference category).*
[c] *Age categories 1 - 6 months, 6 - 12 months and 1 - 3 years compared to neonates (reference group) Significant predictor variables (P < 0.05) are given in italics.*

The interaction between randomized group assignment and morphine dose was not significant, indicating that the relation between the actual morphine dose and the level of observational VAS rated pain and COMFORT 'behaviour' scores did not depend on the randomized group assignment.

The observational VAS rated pain score significantly decreased over time, whereas the COMFORT 'behaviour' score showed no significant time trend.

The SSS and mechanical ventilation did not significantly predict the levels of COMFORT 'behaviour' and observational VAS rated pain.

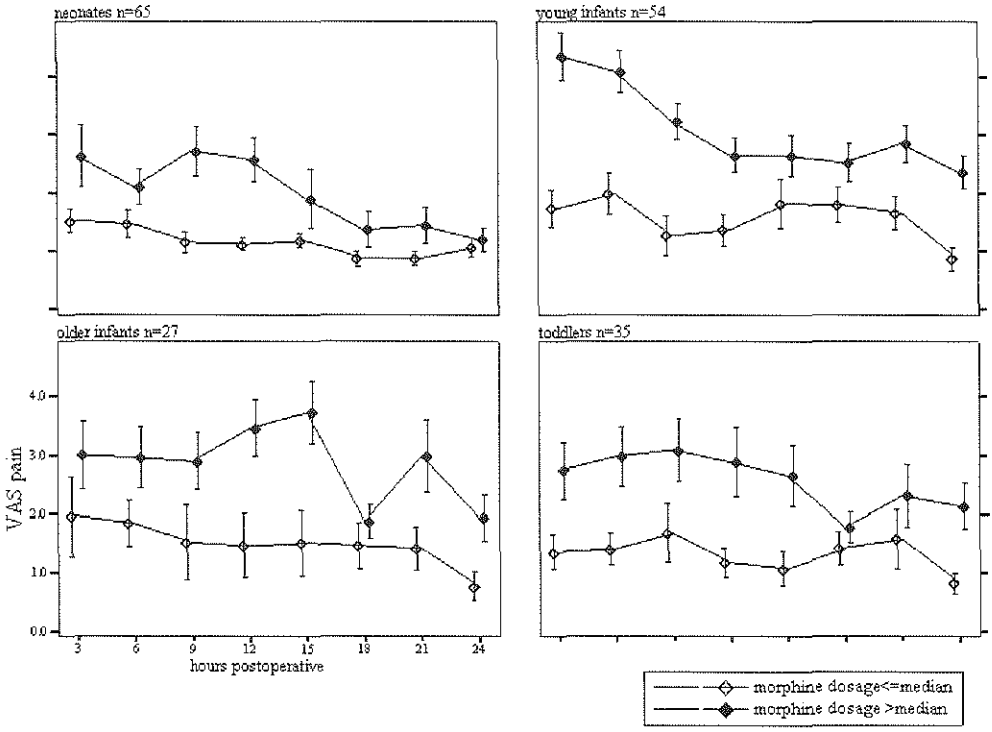

Fig. 2 Mean and SE of VAS pain scores for the four age groups split by median morphine dosage: 77 % of the neonates (50 of 65) had morphine dosage <=median, 30 % of young infants (16 of 54), 33 % of the older infants (9 of 27) and 46 % of the toddlers (16 of 35).

The most significant predictor variables are shown in Figs. 1 and 2, which give the means and standard errors of COMFORT 'behaviour' and observational VAS rated pain scores over time for the four age categories, split by the overall median dose of morphine(10.7 μg/kg/h). As was confirmed by the random regression analyses, average levels of COMFORT 'behaviour' and observational VAS rated pain were different for the 'high' vs. 'low' morphine groups. Age effects were clearly seen, especially when comparing neonates and young infants. The observational VAS rated pain showed a moderate decline in scoring over time. The toddlers showed a slight increase in COMFORT 'behaviour' scores, with limited differences between those below and above the overall median morphine dose level.

Table 4 Predictability of observational VAS pain ($n = 181$)[a]

Outcome variable : observational VAS pain	ß	SE of ß	t	P
Randomized group assignment	-0.06	0.07	-0.88	0.38
Morphine dosage[b]				
10 µg/kg/h	-0.27	0.05	-4.89	*0.0001*
>10 to ≤ 15 µg/kg/h	-0.11	0.05	-2.33	0.02
Age category[c]				
1 - 6 months	0.10	0.04	2.65	*0.01*
6 - 12 months	0.05	0.04	1.20	0.23
1 - 3 years	-0.09	0.04	-2.15	*0.03*
Randomized group assignment age category				
Assignment * 1 - 6 months	-0.04	0.05	-0.76	0.44
Assignment * 6 - 12 months	-0.01	0.06	-0.20	0.84
Assignment * 1 - 3 years	0.16	0.05	3.12	*0.002*
Randomized group assignment * morphine dosage				
Assignment * 10 µg/kg/h	0.09	0.07	1.38	0.17
Assignment * >10 to ≤ 15 µg/kg/h	0.06	0.06	0.98	0.33
Linear time trend	-0.01	0.001	-6.23	*0.0001*
Surgical Stress Score	0.001	0.003	0.24	0.81
Mechanical ventilation	-0.03	0.02	-0.99	0.32

[a] *Random regression modelling for repeated measurements.*
[b] *Morphine dosage category 1 = 10 µg/kg/h and 2 = >10 to ≤ 15 µg/kg/h compared to 3 = > 15 µg/kg/h (reference category)*
[c] *Age categories 1 - 6 months, 6 - 12 months and 1 - 3 years compared to neonates (reference group)*
Significant predictor variables (P < 0.05) are given in italics.

6.6 Discussion

This randomized double-blind controlled trial showed that for 29 % of the infants in the CM assignment and 36 % of the infants in the IM assignment, a dosage of 10 µg/kg/h morphine was effective to prevent postoperative pain. Therefore, we conclude that the (in)effectiveness did not statistically differ between the two morphine conditions. Only for the 1- to 3-year-old infants, the CM assignment was somewhat favorable. This can be explained by the fact that the half-life of morphine reaches adult values with half-life of 2 h ± 1.8 for infants older than 2 months (Kart et al., 1997). The 3-h period between i.v. morphine bolus injections in the IM assignment could therefore, result in morphine plasma levels below the therapeutic range in the 1- to 3-year old age category.

A recent study by Lynn compared continuous morphine infusions after surgery to intermittent i.v. boluses as needed in 83 infants of 0 - 1 year of age (Lynn et al., 2000). I.v. morphine infusions resulted in better analgesia, corresponding to higher total morphine dosing compared to the intermittent group. However, the continuous infusion rates were set to meet a targeted morphine concentration of 20 ng/ml and all infants received additional acetaminophen which hampers the comparison to our results.
The unexpected equal results for the two routes of morphine administration in relation to postoperative pain are promising, especially for clinical settings with a limited availability of infusion pumps (e.g. developing countries). Furthermore, opposed to intermittent boluses, continuous morphine infusions will require a larger fluid volume to be given to small neonates, thus limiting fluid volume available for postoperative nutrition. The difference in nursing workload and costs between the two routes of administration has not been established to our knowledge.

Age was related to pain and actual morphine dosage, although not in a linear way. Neonates had lower COMFORT 'behaviour' scores and observational VAS rated pain scores compared to infants aged 1 - 6 months. Neonates tend to metabolize morphine slower than older infants do (Kart et al., 1997; Lynn et al., 2000; Lynn et al., 1998) which might explain the lower pain scores of the neonates. Furthermore, the majority of neonates (75 %) in this study was at least 37 weeks gestational age. Therefore an increased sensitivity to pain and lower pain thresholds (Anand, 2000; Fitzgerald, 1993) as seen in premature neonates is of limited relevance in this study. Why the young infants (1 - 6 months) had the most pain could not be explained by surgery-related characteristics However, upon closer inspection it appeared that the 1-6 months-old infants differed in two aspects from the neonates: surgical experience and prematurity at birth. Almost all of the neonates (97 %) underwent their first procedure under anesthesia in this trial, whereas of the 1 - 6 months old infants only 35 % had no prior surgical experience. In addition, 30 % of the 1 - 6 months old infants was born before 35 weeks gestational age opposed to none in the neonatal group. Considering the extensive literature on increased pain sensitivity and windup in premature neonates (Anand, 2000; Fitzgerald, 1993) undergoing many painful procedures, surgical history and prematurity may be relevant factors.
A matter of consideration with infants and toddlers is the problem of differentiating between pain, anger, and anxiety. With increasing age, infants are likely to become more aware of their environment and to respond in their unique way. Furthermore, infants become more active when they feel better, which might unintentionally increase the

behavioural pain scores. This could explain the slight increase in COMFORT 'behaviour' scores across time for the toddlers (Fig.1), and the non-significant time trend for COMFORT 'behaviour'. When nurses are trained in using the COMFORT scale, it should be emphasized to score distress behaviour only. The observational VAS rated pain is less sensitive for such misinterpretation as it asks directly to assess the pain intensity. On the other hand, the quality of the observational VAS rated pain depends strongly on the observer's experience and knowledge of infants in pain. By contrast, the COMFORT 'behaviour' is based solely on a 2-min behavioural observation and its reliability can be improved by training.

Of the 62 infants who received 10 μg/kg/h morphine after surgery, 42 were neonates (CM: $n = 20$; IM: $n = 22$). Only one neonate was included in the group who received > 15 - 36.9 μg/kg/h morphine. For term neonates, 10 μg/kg/h, and for infants 15 μg/kg/h, seem adequate doses to begin with after major surgery. In the literature, recommended dosages for morphine i.v. infusion range from 10 to 40 μg/kg/h, mostly depending on age. In a review by Kart et al. (1997b) the recommended dosage for term neonates was calculated to be 7 μg/kg/h and for infants 20 μg/kg/h. Considering the variability within the age categories in the present study, our results confirm the current opinion that dosages should be determined or adjusted for each individual separately (Kart et al., 1997b; Pokela et al., 1993). Another explanation for the inter-individual variability could lie in the genetic heterogeneity in morphine metabolism, as was pointed out for the glucuronide pathway (Coffman et al., 1998).

In our study, the severity of surgical stress was not significantly related to postoperative pain. In other studies, postoperative metabolic and hormonal stress responses were positively correlated with the SSS in neonates (Anand and Ward Platt, 1988), and metabolic and hormonal stress responses decreased thanks to analgesic treatment after surgery in premature neonates (Anand et al., 1987). An explanation for the apparent lack of association between SSS and pain response might be that the SSS in our study was relatively low with limited variability across patients, partly due to the exclusion of premature neonates and cardiac surgery. Since ours is the first study to relate SSS to behavioural pain measures, we may conclude that more research is required to establish knowledge about the stress-pain relationship (Aynsley-Green, 1996).
In the current study, the time-varying covariate mechanical ventilation did not predict the repeated pain assessments. In our sample 42 % (75 of 182 cases) required postoperative

ventilation, equally divided across the two conditions. The majority of the ventilated cases were neonates (51 of 75 cases). Ventilated cases are usually excluded, either because safety is an outcome variable or because pain assessment in these cases is too complex. Although the safety of morphine for the ventilated cases could not be determined, pain assessment for the ventilated cases was not a problem in our study, because we used the COMFORT 'behaviour' which has one item specifically developed for ventilated cases that replaces the item 'crying' used for non-ventilated cases. In the present study, one patient with clinical signs of ventilatory depression was excluded from the trial. The inclusion of ventilated cases in our study had the advantage that our findings may be generalized to the population of the PSICU.

Side effects of morphine, such as pruritis, vomiting and nausea, were not observed in this study. Because of the high incidence of gastrointestinal surgery and urinary catheters, gut motility and urinary retention were not documented. Side effects caused by the bolus administration of 30 μg/kg were neither observed.
Fifteen infants (7 %) were excluded from this trial because they received sedatives and/or other analgesics than morphine. Although this may be seen as a drawback of the current study, in our opinion, a minority of infants remains difficult to be treated adequately for pain in clinical practice. Healthcare providers find it difficult to decide whether agitation is caused by for instance 'fighting the ventilator', distress or pain (Ramelet, 1999). As a result, treatment is based on 'trial and error', rather than evidence-based treatment (Stevens and Koren, 1998).

In summary, the results of this study show that continuous and intermittent i.v. morphine administration after major surgery were equally (in)effective in infants up to 1 year of age. Differences in pain response and morphine dosage were most prominent between neonates and infants 1 - 6 months old, with lower pain responses in neonates (who were on average satisfied with the protocol dosage of 10 μg/kg/h) and higher pain responses in infants aged 1- 6 months, who required higher dosages of morphine. Individual differences in pain response and morphine requirement remained largely unexplained. Surgical stress score was not related to postoperative pain or morphine dosages.
These findings expand our knowledge on postoperative pain and may contribute to better postoperative pain management for infants aged 0 - 3 years after major surgery.

6.7 Acknowledgements

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6.8 References

- Anand K. Effects of perinatal pain and stress. In: E Mayer and C Saper (Eds.). Progress in Brain Research, Vol. 122, Elsevier Science, 2000. pp. 117-129.
- Anand KJS and Aynsley-Green A. Measuring the severity of surgical stress in newborn infants. J Pediatr Surg 1988;23:297-305.
- Anand KJS, Sippell WG and Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. Lancet 1987;1:243-248.
- Anand KJS and Ward Platt MP. Neonatal and pediatric stress responses to anesthesia and operation. Int Anesthesiol Clin 1988;26:218-225.
- Aynsley-Green A. Pain and stress in infancy and childhood--where to now? Paediatr Anaesth 1996;6:167-172.
- Beasley SW and Tibbals J. Efficacy and safety of continuous morphine infusion for postoperative analgesia in the paediatric surgical ward. Aust N Z J Surg 1987;57:233-237.
- Berde CB. Pediatric postoperative pain management. Pediatr Clin North Am 1989;36:921-941.
- Beyer JE and Bournaki M. Assessment and management of postoperative pain in children. Pediatrician 1989;16:30-38.
- Boelen WJC, Scheffer E, Haan de RJ and Groot de CJ. Clinimetric evaluation of the pain observation scale for young children in children aged between 1 and 4 years after ear, nose, and throat surgery. J Dev Behav Pediatr 1999;20:14-19.
- Bray RJ. Postoperative analgesia provided by morphine infusion in children. Anaesthesia 1983;38:1075-1078.
- Buchholz M, Karl HW, Pomietto M and Lynn AM. Pain scores in infants: a modified infant pain scale versus visual analogue. J Pain Symptom Manage 1998;15:117-124.
- Buttner W and Finke W. Analysis of behavioural and physiological parameters for the assessment of postoperative analgesic demand in newborns, infants and young children: a comprehensive report on seven consecutive studies. Paediatr Anaesth 2000;10:303-318.
- Coffman BL, King CD, Rios GR and Tephly TR. The glucuronidation of opioids, other xenobiotics, and androgens by human UGT2B7Y(268) and UGT2B7H(268). Drug Metab Dispos 1998;26:73-77.
- Cohen DE. Management of postoperative pain in children. In: NL Schechter, CB Berde and M Yaster (Eds.). Pain in infants, children, and adolescents, Williams & Wilkins, Baltimore, 1993. pp. 87-96.

- van Dijk M, de Boer JB, Koot HM, Tibboel D, Passchier J and Duivenvoorden HJ. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. Pain 2000;84:367-377.
- Esmail Z, Montgomery C, Court C, Hamilton D and Kestle J. Efficacy and complications of morphine infusions in postoperative paediatric patients. Paediatr Anaesth 1999;9:321-327.
- Fitzgerald M. Development of pain pathways and mechanisms. In: KJS Anand and PJ McGrath (Eds.). Pain in neonates., Vol. 5, Elsevier, Amsterdam, 1993. pp. 19-33.
- Gibbons RD, Hedeker D, Elkin I, Waternaux C, Kraemer HC, Greenhouse JB, Shea MT, Imber SD, Sotsky SM and Watkins JT. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Application to the NIMH treatment of Depression Collaborative Research Program dataset. Arch Gen Psychiatry 1993;50:739-750.
- Gilbert CA, Lilley CM, Craig KD, McGrath PJ, Court CA, Bennett SM and Montgomery CJ. Postoperative pain expression in preschool children: validation of the child facial coding system. Clin J Pain 1999;15:192-200.
- Glass NL. Pediatric postoperative pain management. Anesth Analg 1998;Suppl:28-31.
- Goddard JM and Pickup SE. Postoperative pain in children. Anaesthesia 1996;51:588-590.
- Hendrickson M, Myre L, Johnson DG, Matlak ME, Black RE and Sullivan JJ. Postoperative analgesia in children: A prospective study of intermittent intramuscular injection versus continuous intravenous infusion of morphine. J Pediatr Surg 1990;25:185-191.
- Jona JZ. Advances in neonatal surgery. Pediatr Clin North Am 1998;45:605-617.
- Kart T, Christrup LL and Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 1--Pharmacokinetics. Paediatr Anaesth 1997;7:5-11.
- Kart T, Christrup LL and Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 2--Clinical use. Paediatr Anaesth 1997;7:93-101.
- Lawrence J, Alcock D, McGrath PJ, Kay J, Brock MacMurray S and Dulberg C. The development of a tool to assess neonatal pain. Neonatal Netw 1993;12:59-66.
- Lynn AM, Nespeca M, Bratton SL and Shen DD. Intravenous morphine in postoperative infants: intermittent bolus dosing versus targeted continuous infusions. Pain 2000;88:89-95.
- Lynn AM, Nespeca M, Bratton SL, Strauss SG and Shen DD. Clearance of morphine in postoperative infants during intravenous infusion: the influence of age and surgery. Anesth Analg 1998;86:958-963.
- McGrath PJ. Behavioral measures of pain. In: GA Finley and PJ McGrath (Eds.). Progress in pain research and management, Vol. 10, IASP Press, Seattle, 1998. pp. 83-102.

- McGrath PJ, Johnson G, Goodman JT, Schillinger J, Dunn J and Chapman JA. CHEOPS: A behavioral scale for rating postoperative pain in children. In: HL Fields, R Dubner and F Cervero (Eds.). Advances in Pain Research and Therapy, Vol. 9, Raven Press, New York, 1985. pp. 395-402.
- McIntosh N. Pain in the newborn, a possible new starting point. Eur J Pediatr 1997;156:173-177.
- Merkel SI, Voepel-Lewis T, Shayevitz JR and Malviya S. The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatr Nurs 1997;23:293-297.
- Millar AJW, Rode H and Cywes S. Continuous morphine infusion for postoperative pain in children. S Afr Med J 1987;72:396-398.
- Morton NS. Pain assessment in children. Paediatr Anaesth 1997;7:267-272.
- Pokela M, Olkkola KT, Seppälä T and Koivisto M. Age-related morphine kinetics in infants. Dev Pharmacol Ther 1993;20:26-34.
- Ramelet AS. Assessment of pain and agitation in critically ill infants. Aust Crit Care 1999;12:92-96.
- Scott J and Huskisson EC. Graphic representation of pain. Pain 1976;2:175-184.
- Stevens B and Koren G. Evidence-based pain management for infants. Curr Opin Pediatr 1998;10:203-207.
- Taddio A, Nulman I, Koren BS, Stevens BJ and Koren G. A revised measure of acute pain in infants. J Pain Symptom Manage 1995;10:456-463.
- Tarbell SE, Cohen TI and Marsh JL. The Toddler-preschooler postoperative pain scale: an observational scale for measuring postoperative pain in children aged 1-5. Preliminary report. Pain 1992;50:273-280.

Chapter 7

Evaluation of pain management in neonates after oesophageal atresia

Based on:
Evaluation of pain management in neonates after oesophageal atresia
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Submitted.

7.1 Abstract

Objective
To evaluate postoperative pain management in neonates from 1985 to 2002.

Design
Retrospective study.

Setting
Paediatric Surgical Intensive Care Unit in a level III children's hospital.

Patients and Interventions
Four different periods of pain management were identified: A (1985 - 1990) morphine as needed, intermittently; no validated pain score (PS), B (1990 - 1995) morphine continuously; no validated PS, C (1995 - 1998) morphine continuously, developing validated PS, D (1998 - 2002) morphine continuously, validated PS combined with algorithm.
Over the period 1985 - 2002, we evaluated in eighty-one neonates who had undergone a primary anastomosis of an isolated oesophageal atresia and closure of the tracheo-oesophageal fistula, how the introduction of continuous morphine infusions and a validated pain score combined with an algorithm, effected

a) the amounts of morphine used and the duration of mechanical ventilation during the first 3 days after surgery, and
b) the relation between prescribed and actually administered morphine dosages.

Results
In period A neonates received significantly less morphine than in the periods B, C and D (all $P < 0.005$), no differences were found between the latter three periods. The proportion of patients mechanically ventilated after surgery increased from 84 % in period A, to 90 % in period B, and to 100 % in the periods C and D. The duration of mechanical ventilation after surgery increased during periods A, B and C [median (10 - 90th percentile)] from 24 (0 - 78), to 47 (1 - 96), to 48 (20 - 109), respectively, and decreased in the last period to 34 (15 - 145) hours. Overall, the total duration of postoperative mechanical ventilation did not significantly differ between the four periods. To evaluate the effect of a validated pain score combined with an algorithm (period D), we completed a "subgroup analysis". The odds of being given greater or lower amounts than the median morphine dose did not differ between the periods C and D. However, the odds to be

mechanically ventilated longer than the median duration of 45 h was 4.5 times lower in period D than in period C (95 % CI: 0.05 - 0.94). There was no significant association between the prescribed and the actually administered amounts of morphine in period A. However, in the three later periods the correlation was significant and increased from r = 0.58 (P = 0.007) in period B, to r = 0.91 and 0.88 (both P < 0.001) in period C and D, respectively.

Conclusion
The change from personal interpretation of postoperative pain to individual assessment based on objective pain scores resulted in optimal morphine dosages with an acceptable duration of mechanical ventilation, and a high correlation between prescribed and administered analgesia.

7.2 Introduction

Pain management in children has changed significantly during the last decades. Analgesics used to be given on demand, when pain was proven, but opioids were seldom used and only in children ventilated mechanically.[1-5] Fear for adverse effects of opioids and ignorance of pain perception and pain experience prevented medical and nursing staff from prescribing and administering analgesics as standard practice. Despite all reports of undertreatment, this attitude did not change till Anand et al. reported the deleterious effects of inadequate analgesia during and after surgery in preterm neonates. Patients without analgesia exhibited not only significant stress responses (increased epinephrine, norepinephrine, glucose, and decreased insulin levels), but also increased morbidity and mortality.[6,7]
Fear for respiratory depression of morphine and lack of efficacy data made anaesthetists reluctant to administer large amounts of morphine in small children.[8] From the mid-1980s several studies regarding the pharmacokinetics and safety of opioids were performed in neonates and infants.[9-16] For safety reasons most of these studies were carried out in mechanically ventilated infants.
Gradually pain management after major surgery changed from "on demand" into pain-preventing therapy, so-called pre-emptive analgesia, and morphine administered as a continuous infusion became standard care. Unfortunately, from lack of validated pain measurements for non-verbal children, it was impossible to evaluate the effects of the

different morphine therapies or to determine optimal analgesic doses for different age groups.

In the 1990s a number of studies provided anaesthetists and paediatricians with validated tools for assessment of postoperative pain in non-verbal children.[17-29] Next it was shown that age, kind of surgery and method of morphine administration all effect surgical stress responses and morphine requirements.[30-35] From that time onwards paediatric pain management improved.[36]

The purpose of the present study was to evaluate different periods of pain management from 1985 to 2002, from nurse-biased to standard care. In one diagnostic category of surgical neonates, i.e. neonates with an isolated oesophageal atresia treated by primary anastomosis, we evaluated the effects of a protocol of continuous morphine infusion and a validated pain score combined with an algorithm for postoperative pain management, on a) morphine requirements, b) duration of mechanical ventilation and c) the relation between prescribed and actually administered amounts of morphine.

Table 1 Per- and postoperative management on the surgical PICU of the Sophia Children's Hospital

	Period			
	A (1985-1990)	**B (1990-1995)**	**C (1995-1998)**	**D (1998-2002)**
Anaesthetic procedure	Halothane/ N_2O/O_2/air/ pancuronium awake intubation	Halothane/ N_2O/O_2/air/ atracurium fentanyl 3 µg/kg	Isoflurane/ N_2O/O_2/air/ atracurium Fentanyl 10 µg/kg	Isoflurane/ N_2O/O_2/air/ atracurium Fentanyl 10 µg/kg
Postoperative pain treatment	IM (IV/RC), only during mechanical ventilation	CM, 10-20 µg/kg/h, during mechanical ventilation and SR	CM/IM, initial dose: 10 µg/kg/h, during mechanical ventilation and SR	CM, initial dose: 5-10 µg/kg/h, during mechanical ventilation and SR
Loading dose	Never/rare	Not standardized	Always, 100 µg/kg	Always, 100 µg/kg
Algorithm	No	No	No	Yes
Additional pain relief	Personal interpretation	Personal interpretation	VAS ≥ 4	VAS ≥ 4
Adjusting morphine dosage	Personal interpretation	Personal interpretation	According to protocol	Based on pain scores
Pain assessment	Not standardized	Not standardized	COMFORT and VAS	COMFORT and VAS
Mechanical Ventilation after surgery Yes/No	On indication/rare	On indication	Yes	Yes

IM = intermittent morphine; CM = continuous morphine; IV= intravenously; RC= rectally; SR= spontaneous respiration.

7.3 Patients and methods

This changing attitude regarding pain and pain management was also found on the surgical paediatric intensive care unit (PICU) in the Sophia Children's Hospital, allowing us to distinguish four different periods from 1985 till now (Table 1).
Table 1 gives details about the anaesthetic procedures and postoperative management, i.e. mechanical ventilation yes/no, pain assessment and pain treatment, applied during these periods.

In period A), postoperative pain was treated with intermittent morphine rectally or intramuscularly following nurses' judgement. Mechanical ventilation after surgery was only started on indication.
In period B) patients received continuous morphine infusions preventing personal bias regarding morphine administration. However, no validated scales for measurement of postoperative pain were available, and the infusion rates were adjusted by personal interpretation of pain.
In period C) in a RCT comparing the effects of postoperative continuous and intermittent morphine, the COMFORT Scale (CS) was validated for postoperative pain measurement in non-verbal children. The behavioural part of the CS has been proven to be a valid, reliable and feasible instrument for assessment of pain in neonates and infants aged 0 to 3 years after major surgery.[26] In this study all neonates and infants received an initial morphine dose of 10 µg /kg/hr, according to the results of other studies.[9,13,37]
From that time onwards patients after oesophageal surgery were routinely mechanically ventilated.
In period D), as result of the above study,[34] postoperative morphine was given as a continuous infusion. Neonates and infants > 7 days received an initial dosage of 10 µg/kg/h, neonates ≤ 7 days 5 µg/kg/h, after a loading dose of 100 µg/kg morphine.
The behavioural CS was now part of standard daily care, to evaluate the effects of analgesia and to adjust dosages according to an algorithm, what was developed consequently (Fig 1).
Figure 1 shows the algorithm, providing instructions for pain management, based on COMFORT and VAS scores.

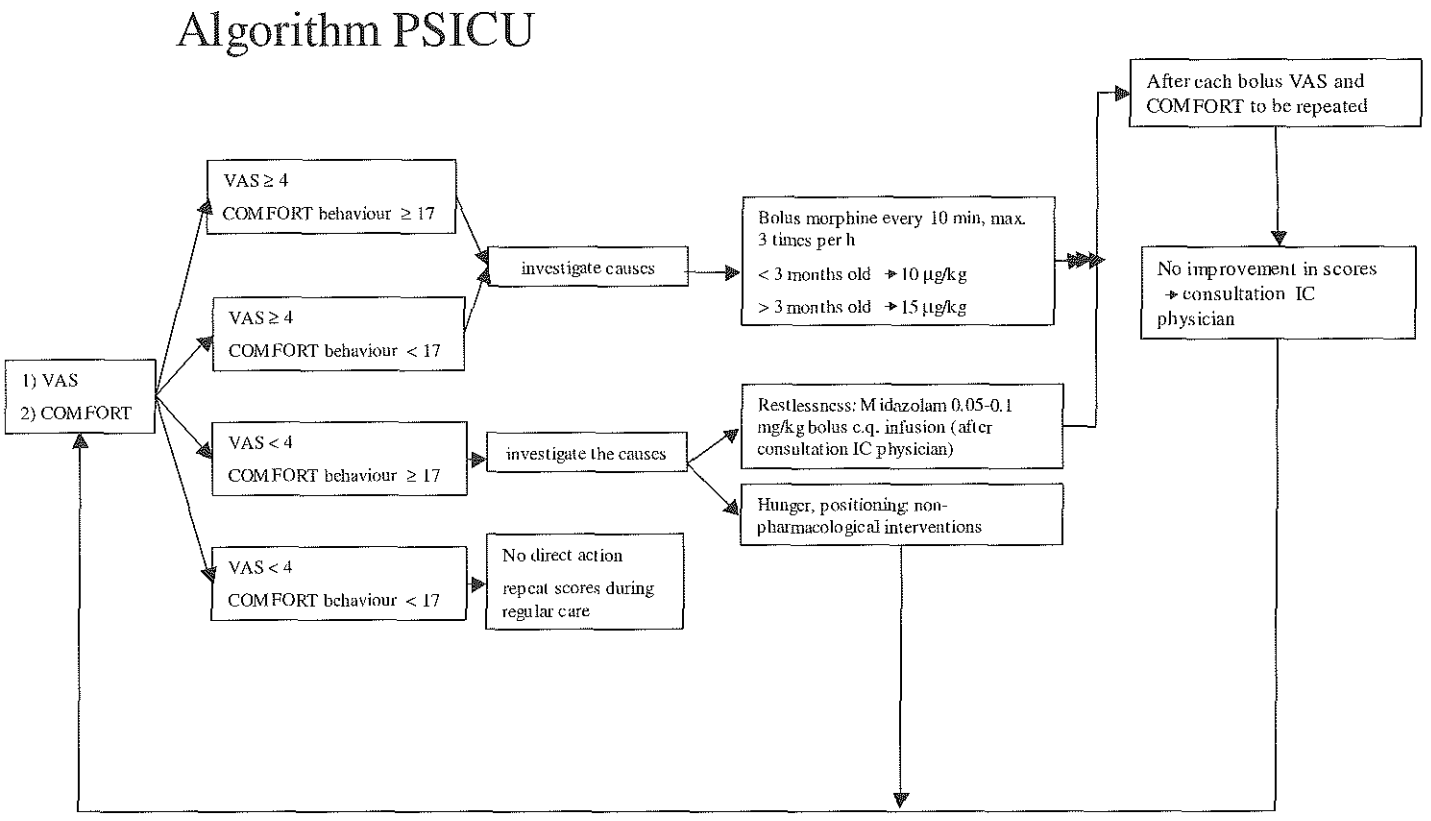

Fig. 1 *Algorithm giving instructions for pain management in the paediatric surgical intensive care unit*

7.4 Methods

A single-centre analysis in a level III children's hospital was carried out.

Inclusion and exclusion criteria
We identified all neonates, admitted to the paediatric surgical intensive care unit (PICU) after a primary anastomosis of an oesophageal atresia and closure of the tracheo-oesophageal (TE) fistula, during the period 1985 - 2002. Patients with gestational age < 35 weeks, those who were complicated by cardiac, hepatic, neurologic or renal disorders (including major associated anomalies), or other surgical procedures, and those who were treated postoperatively with sedatives, muscle relaxants or other analgesics than morphine, were excluded ($n = 90$).
The surgical procedure included a right-sided thoracotomy, using a retropleural approach followed by an end-to-end anastomosis with closure of the TE fistula.

Variables
The following data were collected: age, sex, the dosage of morphine for the first 24 h prescribed by the anaesthetist, the dosage of morphine actually administered during the first, second and third 24 h after surgery, the route of analgesic administration, and the duration of mechanical ventilation. When the route of administration was rectally, the rectal dose was converted to an intravenous one by halving the dose (rectal bioavailability of morphine varies from 10 – 60 %).

Procedure
The data were collected retrospectively as well as prospectively, depending on the period when the operation was carried out. The data of patients operated upon before 1995 were collected retrospectively, using the following sources: patient histories, medication charts, anaesthetic reports, and Therapeutic Intervention Scoring System (TISS) scores.[38] Most of the patients in period C and D participated in clinical trials. In these trials morphine requirement, pain scores, and the duration of mechanical ventilation were prospectively registered, to determine morphine pharmacokinetics in different age groups.

Data analysis
The children were stratified into one of four groups depending on the period of operation. To find out whether the groups differ, One Way ANOVA was performed, after which Student t-test was used to compare each pair of group. Pearson Correlation Coefficient

was used to assess the association between prescribed and actual given amounts of morphine. If the data showed strong skew distribution, their non-parametric variants (i.e. Kruskall Wallis, Mann Whitney U Test, and Spearmann's Rank Correlation) were used.

7.5 Results

A total of 171 infants were identified, 81 of which were included. Twenty-five during period A), 20 during period B), 17 during period C), and 19 during period D).
Kruskall Wallis demonstrated that the median age in period A was significantly lower than that in B, C and D ($P < 0.005$). In all periods more boys than girls were included (all $P = 0.001$). Table 2 presents, besides the patients' characteristics, the amounts of morphine used each day and the total duration of mechanical ventilation for the four different periods.

Morphine
Kruskall Wallis analysis showed significant group differences in the total amount of morphine administered during 72 hours after surgery. In period A neonates received significantly less morphine than in the periods B, C, and D (all $P < 0.005$), no differences were found between the latter three periods.
Figure 2 shows the median doses of morphine during the first, the second and the third day after surgery, in the four periods.

Mechanically ventilation after surgery
From 1985 - 2002 the percentage of patients mechanically ventilated after surgery increased from 84 % in period A, to 90% period B, and to 100% in the periods C and D. The duration of mechanical ventilation after surgery increased during periods A, B and C [median (10 - 90th percentile)] from 24 (0 - 78), to 47 (1 - 96), to 48 (20 - 109), respectively, and decreased in the last period to 34 (15 - 145) hours (Table 2). Overall, the total duration of postoperative mechanical ventilation did not significantly differ between the four periods.

Period C versus D
To evaluate the effect of combining a validated pain score with an algorithm (accomplished in period D), we completed a "subgroup analysis" estimating whether neonates in period D had a greater or lower odds to have a larger morphine requirement

and a longer duration of mechanical ventilation than neonates in period C. For this purpose the variables "morphine requirement" and "duration of mechanical ventilation" were discriminated into: a) getting more or less than the median morphine requirement for the first 72 hours and b) needing mechanical ventilation more or less than the median duration of ventilation. To assess these two medians the data of both periods C and D were combined; medians were 7.3 µg/kg/h and 45 h, respectively. The odds of receiving greater amounts of morphine (i.e. ≥ 7.3 µg /kg/h) did not differ between the two periods. However, the odds to be mechanically ventilated for > 45 h was 0.22 (95% CI: 0.05 – 0.94); i.e. 4.5 times lower in period D than in period C .
Figure 3 shows the proportions of patients in need of postoperative mechanical ventilation in the four periods, with duration ranging from 0 to > 48 h.

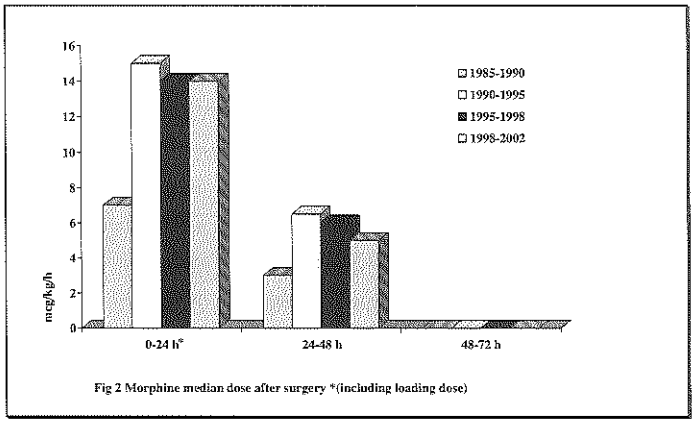

Fig. 2 *Morphine median doses after surgery (µg/kg/h), *(including loading dose)*

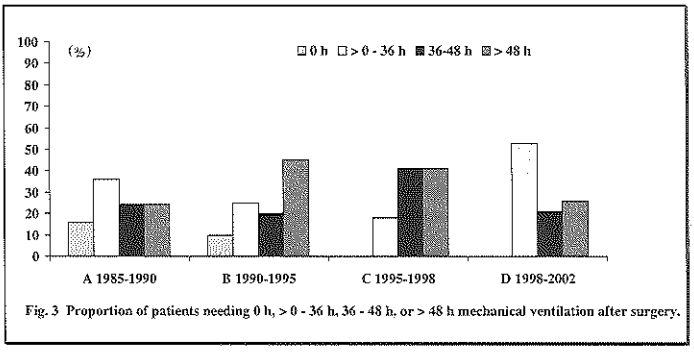

Fig. 3 *Proportions of patients needing mechanical ventilation after surgery for > 0 – 36 h, 36 - 48 h, or > 48 h.*

Table 2 Patient characteristics, morphine dosages and duration of postoperative mechanical ventilation

	A 1985-1990	B 1990-1995	C 1995-1998	D 1998-2002	P value
No. of patients	25	20	17	19	
Postnatal age in days	1 (0-2)*	1 (1-4)	2 (1-7)	1 (0-5)	*A vs. all < 0.005
Gestational age in weeks	40 (36-42)	39 (36-42)	38 (35-42)	39 (36-41)	
Weight in kg	2.9 (2.1-3.8)	2.5 (1.8-3.5)	2.9 (2.0-3.6)	3.0 (2.0-3.6)	
No. of boys/girls	16/9	12/8	16/1	13/6	
% of patients receiving morphine at day 1	100	100	100	100	
day 2	64	80	92	94	
day 3	8	25	38	19	
Morphine dosage during 72 h after surgery (μg/kg/h)	3.0 [1.2-7.8]*	8.0 [3.3-16.2]	8.3 [5.7-14.6]	7.3 [3.5-13.7]	*A vs. all P < 0.05
Morphine dosage (μg/kg/h) at day 1	7.0 [3.0-17.4]	15.0 [10.0-23.7]	14.0 [13.8-24.8]	14.0 [9.0-24.0]	
day 2	3.0 [0-8.0]	6.5 [0-19.1]	6.0 [3.2-14.4]	5.0 [1.5-10.0]	
day 3	0 [0-0.8]	0 [0-9.9]	0 [0-10.0]	0 [0-5.0]	
% of patients mechanically ventilated after surgery	84	90	100	100	
No. of hours of mechanical ventilation after surgery	24 [0-78]	47 [1-96]	48 [20-109]	34 [15-145]	

Values are median (range), median [10 - 90th percentile], or percentage.
Day 1 = the first 24 h after surgery; day 2 = 24 - 48 h after surgery; day 3 = 48 - 72 h after surgery.

Morphine prescribed and administered

Figure 4 shows a scatter plot of the prescribed morphine doses and the actual given amounts of morphine during the first 24 h after surgery in the four periods.

Spearmann Rank Correlation testing demonstrated no significant association between the prescribed and the actually administered amounts of morphine in period A. However, the three later periods showed significant correlation, increasing from r = 0.58 (P = 0.007) in period B, to r = 0.91 and 0.88 (both P < 0.001) in periods C and D, respectively.

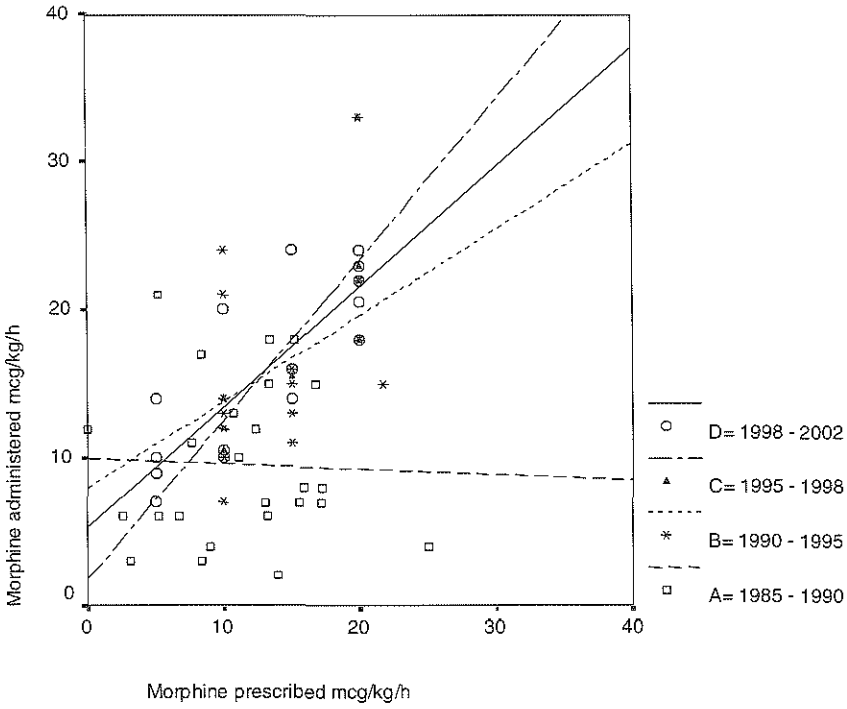

Fig. 4 *Scatter plot showing the relation between prescribed and actual given amounts of morphine during the first 24 h after surgery in four periods.*

7.6 Discussion

From 1985 to 1998, i.e. in the first three periods studied, the increased attention given to pain, including the changeover from intermittent to continuous therapy and the use of a loading dose, resulted in increased use of morphine and, as expected, longer duration of postoperative mechanical ventilation. During the last period (1998 - 2002) the lower

initial morphine doses, and the use of an objective, validated pain scale combined with an algorithm for pain management as standard daily care, did not result in significantly lower morphine doses over the first 3 days after surgery. However, the risk to be mechanically ventilated for more than the median length of 45 h was significantly reduced.

Although the duration of mechanical ventilation after oesophageal surgery is not only dependent on the morphine dosage, but especially on the severity of tracheomalacia, this confounding variable was consistent during all periods. All other potential confounding variables such as major associated anomalies or other surgical procedures were excluded. Misconceptions and lack of information on pain and pain management in children explain the little attention given to these subjects in the past. Fear of respiratory depression, in view of the fact that children seemed to have higher opioid sensitivity compared with adults,[39] fear of addiction, ignorance about the maturity of the neonate's nervous system, they all influenced the clinical practice. Medical treatment was predominantly focussed on the survival of the child, i.e. fighting against low blood pressure and heart rate, as one was still unaware of the deleterious effects of surgical stress.[6,7] Apart from short-term effects, untreated pain is associated with long-term sequelae. Experiments in animals suggest that the effects extend into adulthood. They disrupt the predetermined maturation process of the central nervous system, which result in sprouting of axons into new areas of the dorsal horn.[40,41] These neurophysiological alterations are associated with increased pain sensitiveness in childhood.[42-45] Adequate management of pain in early infancy prevents children from developing an altered pain threshold.[46]

Morphine, ordered as needed, was often interpreted as "as little as possible", and was only given during mechanical ventilation. Following the Royal Children's Hospital of Melbourne, the way of morphine administration in the surgical PICU was changed into i.v. continuous morphine, and, if necessary, morphine was continued when patients were off the ventilator.
In that period a morphine dosage of 10 μg/kg/h, seemed to be a minimally required dose for postoperative pain treatment at all ages, taking into account the possibility of additional doses, on the published amounts varying from 20 to100 μg/kg/h for neonates and infants.[9,10,15,16,37] The results of a clinical trial on our PICU[35] made it likely that a lower dose of morphine would have sufficed for the young neonates. Consequently, from that time onwards neonates ≤ 7 days received an initial dose of 5 μg/kg/h and neonates > 7 days 10 μg/kg/h.

The improvement in pain management over the consecutive periods is evident in the scatter plot giving the amounts of morphine prescribed and actually administered. The increasing correlation between prescription and administration from period A to C shows the growing uniformity in pain management, whereas the slightly reduced correlation in the last period shows the influence of validated pain assessment. With the use of a validated pain protocol, morphine infusions in non-verbal children can be increased, or tapered off, providing tailored analgesia.
There is general agreement that validated pain scales are necessary for adequate pain management, and hence an abundance of pain scales have been and are still being developed. However, as far as we know, no studies are published evaluating the effects of the introduction of a validated pain scale on postoperative pain management in non-verbal children following major surgery.
The introduction of a pain scoring system was not easily accepted in the PICU. It was considered a redundant activity, seeing that experienced PICU-nurses thought they could estimate the amount of pain by personal interpretation. Only after the introduction of a protocol, including a validated pain scale combined with an algorithm for pain management, the pain assessment with pain measurements was found effective and became standard care.

This study shows the usefulness of an objective pain score in non-verbal children. Following proper training, even non-experienced caregivers are able to adequately assess pain in this vulnerable group of patients, taking into account inter-observer variability. However, an algorithm, including instructions for additional analgesia, is an essential part of the pain protocol.
With this validated and feasible guideline for pain management, we were able to start new studies in post-surgical neonates and infants[47] and have developed an infrastructure for future evaluation of analgesic protocols and pain assessment instruments.

7.7 Conclusion

Postoperative pain management in neonates and infants has improved during the last decades. The change from personal interpretation to individual assessment based on objective pain scores resulted in optimal morphine dosages with an acceptable duration of mechanical ventilation, and a higher correlation between prescribed and administered analgesia.

7.8 Acknowledgements

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7.9 References

1. Burokas L. Factors affecting nurses' decisions to medicate pediatric patients after surgery. Heart and Lung 1985;14:373-379.
2. Beyer JE, DeGood DE, Ashley LC, et al. Patterns of postoperative analgesic use with adults and children following cardiac surgery. Pain 1983;17:71-81.
3. Eland JM, Anderson JE. The experience of pain in children. In: Jacox A., ed. Pain: a source book for nurses and other health professionals. Boston:Little, Brown. 1977.
4. Schechter NL, Allen DA, Hanson K. Status of pediatric pain control: a comparison of hospital analgesic usage in children and adults. Pediatrics 1986; 77:11-15.
5. Mather L, Mackie J. The incidence of postoperative pain in children. Pain 1983; 15:271-282.
6. Anand KJS, Sippell WG, Aynsley-Green A. Randomized trial of fentanyl anesthesia in preterm babies undergoing surgery: effects on the stress response. Lancet 1987;1:243-248.
7. Anand KJS, Hickey PR. Halothane-Morphine compared with high dose sufentanil for anaesthesia and postoperative analgesia in neonatal cardiac surgery. The New England J Medicine. 1992,326;1-9.
8. Purcell-Jones G, Dormon F, Sumner E. Paediatric anaesthetist's perception of neonatal and infant pain. Pain 1988;33:181-187.
9. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. Anesthesiology 1987;66:136-139.
10. Lynn AM, Nespeca MK, Opheim KE, Slattery JT. Respiratory effects of intravenous morphine infusions in neonates, infants and children after cardiac surgery. Anesth Analg 1993;77:695-701.
11. Singleton MA, Rosen JI, Fisher DM. Plasma concentrations of fentanyl in infants, children and adults. Can J Anaesth 1987;34:152-155.
12. Greeley WJ, de Bruijn NP. Changes in sufentanil pharmacokinetics within the neonatal period. Anesth Analg 1988;67:86-90.
13. Choonara IA, McKay P, Hain R, Rane A. Morphine metabolism in children. Br J Clin Pharmacol 1989;28:599-604.
14. Chay PC, Duffy BJ, Walker JS. Pharmacokinetic-pharmacodynamic relationships of morphine in neonates. Clin Pharmacol Ther 1992;51:334-342.
15. McRorie TI, Lynn AM, Nespeca MK, Opheim KE, Slattery JT. The maturation of morphine clearance and metabolism. AJDC 1992;146:972-976.
16. Hartley R, Green M, Quinn MW, Rushforth JA, Levene MI. Development of morphine glucuronidation in premature neonates. Biol Neonate 1994;66:1-9.
17. Ambuel B, Hamlett KW, Marx CM, Blumer JL. Assessing distress in pediatric intensive care environments: the COMFORT Scale. Journal of Pediatric Psychology, 1992; 17:95-109.

18. Tarbell SE, Cohen TI, Marsh JL. The Toddler-preschooler postoperative pain scale: an observational scale for measuring postoperative pain in children aged 1- 5. Preliminary report. Pain 1992;50:273-280.
19. Krechel SW, Bildner J. CRIES: a new neonatal postoperative pain measurement score. Initial testing of validity and reliability. Paediatric Anesthesia 1995;5:53-61.
20. Merkel SI, VoepelLewis T, Shayevitz JR, et al. The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatr Nurs 1997;23:293-297.
21. Buchholz M, Karl HW, Pomietto M, et al. Pain scores in infants: a modified infants pain scale versus visual analogue. J Pain Symptom Manage 1998;15:117-124.
22. Schultz AA, Mirphy E, Morton J, et al. Preverbal, Early Verbal Pediatric Pain Scale (PEPPS): development and early psychometric testing. J Pediatr Nurs 1999;14:19-27.
23. Boelen WJC, Scheffer E, Haan de RJ, et al. Clinimetric evaluation of the pain observation scale for young children in children aged between 1 and 4 years after ear, nose, and throat surgery. J Dev Behav Pediatr 1999;20:14-19.
24. Buttner W, Finke W. Analysis of behavioural and physiological parameters for the assessment of postoperative analgesic demand in newborns, infants and young children: a comprehensive report on seven consecutive studies. Paediatr Anaesth 2000;10:303-318.
25. van Dijk M, de Boer JB, Koot HM, et al. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0-3-year-old infants. Pain 2000;84:367-377.
26. van Dijk M, Bouwmeester NJ, Duivenvoorden HJ, Koot HM, Tibboel D, Passchier J, de Boer JB. Efficacy of continuous versus intermittent morphine administration after major surgery in 0-3 year-old infants; a double-blind randomized controlled trial. Pain 2002;98:305-313.
27. van Dijk M, Peters JWB, Bouwmeester NJ, Tibboel D. Are postoperative pain instruments useful for specific groups of vulnerable infants? Clin Perinat 2002, accepted for publication
28. McGrath PA, Johnson G, Goodman JT, et al. CHEOPS: A behavioral scale for rating postoperative pain in children. In Fields HL, Dubner R, Cervero T (eds). Advances in pain research and therapy 1985; 9:305-402. New York: Raven Press.
29. Peters JWB, Duivenvoorde HJ, Grunau RVE, de Boer J, van Druenen MJ, Tibboel D, Koot HM. The value of the neonatal facial coding system for assessing postoperative pain in infants. Submitted.
30. Lynn AM, Nespeca MK, Bratton SL, Shen DD. Intravenous morphine in postoperative infants: intermittent bolus dosing versus targeted continuous infusions. Pain 2000;88:89-95.
31. Faura CC, Collins SL, Moore RA, McQuay HJ. Systematic review of factors affecting the ratios of morphine and its major metabolites. Pain 1998;74:43-53.

32. Farrington EA, McGuinness GA, Johnson GF, Eremberg A, Leff RD. Continuous intravenous morphine infusion in postoperative newborn infants. AJ Perinatology 1993;10:84-87.
33. Scott CS, Riggs KW, Ling EW, et al. Morphine pharmacokinetics and pain assessment in premature newborns. J Pediatr 1999;135:423-429.
34. Bouwmeester NJ,Anand KJ, van Dijk M, et al. Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind randomized trial comparing the effects of continuous versus intermittent morphine. Br J Anaesth 2001;87:390-399.
35. Bouwmeester N J, Hop WCJ, van Dijk M, Anand KJS, van den Anker JN, Tibboel D. Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism (submitted).
36. De Lima J, Lloyd-Thomas AR, Howard RF, Sumner E, Quinn TM. Infant and neonatal pain: anaesthetist's perceptions and prescribing patterns. BMJ 1996;313:787.
37. Beasley SW, Tibballs J. Efficacy and safety of continuous morphine infusion for postoperative analgesia in the paediatric surgical ward. Aust N Z J Surg 1987;57:233-237.
38. Keene AR, Cullen DJ. Therapeutic intervention scoring system: update 1983. Crit Care Med 1983;11:1-3.
39. Way WL, Costley EC, Way EL. Respiratory sensitivity of the newborn infant to meperidine and morphine. Clin Pharmacol Therap 1964;6:454-461.
40. Anand KJS, Coskun V, Thrivikraman KV, Nemeroff CB, Plotsky PM. Long-term behavioral effects of repetitive pain in neonatal rat pups. Physiol Behav 1999;66:627-637.
41. Ruda MA, Qing-Dong L, Hohmann AG, Peng YB, Tachibana T. Altered nociceptive neuronal circuits after neonatal peripheral inflammation. Science 2000;289:628-630.
42. Grunau RVE, Whitfield MF, Petrie JH. Pain sensitivity and temperament in extremely low-birth-weight premature toddlers and preterm and full-term controls. Pain 1994;58:341-346.
43. Grunau RVE. Long-term consequences of pain in human neonates. In: AnandKJS, Stevens BJ, McGrath PJ, eds. Pain in neonates, 2nd revised and enlarged edition. Amsterdam: Elsevier, 2000:55-76.
44. Taddio A, Goldbach M, Ipp M, Stevens B, Koren G. Effect of neonatal circumcision on pain response during vaccination in boys. Lancet 1995;345:291-292.
45. Oberlander TF, Grunau R, Whitfield MF, et al. Biobehavioral pain responses in former extremely low birth weight infants at four months'corrected age. Pediatrics 2000;105:E6.
46. Peters JWB, Koot HM, de Boer J, Passchier J, Bueno-de-Mesquita JM, de Jong FM, Duivenvoorden HJ, Tibboel D. Major surgery within the first three months of life and subsequent bio-behavioural pain responses to immunisation at later age: a case comparison study. Pediatrics, in press.
47. van der Marel CD, van Lingen RA, Pluim MA, et al. Analgesic efficacy of rectal versus oral acetaminophen in children after major craniofacial surgery. Clin Pharmacol Ther 2001;70:82-90

Chapter 8

General discussion and future directives

8.1 Evolution of pain management in general

Pain management in children has changed significantly during the last decades. Before 1987 no serious attention was given to this subject. In 1968, Swafford and Allen1 reported that only 2 of the 60 postoperative children needed analgesia, for, as they wrote, "children tolerate discomfort well and need seldom medication for relief of pain". Eland[2] was the first in 1977, followed by others,[3-5] to report the undertreatment of children compared with adults after comparable surgery. Analgesics were given on demand, when pain was proven, but opioids were seldom used and only in children ventilated mechanically.[6] Fear for adverse effects of opioids and ignorance of pain perception and pain experience prevented medical and nursing staff from prescribing and administering analgesics as standard practice. Despite all reports of undertreatment, this attitude, denigrating the importance of adequate pain relief, did not change till Anand et al. reported the deleterious effects of inadequate analgesia during and after surgery in preterm neonates. Patients without analgesia exhibited not only significant stress responses (increased epinephrine, norepinephrine, glucose, and decreased insulin levels), but also increased morbidity and mortality.[7,8]

End of the eighties

Although these studies convinced anaesthetists and paediatricians that neonates do feel pain and that pain has to be treated, fear for adverse effects of morphine and lack of efficacy data made them reticent to administer large amounts of morphine in small children.[9] From this period several studies regarding the pharmacokinetics and safety of opioids were performed in neonates and infants.[10-17] For safety reasons most of these studies were carried out in mechanically ventilated infants.

Half-way the nineties

The above pharmacokinetic studies convinced many paediatric anaesthetists and intensivists that opioids are not harmful for neonates and children, not even when they breath spontaneously, and that they should be administered to protect infants from the adverse effects of surgical stress.[18] From that time onwards, pain management after major surgery changed from "on demand" into pain-preventing therapy, so-called pre-emptive analgesia, and morphine administered as a continuous infusion became standard care. Unfortunately, from lack of validated pain measurements for non-verbal children, it was impossible to evaluate the effects of the different morphine therapies or to determine optimal analgesic doses for different age groups.

Several studies were set up to develop validated instruments for assessment of postoperative pain in non-verbal children, and to assess the most efficacious dose of morphine in neonates and infants after major surgery. However, combining pain assessment and analgesia was by no means common practice.

End of the nineties

Although McGrath had already started to develop pain measurements for postoperative children in the eighties,[19] later studies provided anaesthetists and paediatricians with validated tools for assessment of postoperative pain in non-verbal children.[20-31] Later it becomes known as well that factors such as age, kind of surgery and method of morphine administration all influence surgical stress responses and morphine requirements.[32-37]

8.2 Evolution of pain management on the paediatric surgical intensive care unit (PICU) of the Sophia Children's Hospital

This changing attitudes regarding pain and pain management were also reflected on the surgical PICU in the Sophia Children's Hospital. Accordingly we may discern four different periods over the span from 1985 till 2002.

In period A), (1985 - 1990), postoperative pain was treated with intermittent morphine rectally or intramuscularly following nurses' judgements. Mechanical ventilation after surgery was started only on indication.

In period B), (1990 - 1995), following the Royal Children's Hospital of Melbourne, the preferred route of morphine administration became i.v. continuous morphine. If necessary, morphine was continued when patients were off the ventilator. A paediatric pain group was set up which developed the first protocols for pain management. Validated scales for measurement of postoperative pain were not yet available, morphine infusion rates were adjusted by personal interpretation of pain. One of the reasons for the scarcity in paediatric pain studies was the lack of instruments for the assessment of continuing pain in non-verbal children.

In period C), (1995 - 1998), in a RCT comparing the effects of postoperative continuous and intermittent morphine, the COMFORT Scale (CS) was validated for postoperative pain measurement in non-verbal children. The behavioural part of the CS has been proven to be a valid, reliable and feasible instrument for assessment of pain in neonates and infants aged 0 to 3 years after major surgery.[38] In this period a morphine dosage of 10 μg/kg/h seemed to be a minimal required dose for postoperative pain treatment for all

ages, based on reported amounts varying from 20 to100 μg/kg/h for neonates and infants, taking into account the possibility of additional doses.[10,16,17,39]
From that period on patients after oesophageal surgery were routinely mechanically ventilated.
From the results of our studies,[29,36,37] we concluded that a lower dose of morphine likely would have sufficed for the young neonates.
In period D), (1998 - 2002), as a consequence of the above studies, postoperative morphine was given as a continuous infusion, for neonates and infants > 7 days an initial dosage of 10 μg/kg/h/, neonates ≤ 7 days 5 μg/kg/h, after a loading dose of 100 μg/kg of morphine.
From that time onwards application of the behavioural CS was part of standard daily care, enabling to evaluate the effects of analgesia and to adjust dosages according to an algorithm developed next.

Against this background, the studies in this thesis have a threefold aim:

1. To develop a valid objective pain scale for the measurement of postoperative pain in neonates and infants
2. To compare the effects of continuous morphine, which is the commonest route of administration, with those of intermittent morphine, which was used before, in neonates and infants after major surgery. Attention was focussed on a) hormonal metabolic stress responses, b) age-related morphine requirements, c) morphine metabolism and d) the correlation with objective pain assessment.
3. To evaluate the effects of the evolution in pain management on a) postoperative morphine requirement and duration of mechanical ventilation in a single-diagnosed group of surgical neonates, and b) the relation between prescribed and actually administered morphine doses.

8.3 The next section outlines the results and conclusions of our studies and gives future directions.

I. Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind , randomized trial comparing the effects of continuous versus intermittent morphine.Br J Anaesth 2001;87:390-399.

The results of this study prompted us to reject our primary hypothesis that continuous infusions of morphine produce would improve postoperative analgesia and lower hormonal-metabolic responses. Clinical bias was eliminated by the double-blind study

design, and total morphine consumption was comparable between the two randomized groups. Only in the older infants, aged 1 - 3 years, we noted greater degrees of stress in the intermittent morphine group than in the continuous morphine group, which may be caused by the relatively greater plasma clearance of morphine in this age group. Thus, it is likely that the longer duration of opioid effect following intermittent morphine boluses in the younger age groups resulted in clinical and physiological effects that were comparable to those of a continuous infusion.
The pattern of surgical stress responses differed significantly between the neonates and the older age groups. In the neonates, developmental differences were found for the postoperative changes in hormonal-metabolic variables (plasma adrenaline, noradrenaline, insulin and lactate), cardiovascular responses, behavioural parameters, and postoperative morphine consumption. In the older age groups, we found comparable patterns of hormonal-metabolic responses, behavioural responses and postoperative morphine consumption.
We found significantly higher adrenaline and noradrenaline plasma concentrations after upper abdominal surgery than after thoracic or superficial surgery. Significantly higher plasma concentrations of noradrenaline occurred following a blood transfusion in neonates as compared with neonates without transfusion, at 6, 12 and 24 h after surgery. These differences were not found in the other age groups.

In this study we have shown that neonates and infants up to 1 year of age may receive intermittent morphine doses, thereby avoiding the excessive fluid intake and the need of infusion equipment. Older infants (1 - 3 years) may require either a continuous infusion, or more frequent dosing regimens (every 1 - 2 hours) or judicious increases in the intermittent doses used for postoperative morphine analgesia. We speculate that combined therapy with different classes of analgesics and sedative drugs will provide more effective control of physiological and behavioural responses, especially in toddlers 1 - 3 years of age, who may have a high level of anxiety in the PICU environment. Further studies are needed to establish the efficacy and safety of such combinations, i.e. morphine combined with midazolam, paracetamol or a NSAID. These studies will not only provide a scientific framework for the postoperative management of neonates and young infants, but may also provide clues to elucidate the development of pain and stress-responsive systems in the developing brain.

II. Therapeutic requirements and plasma concentrations of morphine and its metabolites in postoperative neonates and infants aged 0-3 years, submitted.

We investigated a) the effects of potential confounding variables on morphine requirements in neonates and infants after major surgery, and b) the age-related changes in morphine and metabolite concentrations.
Our studies revealed that age is the most important factor determining optimal doses, differentiating dose requirements between neonates and infants older than 4 weeks. Because concentration is directly proportional to dose, we need to determine clearance in order to predict dose.

Dosage

Morphine requirement was not significantly different between the treatment groups. Most of the neonates had adequate analgesia through the minimal dose of 10 μg/kg/h. The older children needed significantly more morphine, with requirements ranging from (median) 10.9 to 12.3 μg/kg/h. Extra morphine dosages, given in a nurse-controlled way, based on observational validated pain scores, resulted in similar plasma concentrations in the continuous and intermittent morphine group from 12 h after surgery. Even with the additional morphine, the required dose was lower than the recommended dosage of 20 μg/kg/h.[32,40,41] However, in this meta-analysis most of the studies were not designed as randomized clinical trials.

Plasma concentration

Morphine plasma concentrations were significantly dependent on age, bearing in mind that patients with renal impairment were not included. The wide "analgesic range" in reported plasma morphine concentrations 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.[15,16,42,43] To report adequate doses for postoperative analgesia more studies with large numbers are needed in well-defined groups of patients (i.e. age, severe illness, mechanical ventilation, in need of sedation or analgesia, tolerance, cardiac or non-cardiac surgery, method of treatment, race, pain assessment, etc.).

Metabolites

The clinical effect of morphine also relies on the formation of its active metabolite M6G. Morphine is largely metabolised by the age-dependent isoform Uridine 5'-Diphophate Glucuronosyltransferase (UGT)-2B7 to M6G and M3G.[44] The highest plasma concentrations of morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G)

were found in the neonates, signifying that neonates were able to glucuronidate morphine. High morphine plasma levels and low M3G- and M6G-morphine ratios were the result of a low renal function, which was confirmed by the significant correlation between serum creatinine and M6G in the neonates. The decreased clearance of morphine explains its increased analgesic effect in neonates, contributed by the active metabolite M6G. While the M3G-morphine and M6G-morphine ratios increased with advancing age, indicating improved morphine metabolism, the M3G and M6G plasma concentrations decreased with advancing age, indicating improved renal excretion.[33]
Plasma concentrations of morphine and morphine metabolites did not only significantly differ between neonates and the older children, but also between infants aged 4 weeks to 6 months and 1 to 3 years. The major changes in morphine metabolism and elimination apparently take place between 6 and 12 months of age. The M6G/ M3G ratios were relatively constant at all ages, suggesting that 3- or 6-glucuronidation of morphine was dependent on similar regulatory mechanisms.

Safety
Only three children older than 4 weeks (two on continuous and one on intermittent morphine) showed respiratory depression and needed reintubation in the first 24 h after surgery. In all cases it had to be considered as a complication of their surgical operation.

Conclusion
Age is the most important factor in morphine dosage and morphine metabolism. 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. Extra morphine dosages, given in a nurse-controlled way, based on observational validated pain scores, resulted in similar plasma concentrations. Used in this way, both treatments are equally effective and safe. However, because morphine given intermittently does not provide preventive analgesia, continuous morphine infusions are more effective, especially in older infants.

III. Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism, submitted.

To investigate the effect of developmental maturation on morphine metabolism in full term neonates after major non-cardiac surgery, we performed a sub-analysis in the neonatal group. In this group we distinguished between neonates aged ≤ 7 days and > 7 days, because hepatic and renal physiology change prominently in the first week after

birth. The analysis included a) age-related aspects, i.e. analgesia, morphine requirement, morphine and morphine-6-glucuronide (M6G) concentrations; and b) effects of other clinical factors, i.e. apnoea, mechanical ventilation, intermittent versus continuous morphine.
Neonates aged ≤ 7 days required fewer additional morphine doses, maintained higher plasma morphine levels, and converted less morphine to M6G (lower M6G-morphine ratios) than older neonates. Pain scores did not differ between age groups or morphine treatment groups.

Dosage
Only 27 % of the neonates ≤ 7 days of age required extra morphine compared with 66 % of those > 7 days, so a lower dose of morphine than the minimal dose of 10 μg/kg/h, would likely have sufficed for the younger neonates. From a meta-analysis, an initial morphine infusion of 7 μg/kg/h was calculated to be sufficient for postoperative pain treatment in full term neonates, and a dose of 2 μg/kg/h was recommended for preterm neonates.[40,41]

Morphine plasma concentrations
The higher morphine plasma concentrations in the young neonates might, in part, result from a smaller volume of distribution at this age. While a meta-analysis[40,41] showed that the morphine volume of distribution is not dependent on age, in other studies the volume of distribution tended to be somewhat smaller in neonates aged ≤ 7 days compared with older infants, but this difference was not statistically significant.[10,45] A morphine loading dose of 50 μg/kg does probably suffice for neonates aged ≤ 7 days, whereas 100 μg/kg is mostly necessary for older infants.

Metabolites
The M6G-morphine ratio was significantly lower in the neonates aged ≤ 7 days, probably as a result of the low UGT activity at this age.

Safety
None of the spontaneously breathing neonates in the continuous morphine group had respiratory problems. Five neonates, all on intermittent morphine and all ≤ 7 days of age, showed respiratory depression, four needed reintubation in the first 24 h after surgery, but in only one of them this could be attributed to the morphine therapy. In the others the

respiratory problems largely resulted from surgical complications. Morphine plasma concentrations were not correlated with respiratory depression.

Conclusion

Findings from our study suggest that concentrations between 15 and 20 ng/ml are effective in postoperative neonates up to 4 weeks of age. However, as documented earlier, morphine plasma concentrations ranged widely, and no significant correlation was found between plasma levels and the need for extra morphine during the following hours, based on validated pain scores, or between plasma levels and respiratory depression.

IV. Morphine pharmacokinetics using the allometric model

The use of the 'per kilogram size' model (ml/min/kg) has confused interpretation of morphine developmental pharmacokinetics; an overestimation occurs as size decreases. Anderson et al. corrected available clearance data from different age groups using a ¾ power allometric size model to demonstrate that adult values for clearance are reached at about 6 months.[46] The data of morphine and metabolite serum concentrations in children 0-3 years old given either intermittent boluses or morphine infusion (the above studies) were investigated using a population based approach that included size as the primary covariate in an effort to disentangle age related factors from size related factors. Population parameter estimates were obtained using a non-linear mixed effects model (NONMEM).

The volume of distribution of morphine increased exponentially with a maturation half-life of 2 weeks from 72 l/70kg at birth; formation clearance to M3G and M6G increased with a maturation half-life of 78.7 days from 5.8 and 0.6 l/h/70kg at birth to predicted values of 25 and 3 l/h/70kg at 3 years respectively. At 6 months formation clearances were 87 % of those predicted in children at 3 years. Formation maturation of both metabolites was the same. Serum bilirubin concentration was inversely related to metabolite formation clearances.

M3G is the predominant metabolite of morphine in young children, and total body morphine clearance is 87 % that of older children at 6 months. Metabolite elimination clearance of M3G and M6G increased with a maturation half-life of 131 days from 1.53 and 1.1 l/h/70kg at birth to predicted values of 7.2 and 5 l/h/70kg at 3 years respectively. This maturation curve closely approximated that described for the maturation of glomerular filtration rate in infants. Clearance predictions can be used to calculate morphine hydrochloride infusion rates required attaining steady-state serum concentration. Infusion rate is a product of clearance and desired concentration. Derived

from this pharmacokinetic analysis using the allometric model, recommended initial morphine doses for different ages are given at the end of this chapter.

V. Efficacy of continuous versus intermittent morphine administration after major surgery in 0-3-year-old infants; a double-blind randomized controlled trial. Pain2002;98:305-313.

Efficacy of both therapies was assessed by nurses with the COMFORT "behaviour" and visual analogue scale (VAS) for pain, every 3 h in the first 24 h after surgery. Overall, no significant differences were found between continuous and intermittent morphine therapy in reducing postoperative pain. Only the oldest age group, children aged 1 - 3 years, had lower pain responses with continuous morphine. The lowest pain responses were found in the neonates, whereas infants 4 weeks to 6 months had the highest pain scores. Surgical stress scores and mechanical ventilation were not related to postoperative pain.

Conclusion

Continuous morphine and intermittent morphine were equally (in)effective in neonates and infants up to 1 year of age. Differences in pain response were most prominent between neonates and infants 1 - 6 months old.

VI. Evolution of pain management in neonates after oesophageal atresia

Over the period 1985 till 2002, which could be broken down into four different periods of pain management, we evaluated in eighty-one neonates, who had undergone a primary anastomosis of an isolated oesophageal atresia and closure of the tracheo-oesophageal fistula, the effects of the introduction of continuous morphine infusions and a validated pain score combined with an algorithm, on a) the used amount of morphine and the duration of mechanical ventilation during the first 3 days after surgery, and b) the relation between prescribed and actually administered morphine dosages.

The duration of mechanical ventilation after surgery increased till 1998, and decreased in the last period. Analysing the effect of the use of a validated pain score in combination with an algorithm (introduced in the last period D), morphine requirements did not significantly change. However, the odds to be mechanically ventilated longer than the median duration of 45 h was significantly lower in the last period than in period C.

Conclusion

The change from personal interpretation to individual assessment based on objective pain scores resulted in optimal morphine dosages with an acceptable duration of mechanical

ventilation, and in a higher correlation between prescribed and administered analgesia. Even non-experienced caregivers are able to adequately assess pain in this vulnerable group of patients, following appropriate training and taking into account inter-observer variability.
However, an algorithm, including instructions for additional analgesia, is an essential part of the pain protocol.

8.4 Continuous or intermittent morphine

Investigating the effect of continuous morphine and intermittent morphine on surgical stress responses, infants aged 1 - 3 years in the intermittent morphine group showed greater stress than those in the continuous morphine group. Morphine requirement was not significantly different between both treatments. Combining the results of the different studies, we conclude that morphine given intermittently does not provide any clinical advantage, and that a continuous morphine infusion is favourable because it is more feasible, acts analgesic preventive, is possibly safer in neonates, and more effective in older infants. To maintain analgesic plasma concentrations and prevent overdosing careful observation supported by validated pain scores is compulsory.

8.5 Surgical Stress Score (SSS)

Although in the above studies the SSS did not significantly differ between age or treatment groups, multiple regression analysis showed that the SSS significantly affected the required morphine dose. Because the SSS was developed for preterm and full term neonates after cardiac surgery,[47] a new version for infants and children after non-cardiac surgery might improve the utility. A more detailed SSS, including age, high or low abdominal surgery, blood transfusion yes or no, earlier experiences of pain, etc., may help to assess the need for postoperative morphine.

8.6 Mechanical ventilation

Of particular interest is the effect of mechanical ventilation on analgesic requirement. In this thesis significant differences were found between mechanically ventilated and non-

ventilated children. Most of the mechanically ventilated children were found among the neonates and the infants aged 4 weeks to 6 months of age.

Stress responses

The significantly higher plasma concentrations of noradrenaline at baseline in the ventilated versus non-ventilated neonates might be explained by the withdrawal of sedative and analgesic drugs prior to surgery (according to the study protocol) in a limited number of patients. The higher plasma concentrations of noradrenaline in patients aged 1-6 months, who were mechanically ventilated after surgery, probably result from distress induced by fighting the ventilator.

Morphine metabolism

In this thesis, mechanical ventilation in neonates was associated with higher plasma morphine levels, similar plasma M6G levels and lower M6G-morphine ratios.
In some neonates, who were on ventilation preoperatively and had been without morphine therapy > 6 h, morphine was still detectable at the time of surgery. Bearing in mind the individual variability of morphine clearance at this young age, a 6-hour period is apparently too short to effectively clear plasma of morphine.
Data on the clinical consequences of mechanical ventilation on portal hemodynamics and renal function are conflicting.[48-50] A decreased M6G production, combined with a reduced renal clearance, can explain the similar M6G plasma concentrations and higher morphine in mechanically ventilated neonates. Although morphine metabolism is more dependent on the glucuronidation capability, a slower morphine metabolism and a longer elimination time may be the result of a decreased hepatic and renal perfusion due to positive endexpiratory pressure (PEEP). This phenomenon can also explain why neonates who had been mechanically ventilated before surgery needed less morphine after surgery.
Postoperative ventilation did not influence the need for additional morphine over the first 24 h after surgery. However, in spite of the non-significant differences in morphine requirements between postoperatively ventilated and non-ventilated neonates, the mechanically ventilated neonates proved to have higher plasma concentrations of morphine.

Conclusion

It is evident that neonates and infants need analgesia and/or sedation during artificial ventilation in order to control catecholamine responses. We expect that a combined

therapy with different classes of analgesic and sedative drugs will provide more effective control of physiological responses, but further research is needed.
Although clinical consequences of mechanical ventilation are conflicting, the results of our studies would suggest that mechanical ventilation exerts an influence on morphine metabolism in neonates. No such information is available for older infants, because most of the older children were breathing spontaneously.

8.7 Advised morphine dosages for neonates and infants

Morphine plasma concentrations varied widely. We found no consistency between morphine plasma levels and analgesia, or between plasma levels and respiratory depression.
The morphine and metabolite plasma concentrations, the morphine requirements, and the results of the pharmacokinetic morphine study using the allometric model, allowed us to give well-defined morphine dosages for different age groups. A mean steady-state serum concentration of 20 ng/ml can be achieved in children after non-cardiac surgery in an intensive care unit with a morphine hydrochloride infusion of 8.5 μg/kg/h at birth (term neonates), 15 μg/kg/h at 1 month, 22 μg/kg/h at 3 months, 27 μg/kg/h at 12 months postnatal age and 25 μg/kg/h for 1 - 3 year old children.
According to the pharmacokinetic results, the volume of distribution of morphine increased exponentially with a maturation half-life of 2 weeks from 72 l/70kg at birth. Besides the lower glucuronidation capability and reduced renal function, the smaller volume of distribution of morphine at birth might partly be responsible for the higher morphine plasma concentrations in neonates $\leq$ 7 days of age, and hence, a loading dose of 50 μg/kg is probably sufficient for this age group.
At 6 months the production of both metabolites, M3G and M6G, was 87 % of that predicted in children at 3 years. Serum bilirubin concentration was inversely related to metabolite formation clearances. Renal clearance of M3G and M6G closely approximated that described for the maturation of glomerular filtration rate in infants. Hence, hepatic and renal disturbances may require adjusted dosages.

Fortunately, during the last decades paediatric pain has drawn much attention. We are now getting to know that chronic exposure to (non-) noxious stimuli during hospitalisation contributes to an altered pain response and that neurophysiological alterations are associated with increased pain sensitiveness in childhood.[51-57] On the other hand, more information should be collected about physical morphine dependency and

addiction. During prolonged treatment with morphine physical dependency is difficult to avoid. Opioid dependency, however, is not the same as addiction. Opioid withdrawal symptoms can be prevented by tapering off the morphine dosage over the therapy, or can be treated by adding clonidine or benzodiazepines.[58] However, more clinical trials are needed to determine adequate doses.

Although the management of paediatric pain has been improved, in other groups of patients, such as the extremely low-birth-weight infants, the mentally handicapped, the elderly, or the terminal patients dying at home, the know-how to asses and to treat pain is still lacking. This manifestation of "unheard pain" deserves more attention from doctors, nurses and other caregivers, possibly through inclusion of this subject in curriculums.

8.8 References

1. Swafford L, Allen D. Pain relief in the pediatric patient. Med Clin North Am 1968;52:131-136.Burokas L. Factors affecting nurses' decisions to medicate pediatric patients after surgery. Heart and Lung 1985;14:373-379.
2. Eland JM, Anderson JE. The experience of pain in children. In: Jacox A., ed. Pain: a source book for nurses and other health professionals. Boston:Little, Brown. 1977.
3. Mather L, Mackie J. The incidence of postoperative pain in children. Pain 1983; 15:271-282.
4. Beyer JE, DeGood DE, Ashley LC, et al. Patterns of postoperative analgesic use with adults and children following cardiac surgery. Pain 1983;17:71-81.
5. Schechter NL, Allen DA, Hanson K. Status of pediatric pain control: a comparison of hospital analgesic usage in children and adults. Pediatrics 1986; 77:11-15.
6. Burokas L. Factors affecting nurses' decisions to medicate pediatric patients after surgery. Heart and Lung 1985;14:373-379.
7. Anand KJS, Sippell WG, Aynsley-Green A. Randomized trial of fentanyl anesthesia in preterm babies undergoing surgery: effects on the stress response. Lancet 1987;1:243-248.
8. Anand KJS, Hickey PR. Halothane-Morphine compared with high dose sufentanil for anaesthesia and postoperative analgesia in neonatal cardiac surgery. The New England J Medicine. 1992,326;1-9.
9. Purcell-Jones G, Dormon F, Sumner E. Paediatric anaesthetist's perception of neonatal and infant pain. Pain 1988;33:181-187.
10. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. Anesthesiology 1987;66:136-139.
11. Lynn AM, Nespeca MK, Opheim KE, Slattery JT. Respiratory effects of intravenous morphine infusions in neonates, infants and children after cardiac surgery. Anesth Analg 1993;77:695-701.
12. Singleton MA, Rosen JI, Fisher DM. Plasma concentrations of fentanyl in infants, children and adults. Can J Anaesth 1987;34:152-155.
13. Greeley WJ, de Bruijn NP. Changes in sufentanil pharmacokinetics within the neonatal period. Anesth Analg 1988;67:86-90.
14. Choonara IA, McKay P, Hain R, Rane A. Morphine metabolism in children. Br J Clin Pharmacol 1989;28:599-604.
15. Chay PC, Duffy BJ, Walker JS. Pharmacokinetic-pharmacodynamic relationships of morphine in neonates. Clin Pharmacol Ther 1992;51:334-342.
16. McRorie TI, Lynn AM, Nespeca MK, Opheim KE, Slattery JT. The maturation of morphine clearance and metabolism. AJDC 1992;146:972-976.

17. Hartley R, Green M, Quinn MW, Rushforth JA, Levene MI. Development of morphine glucuronidation in premature neonates. Biol Neonate 1994;66:1-9.
18. De Lima J, Lloyd-Thomas AR, Howard RF, Sumner E, Quinn TM. Infant and neonatal pain: anaesthetist's perceptions and prescribing patterns. BMJ 1996;313:787
19. McGrath PA, Johnson G, Goodman JT, et al. CHEOPS: A behavioral scale for rating postoperative pain in children. In Fields HL, Dubner R, Cervero T (eds). Advances in pain research and therapy 1985; 9:305-402. New York: Raven Press.
20. Ambuel B, Hamlett KW, Marx CM, Blumer JL. Assessing distress in pediatric intensive care environments: the COMFORT Scale. Journal of Pediatric Psychology, 1992; 17:95-109.
21. Tarbell SE, Cohen TI, Marsh JL. The Toddler-preschooler postoperative pain scale: an observational scale for measuring postoperative pain in children aged 1- 5. Preliminary report. Pain 1992;50:273-280.
22. Krechel SW, Bildner J. CRIES: a new neonatal postoperative pain measurement score. Initial testing of validity and reliability. Paediatric Anesthesia 1995;5:53-61.
23. Merkel SI, VoepelLewis T, Shayevitz JR, et al. The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatr Nurs 1997;23:293-297.
24. Buchholz M, Karl HW, Pomietto M, et al. Pain scores in infants: a modified infants pain scale versus visual analogue. J Pain Symptom Manage 1998;15:117-124.
25. Schultz AA, Mirphy E, Morton J, et al. Preverbal, Early Verbal Pediatric Pain Scale (PEPPS): development and early psychometric testing. J Pediatr Nurs 1999;14:19-27.
26. Boelen WJC, Scheffer E, Haan de RJ, et al. Clinimetric evaluation of the pain observation scale for young children in children aged between 1 and 4 years after ear, nose, and throat surgery. J Dev Behav Pediatr 1999;20:14-19.
27. Buttner W, Finke W. Analysis of behavioural and physiological parameters for the assessment of postoperative analgesic demand in newborns, infants and young children: a comprehensive report on seven consecutive studies. Paediatr Anaesth 2000;10:303-318.
28. van Dijk M, de Boer JB, Koot HM, et al. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0-3-year-old infants. Pain 2000;84:367-377.
29. van Dijk M, Bouwmeester NJ, Duivenvoorden HJ, Koot HM, Tibboel D, Passchier J, de Boer JB. Efficacy of continuous versus intermittent morphine administration after major surgery in 0-3 year-old infants; a double-blind randomized controlled trial. Pain 2002;98:305-313.
30. van Dijk M, Peters JWB, Bouwmeester NJ, Tibboel D. Are postoperative pain instruments useful for specific groups of vulnerable infants? Clin Perinat 2002, accepted for publication

31. Peters JWB, Duivenvoorde HJ, Grunau RVE, de Boer J, van Druenen MJ, Tibboel D, Koot HM. Neonatal Facial Coding System for assessing postoperative pain in infants: item reduction is valid and feasible. Submitted.
32. Lynn AM, Nespeca MK, Bratton SL, Shen DD. Intravenous morphine in postoperative infants: intermittent bolus dosing versus targeted continuous infusions. Pain 2000;88:89-95.
33. Faura CC, Collins SL, Moore RA, McQuay HJ. Systematic review of factors affecting the ratios of morphine and its major metabolites. Pain 1998;74:43-53.
34. Farrington EA, McGuinness GA, Johnson GF, Eremberg A, Leff RD. Continuous intravenous morphine infusion in postoperative newborn infants. AJ Perinatology 1993;10:84-87.
35. Scott CS, Riggs KW, Ling EW, et al. Morphine pharmacokinetics and pain assessment in premature newborns. J Pediatr 1999;135:423-429.
36. Bouwmeester NJ,Anand KJ, van Dijk M, et al. Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind randomized trial comparing the effects of continuous versus intermittent morphine. Br J Anaesth 2001;87:390-399.
37. Bouwmeester N J, Hop WCJ, van Dijk M, Anand KJS, van den Anker JN, Tibboel D. Postoperative pain in the neonate: age-related differences in morphine requirements and metabolism (submitted).
38. Van Dijk M. Pain unheard? Postoperative pain assessment in neonates and infants. PhD thesis 2001, Rotterdam.
39. Beasley SW, Tibballs J. Efficacy and safety of continuous morphine infusion for postoperative analgesia in the paediatric surgical ward. Aust N Z J Surg 1987;57:233-237.
40. Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 1-Pharmacokinetics. Pediatr Anaesth 1997; 7: 5-11.
41. Kart T, Christrup LL, Rasmussen M (1997) Recommended use of morphine in neonates, infants and children based on a literature review: Part 2-Clinical use. Pediatr Anaesth 7:93-101.
42. Dahlstrom B, Bolme P, Feychting H, Noack G, Paalzow L. Morphine kinetics in children. Clin Pharmacol Ther 1979; 26: 354-65.
43. Olkkola KT, Maunuksela EL, Korpela R, Rosenberg PH. Kinetics and dynamics of postoperative intravenous morphine in children. Clin Pharmacol Ther 1988; 44: 128-36.
44. de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Glucuronidation in humans. Pharmacogenetic and developmental aspects. Clin Pharmacokinet 1999; 36:439-52.
45. Pokela ML, Olkkola KT, Seppälä T, Koivisto M (1993) Age-related morphine kinetics in infants. Dev Pharmacol Ther 20:26-34.
46. Anderson BJ, McKee AD, Holford NH. Size, myths and the clinical pharmacokinetics of analgesia in paediatric patients. Clin Pharmacokinet 1997; 33:313-27.

47. Anand KJS, Aynsley-Green A. Measuring the severity of surgical stress in newborn infants. J Pediatr Surg 1988; 23: 297-305.
48. Richard C, Berdeaux A, Delion F, Riou B, Rimailho A, Giudicelli JF, Auzepy P (1986) Effect of mechanical ventilation on hepatic drug pharmacokinetics. Chest 90:837-41
49. Mutlu GM, Mutlu EA, Factor P (2001) GI Complications in patients receiving mechanical ventilation. Chest 119:1222-41
50. Coffman B, Rios GR, King CD, Tephly TR (1997) Human UGT2B7 catalyzes morphine glucuronidation. Drug Metab Dispos 25:1-4
51. Ruda MA, Qing-Dong L, Hohmann AG, Peng YB, Tachibana T. Altered nociceptive neuronal circuits after neonatal peripheral inflammation. Science 2000;289:628-630.
52. Anand KJS, Coskun V, Thrivikraman KV, Nemeroff CB, Plotsky PM. Long-term behavioral effects of repetitive pain in neonatal rat pups. Physiol Behav 1999;66:627-637.
53. Grunau RVE, Whitfield MF, Petrie JH. Pain sensitivity and temperament in extremely low-birth-weight premature toddlers and preterm and full-term controls. Pain 1994;58:341-346.
54. Grunau RVE. Long-term consequences of pain in human neonates. In: AnandKJS, Stevens BJ, McGrath PJ, eds. Pain in neonates, 2nd revised and enlarged edition. Amsterdam: Elsevier, 2000:55-76.
55. Taddio A, Goldbach M, Ipp M, Stevens B, Koren G. Effect of neonatal circumcision on pain response during vaccination in boys. Lancet 1995;345:291-292.
56. Oberlander TF, Grunau R, Whitfield MF, et al. Biobehavioral pain responses in former extremely low birth weight infants at four months'corrected age. Pediatrics 2000;105:E6.
57. Peters JWB, Koot HM, de Boer J, Passchier J, Bueno-de-Mesquita JM, de Jong FM, Duivenvoorden HJ, Tibboel D. Major surgery within the first three months of life and subsequent bio-behavioural pain responses to immunisation at later age: a case comparison study. Pediatrics, in press.
58. Anand KJS. Pharmacotherapy with systemic analgesics. In: Anand KJS, McGrath PJ. Eds. Pain in neonates, Elsevier Amsterdam 1993;6:155-198.

Chapter 9

Summary/Samenvatting

9.1 Summary

One of the reasons for the scarcity in paediatric pain studies was the lack of instruments for the assessment of continuing pain in non-verbal children. The introduction of continuous morphine infusions about a decade ago without proper evaluation of its effects, together with the evolution of pain assessment instruments prompted us to design a study with the following research questions:
1. How reliable, valid and feasible is the multidimensional COMFORT scale to assess postoperative pain in neonates and infants < 3 years of age?
The COMFORT scale was adapted for the Netherlands and its behavioural part has been proven to be a valid instrument for measurement of postoperative pain in neonates and infants after major surgery (PhD thesis M. van Dijk).
2. Is there an improved efficacy and safety of postoperative analgesia with continuous morphine infusions compared with intermittent doses, in neonates and infants after major surgery?

Hence, the aim of this study, which was sponsored by NWO (grant nr. 940-31-031), was:
1. to compare the effects of continuous morphine, as the most used method of administration, with intermittent morphine, which was used before, in neonates and infants after major surgery, regarding a) hormonal metabolic stress responses, b) age-related morphine requirements, c) morphine metabolism and d) the correlation with objective pain assessment
2. to evaluate the effects of the evolution in pain management on a) postoperative morphine requirement and duration of mechanical ventilation in a single-diagnosed group of surgical neonates, and b) the relation between prescribed and actual administered morphine doses.

Study design:
After approval of the study protocol by the hospital medical ethical committee and after written consent from the parents, we included children aged 0 to 3 years, admitted to the paediatric surgical intensive care unit (PICU) following non-cardiac thoracic and abdominal surgery.
Patients were excluded if they had received analgesic or sedative drugs < 6 h prior to surgery, if they were receiving neuromuscular blockade, or if they suffered from hepatic, renal, or neurologic disorders or an altered muscle tone.
Patients were stratified for age into 4 groups: I. 0 - 4 weeks, II. 4 - 26 weeks, III. 6 - 12

months, IV. 1 - 3 years, and were randomly assigned to receive either intravenous continuous morphine (CM) or intermittent morphine (IM). The pharmacists prepared all study drugs and strata-specific schedules for randomisation, and clinical staff were blinded to the study group allocation until the data collection was complete. Anaesthetic management was completely standardized in all patients. Anaesthesia was induced intravenously with thiopentone 3-5 mg/kg or by inhalation with halothane in oxygen. Fentanyl 5 μg/kg was given before orotracheal intubation, which was facilitated with atracurium 0.5 - 1 mg/kg or suxamethonium 2 mg/kg. Ventilation was controlled and anaesthesia was maintained with isoflurane 0.5 MAC in 60 % nitrous oxide in oxygen or air in oxygen. Perioperative fluids were standardized to maintain a glucose infusion rate between 4 - 6 mg/kg/min; body temperature was kept within normal ranges. A peripheral artery was cannulated and the measured mean arterial blood pressure (MAP) and heart rate (HR) data were used as preoperative baseline values. After the first arterial blood sample (baseline), patients received a second dose of 5 μg/kg of fentanyl before surgical incision. Additional doses of 2 μg/kg of fentanyl were administered when HR and/or MAP were 15 % above baseline value. At the end of surgery, the neuromuscular block was antagonized and the tracheal tube was removed, or the artificial ventilation was continued in patients who required ventilatory assistance after surgery.

Directly after surgery all patients received an intravenous loading dose of morphine HCl (100 μg/kg in 2 min) followed by a morphine infusion of 10 μg/kg/h for children in the CM group, combined with three-hourly intravenous placebo (saline) boluses. Children in the IM group received a continuous placebo infusion (saline), combined with three-hourly intravenous morphine HCl doses of 30 μg/kg. The first intermittent bolus (morphine or placebo) was given at 3 h after surgery. Additional analgesia was given by the PICU nurse when there were signs of pain, indicated by VAS scores ≥ 4. During the first hour after surgery, one-third of the loading dose of morphine HCl could be repeated every 15 min, and thereafter 5 μg/kg of morphine HCl could be given every 10 min if required. No other analgesic or sedative drugs were used.

Arterial blood samples were taken after induction of anaesthesia, at the end of surgery, and at 6, 12, and 24 h after surgery to determine blood gases, plasma concentrations of adrenaline, noradrenaline, insulin, glucose, lactate, morphine (M) and the metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). From 24 - 36 h after surgery, urine was collected for determination of the 3-methyl histidine/creatinine molar ratio (3MH/CR), as a measure of protein breakdown.

After the surgical procedure, the Surgical Stress Score (SSS) was computed by the surgeon and anaesthetist. PICU nurses performed regular assessments prior to surgery (baseline) and every 3 h up to 36 h after surgery. Nursing interventions included pain assessment using a visual analogue scale (VAS) and COMFORT scale (CS) blood sampling (as indicated), giving the intermittent bolus (placebo or morphine), and then nursing as needed. Thus, plasma concentrations of hormonal and metabolic stress responses were measured at time points corresponding with trough plasma morphine concentrations in the IM group.

The SSS consists of 7 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), cardiac surgery. The total scores in this study (excluding cardiac surgery and prematurity < 35 weeks) could range from 3 to 24, and were used to classify the degree of surgical stress.
The Visual Analogue Scale (VAS) was used as an observational instrument. VAS scores range from 0 to 10, scores < 4 indicated absent or mild pain and scores ≥ 4 indicated moderate to severe pain.
The COMFORT " behaviour" scale has been proven to be a valid, reliable and feasible instrument for assessment of pain in neonates and infants aged 0 to 3 years after major surgery as a measure of postoperative pain in this age group. This scale consists of six behavioural items: alertness, calmness, respiratory response for ventilated or crying for non-ventilated children, movement, muscle tone, and facial tension. Total scores range from 8 to 40.

Chapter 2 reports the efficacy of continuous morphine versus intermittent morphine through hormonal-metabolic responses (plasma concentrations of epinephrine, norepinephrine, insulin, glucose, lactate), and hemodynamic responses (heart rate, mean arterial pressure) to postoperative pain in children aged 0-3 years. Safety was determined by the incidence of respiratory depression, because this is the most dangerous complication of opioid therapy.
Minor differences occurred between the randomized treatment groups, with the oldest IM group (aged 1-3 years) showing higher blood glucose concentration ($P = 0.003$), mean arterial pressure ($P = 0.02$), and COMFORT score ($P = 0.02$) than the CM group.
Ontogeny of the surgical stress response was illustrated by several differences between the stratified age groups. In the neonates, preoperative plasma concentrations of noradrenaline ($P = 0.01$) and lactate ($P < 0.001$) were significantly higher, while the

postoperative plasma concentrations of adrenaline were significantly lower (P<0.001) and plasma concentrations of insulin significantly higher (P < 0.005) than in the older age groups. Postoperative pain scores (P < 0.003) and morphine consumption (P < 0.001) were significantly lower in the neonates than in the older age groups. Our results show that continuous infusion of morphine does not provide any major advantages over intermittent morphine boluses for postoperative analgesia in neonates and infants. These data further illustrate the ontogeny of hormonal-metabolic responses to surgical stress, with important differences between neonates and older infants in the patterns of plasma catecholamines, insulin and lactate concentrations postoperatively.

Chapter 3 describes the effects of treatment (continuous morphine versus intermittent morphine) and the effects of age on morphine metabolism by analysis of plasma concentrations of morphine (M), morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G) and the ratios of M3G/M, M6G/M and M6G/M3G. Clinical variables such as gestational age, sex, birth weight, study weight, the therapeutic regimens used, and the need for preoperative or postoperative mechanical ventilation may affect morphine requirements and plasma concentrations of morphine and its metabolites in neonates and infants undergoing surgery.

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 as 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/M ratio (P<0.03) than the older groups. The M6G/M3G ratio was similar in all age groups.
Neonates require a narrower therapeutic window for postoperative morphine analgesia than older age groups, with no differences in the safety or effectiveness of intermittent doses compared to continuous infusions in any of these age groups.

Chapter 4 describes the developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. In an effort to disentangle age-related factors from size-related factors, a population-based approach was used that included size as the first covariate.

The formation clearances of morphine base to its glucuronide metabolites as well as metabolite elimination clearances were estimated using non-linear mixed effects models. Population parameter estimates and their variability (%) for a one compartment, first order elimination model were as follows: volume of distribution 115 l (54), formation clearance to M3G 24.3 (91) l/h, formation clearance to M6G 2.9 (87) l/h, elimination clearance of M3G 7.2 (65) l/h, elimination clearance of M6G 5.0 (76) l/h; standardised to a 70 kg person using allometric '¼ power' models. Clearance by other routes contributed 50 % of total body clearance. The volume of distribution increased exponentially with a maturation half-life of 2 weeks from 72 l/70kg at birth; formation clearance to M3G and M6G increased with maturation half-life of 79 days from 5.2 and 0.6 l/h/70kg respectively at birth. Serum bilirubin concentration was inversely related to metabolite formation. Metabolite clearance increased with age (maturation half-life 131 days) with a time course similar to that described for glomerular filtration rate in infants.
M3G is the predominant metabolite of morphine in young children and total body morphine clearance is 87 % that of older children at 6 months. A mean steady-state serum concentration of 20 ng/ml can be achieved in children after non-cardiac surgery in an intensive care unit with a morphine hydrochloride infusion of 8.5 µg/h/kg at birth (term neonates), 15 µg/h/kg at 1 month, 22 µg/h/kg at 3 months, 27 µg/h/kg at 12 months postnatal age and 25 µg/h/kg for 1 - 3 year old children.

Chapter 5 describes the age-related differences in morphine requirements and metabolism in the postoperative neonate. In this study we investigated the effect of developmental maturation on morphine metabolism in full term neonates after thoracic or abdominal surgery. We distinguished between neonates (defined as aged < 28 postnatal days) aged ≤ 7 days and > 7 days, because hepatic and renal physiology change prominently in the first week after birth. The analysis included a) age-related aspects, i.e. analgesia, morphine (M) need, morphine and morphine-6-glucuronide (M6G) concentrations; and b) effects of other clinical factors, i.e. apnoea, mechanical ventilation, intermittent versus continuous morphine.
Sixty-eight neonates (52 aged ≤ 7 days, 16 aged > 7 days), admitted to Paediatric Surgical Intensive Care Unit, following abdominal or thoracic surgery, received morphine 100 µg/kg after surgery, and were randomly assigned to either continuous morphine (CM, 10 µg/kg/h) or intermittent morphine boluses (IM, 30 µg/kg/3 h).

Neonates aged ≤ 7 days differed significantly from neonates > 7 days in morphine requirement [median 10 vs. 10.8 μg/kg/h, (P < 0.001)], morphine plasma concentration [23.0 vs. 15.3 ng/ml, (P = 0.027)], and M6G/M ratio [0.6 vs. 1.5, (P = 0.018)]. Pain scores did not differ between age groups or morphine treatment groups.
Neonates who were mechanically ventilated > 24 h (n = 37) had significantly higher morphine plasma concentrations than the spontaneously breathing neonates (n = 15) at 12 and 24 h after surgery (29.1 vs. 13.1 ng/ml and 26.9 vs. 12.0 ng/ml, respectively; both P < 0.001).
Morphine plasma concentrations were not correlated with effective analgesia or respiratory depression. Five neonates showed respiratory insufficiency, all on IM, however the difference between CM and IM was not significant. Neonates aged ≤ 7 days require significantly less morphine postoperatively than older neonates do. Mechanical ventilation decreases morphine metabolism and clearance. Both intravenous morphine regimens (CM and IM) were equally effective and safe.

Chapter 6 describes the efficacy of postoperative intermittent and continuous morphine through behavioural responses (VAS and COMFORT scale) to postoperative pain in children aged 0-3 years. The repeated COMFORT "behaviour" and VAS pain scores were compared between the two treatment groups.
Efficacy was assessed by the caregiving nurses with the COMFORT "behaviour" and VAS for pain, every 3 h in the first 24 h after surgery. Random regression modelling was used to simultaneously estimate the effect of randomized group assignment, actual morphine dose (protocol dosage plus extra morphine when required), age category, surgical stress, and the time-varying covariate mechanical ventilation on COMFORT "behaviour" and the observational VAS rated pain, respectively. Overall, no statistically differences were found between CM and IM morphine administration in reducing postoperative pain. A significant interaction effect of condition with age category showed that the CM assignment was favourable for the oldest age category (1 – 3 years old). The greatest differences in pain response and actual morphine dose were between neonates and infants aged 1 – 6 months, with lower pain response in neonates who were on average satisfied with the protocol dosage of 10 μg/kg/h. Surgical stress and mechanical ventilation were not related to postoperative pain or morphine doses, leaving the interindividual differences in pain response and morphine requirement largely unexplained.

Chapter 7 describes the process of changing postoperative pain treatment in the paediatric surgical ICU of the Sophia Children's Hospital, from 1985 up to the present. Four different periods of pain management were identified: A (1985 - 1990) morphine as needed, intermittently; no validated pain score (PS), B (1990 - 1995) morphine continuously; no validated PS, C (1995 - 1998) morphine continuously, developing validated PS, D (1998 - 2002) morphine continuously, validated PS combined with algorithm.

Over the period 1985 - 2002, we evaluated in eighty-one neonates who had undergone a primary anastomosis of an isolated oesophageal atresia and closure of the tracheo-oesophageal fistula, how the introduction of continuous morphine infusions and a validated pain score combined with an algorithm, effected a) the amounts of morphine used and the duration of mechanical ventilation during the first 3 days after surgery, and b) the relation between prescribed and actually administered morphine dosages.

In period A neonates received significantly less morphine than in the periods B, C and D (all $P < 0.005$), no differences were found between the latter three periods. The proportion of patients mechanically ventilated after surgery increased from 84 % in period A, to 90 % in period B, and to 100% in the periods C and D. The duration of mechanical ventilation after surgery increased during periods A, B and C [median (10 - 90th percentile)] from 24 (0 - 78), to 47 (1 - 96), to 48 (20 - 109), respectively, and decreased in the last period to 34 (15 - 145) hours. Overall, the total duration of postoperative mechanical ventilation did not significantly differ between the four periods. To evaluate the effect of a validated pain score combined with an algorithm (period D), we completed a "subgroup analysis". The odds of being given greater or lower amounts than the median morphine dose did not differ between the periods C and D. However, the odds to be mechanically ventilated longer than the median duration of 45 h was 4.5 times lower in period D than in period C (95 % CI: 0.05 - 0.94). There was no significant association between the prescribed and the actually administered amounts of morphine in period A. However, in the three later periods the correlation was significant and increased from $r = 0.58$ ($P = 0.007$) in period B, to $r = 0.91$ and 0.88 (both $P < 0.001$) in period C and D, respectively.

The change from personal interpretation of postoperative pain to individual assessment based on objective pain scores resulted in optimal morphine dosages with an acceptable duration of mechanical ventilation, and a high correlation between prescribed and administered analgesia.

Chapter 8 contains a general discussion and options for future pain management.

9.2 Samenvatting

Eén van de redenen dat er weinig onderzoek werd gedaan naar pijn bij kinderen was het gemis aan betrouwbare methodes om aanhoudende pijn te meten, met name bij kinderen die zelf hun pijn nog niet onder woorden konden brengen. Ongeveer 10 jaar geleden werd in het Sophia Kinderziekenhuis het beleid voor pijnbestrijding na grote operaties veranderd. Morfine werd niet meer voorgeschreven op een "zo nodig" basis, wat vaak geïnterpreteerd werd als "zo weinig mogelijk", maar als een continu infuus. Het gemis aan een betrouwbaar instrument om het effect van beide methodes te vergelijken en het feit dat in deze periode wel veel methodes ontwikkeld werden om kortdurende pijn bij jonge kinderen te meten, zoals de reactie na het geven van een hielprikje, noopten ons om een onderzoek op te zetten met de volgende vragen:
1. Hoe betrouwbaar, valide en praktisch in gebruik is de multidimensionele COMFORT schaal voor het beoordelen van postoperatieve pijn bij baby's, peuters en kleuters in de leeftijd van 0 – 3 jaar?
De COMFORT schaal werd aangepast voor Nederland en er is aangetoond dat het deel met gedragsitems een betrouwbaar instrument is om postoperatieve pijn te meten bij pasgeborenen, peuters en kleuters na grote operaties (Proefschrift Monique van Dijk).
2. Is er een verhoogde effectiviteit en veiligheid in postoperatieve pijnbestrijding met een continu morfine-infuus, vergeleken met intermitterende morfinedoseringen, bij pasgeborenen, peuters en kleuters na grote operaties?

Doel van dit onderzoek, wat werd mogelijk gemaakt door een subsidie van NWO (nr. 940-31-031) was:
1) een vergelijking van het effect van continue morfine toediening, als meest gebruikte methode, met intermitterende morfine giften, wat voorheen gebruikelijk was, bij pasgeborenen en jonge kinderen na grote operaties, wat betreft a) hormonaal en metabole stress reacties, b) leeftijdsgerelateerde morfinebehoefte, c) morfinemetabolisme en d) de correlatie met een objectieve pijnscore.
2) een evaluatie van het effect van de ontwikkeling in pijnbehandeling op a) het morfinegebruik en de beademingsduur bij pasgeboren na operatie van een geïsoleerde oesofagusatresie en b) de relatie tussen voorgeschreven en daadwerkelijk toegediende hoeveelheden morfine.

Hoofdstuk 2 beschrijft het effect van continu morfine vergeleken met intermitterend morfine, wat betreft hormonaal-metabole reacties (plasmaspiegels van adrenaline, noradrenaline, insuline, glucose en lactaat) en hemodynamische reacties (hartfrequentie, gemiddelde arteriële bloeddruk), op postoperatieve pijn bij kinderen van 0 tot 3 jaar. De veiligheid van beide methodes werd bepaald door de frequentie van ademhalingsdepressie, daar dit de gevaarlijkste complicatie is bij behandeling met opioïden.
Slechts kleine verschillen werden gevonden tussen beide behandelmethodes, waarbij de oudste groep (1 – 3 jaar) met intermitterend morfine hogere glucosespiegels ($P = 0.003$), hogere gemiddelde arteriële bloeddruk ($P = 0.02$) en hogere COMFORT scores ($P = 0.02$) had dan de groep met continue morfine. De ontstaansvorm van de chirurgische stress reactie werd duidelijk uit de verschillen tussen de leeftijdsgroepen. Bij de pasgeborenen waren de plasmaspiegels van noradrenaline ($P = 0.01$) en lactaat ($P < 0.001$) voor operatie significant hoger, maar na operatie waren de plasmaspiegels van adrenaline ($P < 0.001$) significant lager en van insuline significant hoger ($P < 0.005$) dan bij de oudere leeftijdsgroepen.
Postoperatieve pijnscores ($P < 0.003$) en morfinegebruik ($P < 0.001$) waren significant lager bij de pasgeborenen dan bij de oudere kinderen. Onze resultaten tonen aan dat een continu morfine infuus geen voordelen biedt boven intermitterende morfine doseringen als postoperatieve pijnbestrijding bij pasgeborenen en jonge kinderen. Daarnaast geven deze resultaten meer informatie over het ontstaan en de ontwikkeling van de hormonaal-metabole reacties op chirurgische stress, met belangrijke verschillen tussen pasgeborenen en oudere kinderen, zichtbaar in de postoperatieve catecholamines, insuline en lactaat concentraties.

Hoofdstuk 3 beschrijft de effecten van behandeling (continu tegenover intermitterend morfine) en de effecten van leeftijd op het morfinemetabolisme door het analyseren van plasmaconcentraties van morfine (M), morfine-3-glucuronide (M3G) en morfine-6-glucuronide (M6G) en de M3G-, M6G- en M3G/M6G-ratio's. Klinische variabelen zoals zwangerschapsduur, geslacht, gewicht bij geboorte en tijdens onderzoek, de methode van morfinetoediening, de behoefte aan pre- of postoperatieve beademing kunnen invloed hebben op het morfinegebruik en de plasmaconcentraties van morfine en morfinemetabolieten.
Met behulp van multipele regressie analyse werd vastgesteld dat leeftijd de belangrijkste factor was qua invloed op de morfinebehoefte en de morfine plasmaconcentraties. Significant minder pasgeborenen hadden extra morfine nodig vergeleken met alle andere

leeftijdsgroepen ($P < 0.001$). De behandelmethode (intermitterend versus continu) had geen significante invloed op de morfinebehoefte. Pasgeborenen hadden significant hogere plasmaspiegels van morfine, M3G en M6G (alle $P < 0.001$) en een significant lagere M6G/M ratio ($P < 0.03$) dan de oudere leeftijdsgroepen. De M6G/M3G ratio was gelijk in alle leeftijdsgroepen.
De therapeutische breedte wat betreft postoperatieve morfine toediening is bij pasgeborenen kleiner dan bij oudere kinderen. Vanaf de leeftijd van 1 maand wordt analgesie bereikt met een morfine infuus van 10.9 tot 12.3 µg/kg/h, bij plasma concentraties van < 15 ng/ml.
In al deze leeftijdsgroepen werd geen verschil gevonden in veiligheid of effectiviteit tussen continue of intermitterende morfine toediening.

Hoofdstuk 4 beschrijft de ontwikkeling in farmacokinetiek van morfine en morfinemetabolieten in pasgeborenen en jonge kinderen. In een poging om leeftijdsgebonden factoren te ontrafelen van grootte, c.q. gewichtsgebonden factoren, werd een op de populatie gebaseerde benadering gebruikt met grootte als eerste co-variant.
De klaring van morfine door omzetting naar glucuronides en de klaring van de metabolieten door renale eliminatie werden beraamd aan de hand van non-linear mixed effects models.
Populatie gemiddelden and variabiliteit (%) voor een één-compartiment, eerste orde eliminatie model, waren als volgt: distributievolume 115 l (54), omzetting van morfine naar M3G 24.3 (91) l/h, omzetting van morfine tot M6G 2.9 (87)lL/h, renale eliminatie van M3G 7.2 (65) l/h, renale eliminatie van M6G 5.0 (76) l/h; gestandaardiseerd voor een 70 kg persoon gebruik makend van het allometrische '¼ power' model. Klaring via andere routes droeg voor 50 % bij aan de totale morfineklaring. Het distributievolume nam exponentieel toe met een halfwaardetijd van 2 weken beginnend met 72 L/70kg bij de geboorte; omzetting tot M3G en M6G nam toe met een halfwaardetijd van 79 dagen beginnend met respectievelijk 5.2 en 0.6 l/h/70kg bij de geboorte. De bilirubine plasmaconcentratie was omgekeerd evenredig met de omzetting tot metabolieten. De klaring van metabolieten nam toe met de leeftijd (halfwaardetijd 131 dagen) in een tijdsverloop overeenkomend met dat beschreven voor de glomerulaire filtratiesnelheid bij kinderen.
M3G is de voornaamste morfinemetaboliet bij jonge kinderen en de totale morfineklaring op de leeftijd van 6 maanden is 87 % van die van oudere kinderen. Bij kinderen op een intensive care unit na niet-cardiochirurgische ingrepen kan een gemiddelde steady-state

serumconcentratie van 20 ng/ml worden bereikt met een morfine HCl infuus van 8.5 µg/kg/h bij geboorte (a terme pasgeborenen), 15 µg/kg/h op de leeftijd van 1 maand, 22 µg/kg/h bij 3 maanden, 27 µg/kg/h bij 12 maanden en 25 µg/kg/h voor kinderen van 1 tot 3 jaar.

~~**Hoofdstuk 5** beschrijft de effectiviteit van postoperatief intermitterend en continu toegediende morfine aan de hand van gedragsuitingen van pijn (VAS en COMFORT schaal) bij kinderen van 0 - 3 jaar. Voor dit doel werd door de verpleegkundigen gedurende de eerste 24 uur na de ingreep elke drie uur de COMFORT 'gedragscore' en de VAS bepaald. Met random regressie analyse werd het effect van de wijze van morfinetoediening en de hoeveelheid toegediende morfine op COMFORT 'gedrag' en VAS pijn geschat, rekening houdend met de leeftijdsgroep, de "Chirurgische Stress Score" en het wel of niet kunstmatig beademd zijn. Globaal bleken CM en IM even effectief postoperatieve pijn te verminderen, hoewel voor de leeftijdsgroep van 1 tot 3 jaar CM enigszins effectiever bleek te zijn. De wijze van morfinedosering en de leeftijdsgroep waren beide voorspelbaar voor de mate van postoperatieve pijn. De grootste verschillen in pijnreactie en daadwerkelijke morfinedoseringen kwamen voor tussen pasgeborenen en zuigelingen van 1 tot 6 maanden, met lagere pijnscores bij pasgeborenen. Voor de meeste pasgeborenen volstond de dosering van 10 µg/kg/h volgens het protocol. "Chirurgische Stress Score" en kunstmatige beademing waren niet gerelateerd aan postoperatieve pijn of morfinedoseringen, hetgeen de individuele verschillen in pijnrespons en morfinebehoefte grotendeels onverklaard laat.~~

Hoofdstuk 6 evalueert de effecten van continue of intermitterende toediening van morfine voor de behandeling van postoperatieve pijn bij kinderen van 0 – 3 jaar met behulp van gedragsobservaties (VAS en Comfort schaal).
Het beloop in de tijd van de Comfort "gedrag" en de VAS pijnscores werd vergeleken voor de beide behandelmethodes. Door de voor de patiënt verantwoordelijke verpleegkundige werd elke 3 uur, gedurende de eerste 24 uur na de operatie, de werkzaamheid van morfine gescoord met behulp van de Comfort "gedrag"- en VAS pijnschaal.
Met behulp van randomregressie-analyse werd het effect bepaald van de randomisatie (intermitterend versus continu), de hoeveelheid morfine (volgens protocol en extra morfine), de leeftijd, de chirurgische stress, en de tijdafhankelijke co-variabele kunstmatige beademing, op de Comfort "gedrag"- en de VAS pijnscore. Er werden geen

statistisch significante verschillen vastgesteld tussen continue en intermitterende morfine toediening.
Een belangrijk leeftijdseffect was aanwezig. Continue morfine toediening had de voorkeur in de groep kinderen van 1 tot 3 jaar.
Het grootste verschil in pijnreactie en morfinebehoefte werd vastgesteld tussen pasgeborenen en kinderen van 1 tot 6 maanden.
De pasgeborenen vertoonden minder pijn en waren in het algemeen tevreden met de dosering volgens het protocol, 10 µg/k/h.
Er werd geen duidelijke relatie gevonden tussen de morfinebehoefte en de mate van postoperatieve pijn en de chirurgische stress of de kunstmatige beademing.

Hoofdstuk 7 beschrijft het proces van verandering in pijnbehandeling op de kinderchirurgische intensive care afdeling van het Sophia Kinderziekenhuis, vanaf 1985 tot heden. Vier verschillende periodes van pijnbehandeling konden worden onderscheiden: A (1985 – 1990) morfine werd gegeven op een "zo nodig" basis, op intermitterende wijze; geen betrouwbare pijnscores, B (1990 – 1995) morfine als continu infuus; geen betrouwbare pijnscores, C (1995 – 1998) morfine als continu infuus, ontwikkeling van een betrouwbare methode voor het meten van pijn, D (1998 – 2002) morfine als continu infuus, gebruik makend van een betrouwbare pijnschaal gecombineerd met een algoritme.
In de periode 1985 tot 2002, werden 81 pasgeborenen geselecteerd, die allen een primaire anastomosis hadden gekregen voor een geïsoleerde oesofagusatresie met sluiting van de tracheo-oesofageale fistel. Het effect van de introductie van continue morfine toediening en een betrouwbare pijnschaal gecombineerd met een algoritme werd beoordeeld op a) het morfinegebruik gedurende de eerste 3 dagen na de ingreep en de duur van de kunstmatige beademing, en b) de relatie tussen de voorgeschreven en daadwerkelijk gegeven hoeveelheid morfine. In periode A ontvingen de pasgeborenen significant minder morfine dan in de periodes B, C en D (alle $P < 0.005$), terwijl er geen verschillen werden gevonden tussen de latere periodes. Het percentage patiënten dat postoperatief beademd werd groeide van 84 % in periode A tot 90 % in periode B en tot 100 % in de periodes C en D. De duur van de postoperatieve beademing nam toe in de periodes A, B en C [mediaan (10 - 90ste percentiel)] van respectievelijk 24 (0 - 78), tot 47 (1 - 96), tot 48 (20 - 109) uur en nam af in de laatste periode tot 34 (15 – 145) uur. Globaal was er tussen de vier periodes geen significant verschil in totale beademingsduur. Ter beoordeling van het effect van een gevalideerde pijnscore gecombineerd met een algoritme (periode D), werd een subgroepanalyse uitgevoerd in periode C en D. Het risico om meer of minder dan de

mediane morfinedosis te krijgen was niet verschillend in periode C of D. Echter, het risico om postoperatief langer dan de mediane duur van 45 uur beademd te worden was 4,5 keer zo laag in periode D dan in C (95 % CI: 0.05 – 0.94). In periode A was er geen significante correlatie tussen de voorgeschreven en daadwerkelijk toegediende hoeveelheden morfine. In de drie latere periodes was de correlatie echter significant en nam toe van r = 0.58 (P = 0.007) in periode B, tot respectievelijk r = 0.91 en 0.88 (beide < 0.001) in de periodes C en D. De verandering van persoonlijke interpretatie van postoperatieve pijn in een individuele beoordeling gebaseerd op objectieve pijnscores, resulteerde in optimale morfinedoseringen met een acceptabele duur van postoperatieve beademing en een hoge correlatie tussen voorgeschreven en toegediende analgetica.

Hoofdstuk 8 bestaat uit een algemene discussie met suggesties voor toekomstig pijnbeleid.

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