PAIN

Postoperative Analgesia in Infants and Neonates

Ilse Ceelie

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PART 1

Introduction

The golden rule is that there are no golden rules

Bernard Shaw

CHAPTER 1.1

General introduction

Ceelie I, de Wildt SN, van Dijk M, Tibboel D

General Introduction

Pain affects almost everyone at some point in his or her life. A definition drawn up by the International Association for the Study of Pain (IASP) has it that pain is always subjective.[1] This would seem to imply that the way in which pain is perceived varies from person to person and may also be influenced by the setting and previous experiences. The same definition states that "inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment". This truth has a bearing on neonates and children with profound cognitive impairment, who are not able to verbally express their pain, anxiety or other sources of distress. Therefore caregivers in the hospital setting need to find other ways to recognize pain. Early recognition is important because pain requires prompt and adequate treatment, also to prevent possible long-term sequelae.[2,3] Stress hormone levels have been studied in premature neonates who underwent surgery without perioperative analgesia; levels of cortisol, aldosterone, and other corticosteroids were markedly increased[4,5,6] signifying high stress. In the intensive care unit (ICU) setting, stress and agitation resulting from pain and anxiety can lead children to accidentally remove medical devices endangering the child's safety.[7]

Pain (and therefore stress) is a common condition on the ICU. Previous studies have shown that children in the ICU setting daily undergo many painful procedures, including IV canula insertion or removal, suctioning and heelstick.[8,9] What's more, a 2008 survey showed that 80% of these procedures are performed without analgesics.[9]

Achieving optimal pharmacological treatment of pain in children is not easy. Since children show great individual variability, and organ systems are still maturing during childhood, findings from studies in adults cannot be extrapolated to this population.[10] Out of necessity treatment is thus largely based on clinical experience rather than on evidence based guidelines. We therefore need to learn more about the pharmacokinetics and pharmacodynamics of drugs and analgesics in particular. To promote research in the field of drugs in children, the American government has previously issued several acts, such as the 'Food and Drug Administration Modernization Act' in 1997, the 'Best Pharmaceuticals for Children Act' in 2002, and the 'Pediatric Research Equity Act' in 2003. Similar legislation ('The Pediatric Regulation') came in place In the European Union in January 2007 (Full text on www.fda.gov and www.emea.europe.eu).

Newer drugs, such as IV paracetamol, have an analgesic potential and it would be worthwhile to study if they result in fewer adverse events than the routinely used opioids. The adverse events of drugs commonly used on the ICU are potentially life threatening. Otherwise, they will badly affect the child's condition and result in longer ICU stay. The mechanisms behind adverse events are not fully elucidated and need to be further researched.

The American Academy of Pediatrics has issued the following statement on pain treatment: 'to treat pain adequately, ongoing assessment of the presence and severity of the pain and the child's response to the treatment is essential.'[11] Self-report remains the 'gold standard' for pain assessment.[12] In the pediatric ICU setting, however, many patients are non-verbal; either they are to young, temporarily unable to speak due to sedation or mechanical ventilation, or cannot provide self-report due to intellectual disabilities.[13] A range of validated pain assessment tools for non-verbal children is available.[14] For example the COMFORT-behavior scale for postoperative patients under the age of 3 and all age groups on mechanical ventilation,[15] and the CPB (checklist pain behaviour) for the intellectually disabled.[16]

After assessment of pain the treatment of pain is the next step, and standard treatment includes opioids. Treatment with opioids means balancing between effective dosages and preventing oversedation, seeing that opioids have sedative properties as well. Oversedation may lead to longer duration of mechanical ventilation and ICU admission.[17,18] Inadequate dosages may cause a wide range of endocrine, metabolic and inflammatory reactions leading to increased sympathetic activity.[4,5] Besides inadequate pain relief, this may result in prolonged recovery times after procedures, complications, and longer admission duration. Finally, inadequately treated postoperative pain poses a risk for the development of chronic pain.[19] Overall, timely treatment of pain may reduce stress and long-term sequelae, and as a positive side effect this may reduce health care costs.[20]

Hence, the benefits of adequate pain treatment in children are evident. Nevertheless, evidence-based treatment guidelines are largely lacking. In this thesis we aim to provide insight in the assessment of pain by evaluating adherence to a postoperative pain treatment protocol, describing side effects of regularly used drugs on the ICU, and evaluating whether new surgical technique are less painful. Finally we provide evidence of the morphine-sparing potential of intravenous paracetamol in young infants and neonates after major non-cardiac surgery.

The outline of this thesis is as follows:

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1.2 How to optimize the treatment of acute pain in non-verbal patients

1.3 Endpoints in pediatric pain studies

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CHAPTER 1.2

How to optimize the treatment of acute pain in non-verbal children

Ceelie I, de Wildt SN, van Dijk M, Tibboel D

Pediatric Clinical Research Manual Supplement 4. S4.1- S4.16, 2008

Introduction

As the definition of pain formulated by the International Association for the Study of Pain (IASP) has it, pain is always subjective and the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment.[1] Different pediatric patient populations, including (preterm) neonates and children with a profound cognitive impairment, indeed show inability to communicate verbally.[2] While earlier it was believed that young infants are incapable of experiencing pain, we now know that this is not the case.[3] Pain processing anatomical structures are present in the fetus already from mid to late gestation. The nociceptive impulses are transmitted, however, by unmyelinated fibers that slow down pain impulse transmission. This lower speed nevertheless is neutralized by shorter distances in the infant's central nervous system.[3-5] Furthermore, the relatively few neurotransmitters in preterm infants' descending neural tract fibers would suggest underdeveloped inhibitory pathways and thus higher sensitivity to pain in comparison to older children.[6]

Neonates undergoing painful clinical procedures show changes in cardiovascular variables, transcutaneous partial pressure of oxygen, and palmar sweating.[3] Hormonal studies[7] in preterm and full-term neonates who underwent surgery under minimal anesthesia documented a marked release of hormones such as cortisol, aldosterone, and other corticosteroids[8] compatible with more stress. In the intensive care unit (ICU) setting, children may show such stress and agitation resulting from pain and anxiety that they run the risk of getting disconnected from medical devices.[9]

Multiple lines of evidence in animal studies suggest that exposure to acute pain during the neonatal period leads to prolonged hypersensitivity, even after complete healing of the initial injury. Real longitudinal data in humans are lacking however.[10-13]

Peters et al.[14] concluded that infants who had been operated upon in early infancy reacted with greater distress during subsequent surgery in the same dermatome in comparison to children without prior operations.

Hence, painful events may lead to a large variation in potential adverse outcomes. Even today 79.2% of a large cohort of newborn infants received no specific analgesia when experiencing a painful procedure.[15]

Pain assessment

The first step in the treatment of pain is reliable assessment. The IASP considers self-report the gold standard for the report of pain. Neonates or patients with cognitive impairment, who are unable to verbalize their pain, therefore may be at risk for under treatment of pain. It is generally accepted that self-report is reliable from the age of 4 years with individual exceptions above and below this age. The most used self-report scales in pediatric patients are the Visual Analogue Scale, the Numeric Rating Scale and the Faces Pain Scale-Revised.[16] These are beyond the scope of this article and will not be discussed.

As clinicians came to realize that non-verbal pediatric patients respond to pain in non-verbal ways,[17,18] efforts were directed at developing observation tools, either including behavioural indicators only (unidimensional) or both physiological and behavioural (multidimensional) signs.[19] The most commonly used behavioural indicators of pain are facial expression, cry/vocalisation and body movement. Physiological measures of pain are: heart rate fluctuations, blood pressure and oxygen saturation. Use of these parameters is debated, however, because they can vary due to medical conditions or interventions and seem not to be specific for pain.[20,21] Some of these pain assessment tools are listed in Table 1.

A great abundance of pain scores is available now, illustrative of the need for different pain scores to capture differences in cognitive development in children of different ages. Also, as all behavioural pain scores are ultimately subjective and cannot be validated against a gold standard of pain assessment, the search for the perfect pain score is ongoing.

An even more challenging task than finding an appropriate pain assessment tool is effective implementation of pain assessment.[29] This is a process which requires ongoing education, commitment of nurses or physicians to check compliance, and face-to-face contact with practitioners to promote enthusiasm.[29,30]

	Premature and term neonates	Infants	Cognitively impaired patients
Acute and postoperative pain	- Premature pain profile (PIPP)[22] - Neonatal Facial Coding System (NFCS)[18] - CRIES[23]	- COMFORT-behaviour scale[24] - Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)[25]	- Faces, Legs, Activity, Cry and Consolability (FLACC)[26] - Checklist Pain Behaviour (CPB)[27] - Non-communicating Children's Pain Checklist[28]

TABLE 1. Acute and postoperative pain assessment tools.

Product	Age	Loading dose Maintenance dose	Maximum dose
Acetaminophen [44]	28-32 weeks GA premature	20 mg/kg 20 mg/kg every 12h rectal	* max. 40 mg/kg/24 hours, max 24 hours
	32-36 weeks GA premature	30 mg/kg 20 mg/kg every 8h rectal	
	Neonate	25 mg/kg 15 mg/kg every 6h oral 30 mg/kg 20 mg/kg every 8h rectal	* max. 60 mg/kg/24 hours, max 24 hours
	1 month and older (term)	30 mg/kg 15 mg/kg every 4h oral 40 mg/kg 25-30 mg/kg every 6-8h rectal	* max 90-100 mg/kg/24 hours
	Children>12 years	325-650 mg every 4-6h or 1000 mg 3-4 times/ day oral, rectal	* max. daily 4 g
Acetaminophen intravenous [77]	Age: <1 year	7.5 mg/kg every 6h	
	>1 year *Body weight > 50 kg*	15 mg/kg every 6-8h 1000 mg every 6h	* max. daily 4 g
	Body weight < 50 kg	15 mg/kg every 4-6h	* max. daily 3 g
Diclofenac [56]	> 6 months	2 mg/kg 1 mg/kg every 8h oral, rectal, iv	
Ibuprofen [78]	> 6 months	5 mg/kg every 8h	
Tramadol [79]	> 1 year	1-2 mg/kg every 6-8h oral, rectal, iv	
Morphine continuous intravenous [52]	Nb. Monitor patients and adjust dose in first month of life	Loading dose first hour 0.1-0.2 mg/kg Maintenance dose <1 week 0.005-001 mg/kg/hour > 1week 0.01-0.02 mg/kg/hour	* max 0.04 mg/kg/ hour in non ventilated patients

TABLE 2. Dose recommendations analgesics.

A range of contextual factors must be taken into account when assessing pain: e.g. gestational age, behavioural state, severity of illness, type of pain, noise, mechanical ventilation and anxiety. For instance, preterm neonates obviously have less energy than full-term newborns.[31] When severely ill, they may display less explicit pain reactions.[17,32] On the other hand, background noise and light levels may invoke stress and alter the infant's behavior.

Pain and distress can occur simultaneously, may influence each other and evoke comparable responses. It is difficult, therefore, to discriminate between the two. The most sensible way to address this challenge is to carefully observe the effects of pain reducing or distress reducing interventions. Additionally, caregivers should

be open to the impact of other factors that affect the level of pain and distress of the neonate as well.

Children with profound cognitive impairment often suffer from pain caused by associated physical conditions such as gastro-oesophageal reflux, contractures, constipation and urinary tract infections. As many of these children are not able to communicate verbally according to their age, and suffer from cognitive and motor limitations, it is hard to recognize their pain and therefore treat it properly.[33] For similar procedures cognitive impaired children tend to receive less analgesia than other children of the same age. Three observation pain scales are available for profound cognitive impaired patients: the Non-Communicating Children's Pain Checklist[28], CPB (Checklist Pain Behaviour)[27] and the revised FLACC (Faces, Legs, Activity, Cry and Consolability).[26] Next to application of these scales it may be useful to ask the opinion of parents or other daily caregivers because they know the child and its behaviour.[28]

Pain treatment

The American Academy of Pediatrics holds the view that ongoing assessment of the presence and severity of the pain and the child's response to the treatment is essential for adequate pain treatment.[34] In addition, availability of a treatment algorithm that allows for re-assessment and re-evaluation is equally essential. An example of a postoperative pain algorithm with reassessment used in our hospital is shown in Figure 1.[35]

Non-pharmacological treatment of acute, procedural pain (heel lancing or a vena puncture) should be considered as a first step to reduce pain and/or associated distress. Various non-pharmacological therapies have been proven effective to treat mild to moderate pain. These include non-nutritive sucking[36,37] (with or without sucrose), kangaroo care[38], music therapy[39], massage[40] and multi-sensorial stimulation.[41] Other effective measures are noise control, maintaining the day and night light pattern and the sleep-wake cycle, massage, and communication.[42]

When non-pharmacological interventions for acute procedural pain do not have the required effect, they may be combined with local anaesthetics such as EMLA (a lidocaine/prilocaine mixture) or Ametop gel (4% amethocaine, not under the age of 1 month).

In general, the classical World Health Organisation (WHO) steps for the provision of analgesia are also followed in children. Systemic analgesia should be considered

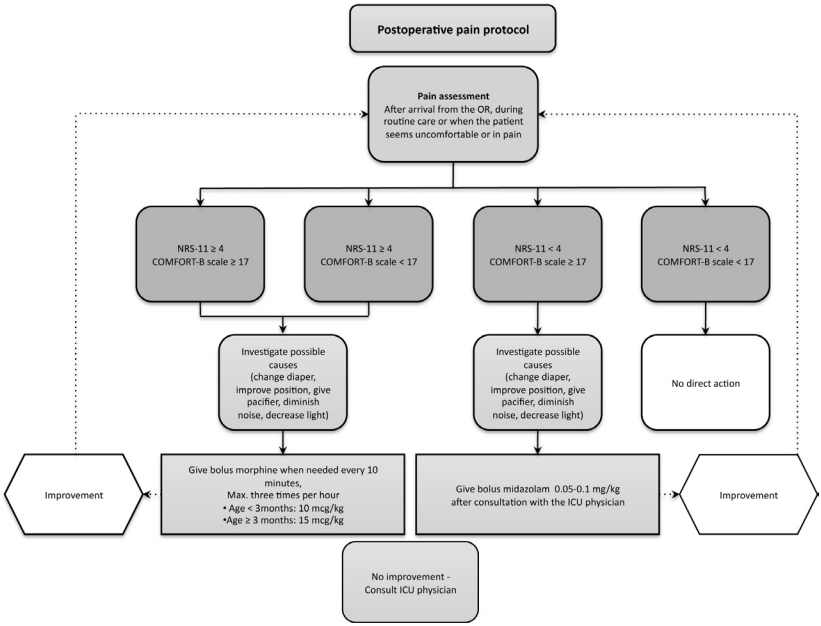

FIGURE 1. Example of a postoperative pediatric pain algorithm.

in case of recurrent procedures or more painful procedures. Acetaminophen can be administered orally, rectally and intravenously to neonates. Pain relief is achieved more quickly (0.5-2 hours) by oral administration than by rectal administration. On the other hand, rectal administration provides longer-lasting pain relief.[43-45] The use of intravenous acetaminophen allows greater dosing accuracy, less pharmacokinetic variability attributable to absorption, and more rapid onset of effect compared to oral or rectal administration.[46-48]

The highest potential with regard to the morphine sparing effect between NSAIDs and paracetamol, is found in NSAIDs.[49,50] In contrast, acetaminophen has the better safety profile because NSAIDs have potential renal and gastrointestinal side effects and bleeding propensity.[46] An excellent overview of these and other forms of procedural analgesia and sedation in children was published by Krauss and Green.[51]

Systemic opioids – i.e. morphine – are indicated for severe pain. In our experience, to obtain sufficient pain relief in postoperative term neonates younger than 1 week, an opioid regime with lower doses corrected for body weight is feasible.[52] We

support the concept of pre-emptive analgesia to prevent and treat postoperative pain. It is suggested that this may also prevent the development of hypersensitivity (lowering of pain thresholds) after repeated or long lasting pain experiences.[53] In non-surgical ventilated preterm neonates there is no proven beneficial effect of routine administration of morphine.[54] Also, morphine given as a loading dose followed by continuous intravenous infusions does not appear to provide adequate analgesia for acute heel stick induced pain in the same population.[55] Our own group showed that in contrast to adults concomitant paracetamol for postoperative pain relief in infants does not result in a morphine sparing effect.[35]

As the group of cognitively impaired children is heterogeneous and tends to react idiosyncratic[28] it is even more important in this population to titrate analgesics to meet individual needs. Co-medication (for example antiepileptic drugs) may complicate pharmacologic therapy because of drug-drug interactions. For example, barbiturates and carbamazepine (antiepileptic drugs) may dampen the analgesic effect of acetaminophen. Also, barbiturates and carbamazepine may increase the hepatotoxic potential of acetaminophen.[56]

Variation in response to pain and pain treatment

Neonates generally require lower, for body weight corrected drug doses, to acknowledge developmental immaturity of drug disposition and effect pathways.[57] Developmental changes in absorptive surfaces such as the gastrointestinal tract and skin can influence the rate and extent of bioavailability. Rectal absorption in infants, for example, differs from that in adults by a greater number of pulsatile contractions in the rectum, enhancing the expulsion of solid forms of drugs such as acetaminophen.[58] Furthermore, drug distribution may change with shifting body composition and amounts of plasma proteins. Metabolism is influenced by the maturation of the drug metabolizing enzymes and postnatal renal excretion increases in line with the acquisition of renal function.[57]

Severity and/or type of illness has been shown to change drug disposition and effect. Little is known, however, of the impact of illness severity on drug response in critically ill children. Recent data from adults suggest that disease-related changes in drug response may partially be explained by inflammatory processes affecting drug metabolism and drug transporters.[59] In critically ill patients, down regulation of drug metabolizing enzyme and drug transporter activity may occur, potentially

leading to higher plasma levels of drugs. For drugs in which central nervous system penetration is limited by transporters, inhibition of transporter expression by inflammation may lead to higher blood-brain penetration and thus, theoretically to a higher risk of central nervous system adverse effects.[59] The effect of drug therapy on other disease related changes in children, such as alterations in liver blood flow and protein binding also remain unclear. The treatment of pain in critically ill patients may be further complicated as this population may display less explicit pain reactions. Consequently, adequate pain assessment and pain treatment are even more difficult in this population.[60]

In addition, genetic variation may explain interindividual responses to pain and pain medication. Many of the pain-relevant genetic variants are thought to be common in the general population (with allelic frequencies of 10–50%) and to act together on pain, resulting in the individual's genetic "pain profile".[61,62] There are few data on the effect of genetic variability on pain In children. Hereditary insensitivity to pain syndromes, the so-called 'channelopathy–associated insensitivity to pain' (e.g. HSAN I-V syndromes)[63], the common genetic variants without disease characteristics (e.g. COMT, ß-arrestin) and the genetic variants related with variation in response to specific analgesic drugs (e.g. CYP2D6, OPRM) are potential targets for individualized analgesia.

Drug withdrawal

Some children will develop withdrawal symptoms after prolonged use of opioid and/or sedative drugs, necessitating prolonged and slow weaning of their medication. Use for more than 5-7 days, high cumulative doses and a too rapid tapering off or abrupt discontinuation of analgesics are associated with an increased risk of withdrawal symptoms in both children and adults.[64-66]

Recently, our group developed and validated an assessment tool to assess these symptoms in critically ill children, the Sophia Observation withdrawal Symptoms-scale (SOS).[67] The scale was validated in pediatric intensive care patients from 0 to 16 years old and can be used for opioid and sedative withdrawal.[67]

Future directions to optimize the treatment of pain

Randomized clinical trials (RCT) of analgesic drugs in children are scarce. Few analgesic drugs have been evaluated by more than one or two randomized RCTs, and sometimes these were even underpowered.[9,68,69]

To improve evidence-based treatment of pain in non-verbal children we suggest the following approach for future research:

- The use of validated pain assessment tools. The choice of a pain assessment tool depends, among other things, on the patient population and, for example, severity of surgery.

  In a clinical setting one would do well to limit the number of pain assessment tools. In our opinion it is not necessary to develop more pain assessment tools except for the fields that are missing (prolonged pain in profound cognitive impaired patients).

- The use of potentially objective measures: Near-infrared spectroscopy (NIRS) and skin conductance. NIRS measures regional changes in oxygenated and deoxygenated haemoglobin concentration. It is based on the assumption that increased tissue oxygenation represents an increase in regional cerebral blood flow. This is in turn associated with higher neuronal activity as seen in noxious events (which are encoded by frequency of firing and number of activated neurons).[70] In adults this hemodynamic and electrophysiological analysis has confirmed it's central importance in pain perception and modulation.[71] A recent study in pediatric patients compared NIRS measurements for pain due to heel lancing with the PIPP (premature infant pain profile); the results were promising.[72] The measurement of stress by skin conductance (for example Med-Storm Innovation AS, Oslo, Norway), is based on neurophysiologic arousal with increased activity in the sympathetic nervous system, leading to sweating in the palm and sole. The level of increase may serve as a surrogate measure of stress.[73]

- Alternative objective pain measures are pain imaging techniques such as fMRI and PET scans, currently only used in the research setting. PET scans performed solely for research reasons may, however, meet with ethical and practical obstacles as they involve administration of radioactive labelled drug to pediatric patients and age-matched controls.

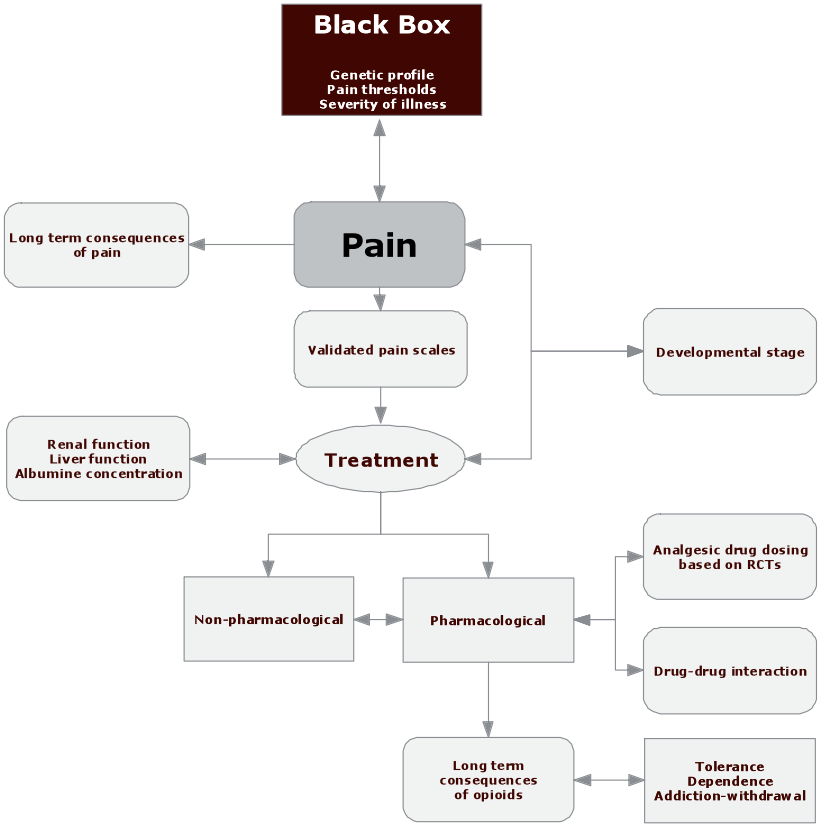

FIGURE 2. Overview of determinants of pain.

- Neurophysiological measurements such as EEG and somatosensory response. This modality has so far not revealed a specific pain signal to be used in daily clinical practice.

- Hormonal stress markers such as salivary cortisol and (nor) epinephrine.[74] These biomarkers may have additional value in the context of analgesia protocols.

- To further elucidate interindividual variation in response to pain and its treatment, information regarding relevant co-variates such as DNA for genetic

analysis, disease severity (C-reactive proteine and PRISM scores) and age should be collected.

- In drug studies, pharmacokinetics of the parent drug and (active) metabolites in relation to pharmacodynamics. These days plasma levels of drug are easier to measure in children, because more sophisticated analytical methods (e.g. LC-MS-MS) and statistical analyses (e.g. population pharmacokinetic pharmacodynamic analyses using non-linear mixed effects modelling NONMEM) require smaller and fewer samples.[75] American legislation ('Food and Drug Administration Modernization Act' in 1997, 'Best Pharmaceuticals for Children Act' in 2002 and 'Pediatric Research Equity Act' in 2003) has come into force to promote drug development and authorisation of medicines for use in pediatric patients. Similar legislation was introduced in the European Union in January 2007 ('The Pediatric Regulation') (Full text on www.fda.gov and www.emea.europe.eu). These legislations and the availability of important tools such as clinical trial registers (http://clinicaltrials.gov) are providing essential help to researchers.

- The short and long-term consequences of prolonged opioid use in newborns and infants are largely unknown. We suggest long-term follow up of these patients on behavioral and physical areas such as QST measurements and eventually neurometer values.[76]

In summary, the treatment of pain in non-verbal children has much improved over the years. Efforts have been directed at developing tools to measure pain and implementing these tools in clinical care as part of pain treatment protocols.

Also, these tools are being used as primary endpoints in studies on the effects of analgesic drugs.

Nevertheless, further research is needed to develop more objective pain measurements, to identify causes of variation in pain and response to pain treatment (both non-pharmacological and pharmacological PK-PD), and to develop age and disease specific pain treatment protocols for this vulnerable population (Figure 2).

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CHAPTER 1.3

Endpoints in pediatric pain studies

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Introduction

Neurobiology of pediatric pain: essentials for drugs-related studies

The neonatal stage of life is characterized by high sensitivity to pain and great vulnerability to neuronal cell death.[1] Anecdotal reports have shown prolonged allodynia and hyperalgesia after pain and tissue damage within the first weeks of life, extending beyond the period associated with tissue healing.[2-7] For example, 4–6 months-old term infants who had undergone circumcision responded more intensely to immunization than did their uncircumcised peers.[5] On the other hand, children who had undergone major surgery in combination with preemptive analgesia within the first months of life did at 14 and 45 months of age not show different behavioural pain responses and saliva cortisol concentrations when exposed to vaccinations compared to age matched controls.[8] Thus, the question is whether preemptive administration of analgesics indeed prevents from possible long-term consequences of neonatal pain. There are some clues from animal experiments. Neonatal nerve ligation in rodents led to long-term hyperalgesia, which was not attenuated when local anesthetics were administered.[9] Neonatal exposure to carrageen or Freud adjuvants CFA led to hyposensitivity or no alterations, but to hypersensitivity when adult animals were re-exposed to inflammatory pain.[10-14] In contrast, formalin injections or laparotomy in newborn rats led to thermal hyposensitivity at adult age[13-15], which was attenuated by morphine administration.[15]

Tissue damage and neonatal pain disturb normal development of the nociceptive neural circuits, as expressed by structural and functional neuroanatomical changes both peripherally[9,16,17] and at spinal cord level.[11,18] Moreover, changes in spinal gene expression involved in the transmission of nociception have been documented.[13] These animal experiments may provide an explanation for the long-term effects found in human children.

In summary, we do not know whether adequate analgesia prevents the development of long-term alterations in pain sensitivity. And, if alterations occur, will they be restricted to the dermatome of tissue injury (spinal changes) or be generalized all over the body (supraspinal changes).[4]

Exposing neonates to pain or tissue damage is developmentally inappropriate and analgesics may not prevent them from developing subsequent pain hypersensitivity. A next question is whether this pain hypersensitivity will still exist 15 years after tissue injury or has recovered or reverted to hyposensitivity. The few studies

on this issue provide no or little information of the total analgesic dosages during hospital stay.[19,20] It would seem, therefore, that we need to perform more randomized controlled analgesic trials (RCT) in children and perform follow-up studies in these same patients through childhood and adolescence to gain insight in the long term effects of neonatal pain and neonatal analgesia.

Endpoints in clinical trials

A clinical trial endpoint is a measure that allows us to decide whether the null hypothesis of a clinical trial should be accepted or rejected.[21] Possible endpoints in pediatric analgesic trials are: pain intensity, time to first (rescue) analgesia, total analgesic consumption, adverse effects and long-term effects.[22,23] RCTs may have more than one endpoint, in which case it is customary to differentiate between primary and secondary outcomes.

Assessing pain intensity in (preverbal) children is more difficult than in adults. Adults' self report of pain is generally accepted as the gold standard[24] of pain assessment. The discussion merely limits itself to the question which of the available self-report scales is most appropriate in a given situation. Pain intensity in young children can be assessed with validated observational pain assessment instruments or multidimensional pain assessment instruments that include both behavioural and physiological parameters. Self-report is feasible from the age of 4 to 5 years. Because observational pain instruments provide subjective outcomes, it is crucial that observers are well trained and that interrater reliability has been tested and proven good. Establishing cutoff points that differentiate between different levels of pain intensity is an important requirement, because rescue medication is given when scores exceed specific values.

An important reference article is the one from the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (Ped-IMMPACT), in which core domains and measures for clinical pain trials have been defined.[22]

The type of outcome measure also depends on the type of pain under study. Physiological parameters, for example, are more promising for acute painful procedures such as heel lances or venipunctures than for chronic pain. In the next paragraph the different types of endpoints will be presented with a focus on postoperative pain. Endpoint Pain intensity:

Behavioral assessments

The International Association for the Study of Pain (IASP) underlines that the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment.[25] Based on this note, behavioral-based pain observation instruments have been developed. The Children's Hospital Eastern Ontario Pain Scale (CHEOPS),[22,26] and the Faces, Legs, Arms, Cry and Consolability (FLACC)[27,28] have been validated for postoperative pain in 1 to 7-year-old children. The COMFORT-behavior scale has been validated to that aim in 0 to 3-year-old children in the intensive care setting.[29] These scales have several items in common; facial expression, cry and body movements.

Children with severe intellectual disabilities may show idiosyncratic behavior when they are in pain. It may be advised against, therefore, to apply pain scales developed for children without intellectual disabilities to these children.[30,31] At least four validated postoperative pain instruments for children with intellectual disabilities have been developed. One is the revised FLACC, which allows for individualized behavior added to each of the 5 items of the scale. It has been validated for postoperative pain[32] and proved to have a high degree of clinical utility.[33] The second scale is the Paediatric Pain Profile (PPP), a 20-item scale that has been validated for postoperative pain.[34,35] The PPP consists of three sets of recordings: two retrospective parent ratings of the child's behaviour – i.e. when the child was at his or her best and during painful episodes – and a prospective rating by the nurse, e.g. postoperatively. Although completing the PPP may take up more time than the FLACC, it may be well worthwhile for research purposes. The third scale is the non-communicating children's pain checklist (NCCPC)[36] of which the postoperative version (NCCPC-PV)[37] includes 27 items and requires a 10 minutes observation. A fourth scale is the Checklist Pain Behaviour (CPB), which has been validated for postoperative pain and reduced without loss of information to a 10 item version.[38,39] In addition, a recent study described the use of an individualized Numeric Rating Scale based solely on the child's individual pain indicators as described by parents and caregivers.[40] The psychometric properties of this scale are promising; nevertheless, the essential involvement of the parents may be a drawback especially when the scale is used for research purposes.[41]

Self report

Examples of self report tools for 2 to 3 year old toddlers are the Poker Chip Tool[42] and the Faces Pain Scale-Revised, recommended for research purposes in over 4-year-olds.[43,44] The Numeric Rating Scale pain (NRS-11)[45] and Visual Analogue Scale pain (VAS)[46] should preferably not be used in children below the age of 8 years because it requires a certain cognitive level of development to translate pain intensity into numbers or distances on a 10 cm ruler. The Poker Chip Tool, Faces Pain Scale-revised and VAS have also been suggested by the Pediatric Initiative on Methods, Measurements and Pain Assessment in Clinical Trials (PedIMMPACT) and also came up as valid in two reviews.[22,44,47]

Physiological parameters

As behavior-based assessment instruments remain subjective, researchers continue to search for neurobiological-based and more 'objective' parameters of pain intensity.[48] Several instruments indeed go some way in this direction by including physiological items as well, such as the PIPP and the COMFORT scale.[49,50] However, heart rate and blood pressure proved not been sensitive enough for postoperative pain assessment, probably because treatment, blood loss, fever and other conditions will influence these parameters.[51,52]

New methods, such as near-infrared spectroscopy (NIRS) and skin conductance, may help to objectify pain or stress in nonverbal humans.

NIRS measures regional changes in oxygenated and deoxygenated hemoglobin concentration. The technique is based on the assumption that increased tissue oxygenation represents a greater regional cerebral blood flow. This, in its turn, is associated with higher neuronal activity as seen in noxious events (encoded by frequency of firing and number of activated neurons).[53] The use of NIRS in pediatrics has been limited to acute pain in neonates.[54-56] One study compared NIRS measurements during 33 heel lance procedures in 12 stable newborns with facial expression. Brain activity in most of the newborns was related to facial expression. Some newborns did not show a change in facial expression, however, although NIRS readings revealed increased cortical activity during the procedure.[55]

The measurement of stress by skin conductance is based on neurophysiologic arousal with increased activity in the sympathetic nervous system, leading to sweating in the palms of the hand and the foot soles. The level of increase may serve as a surrogate measure of stress and not of pain per se.[57]

Biomarkers

Hormonal stress markers such as salivary cortisol and (nor) epinephrine may have additional value in the context of analgesia trials.[58] Nevertheless, because stress and pain are correlated but difficult to distinguish, these hormone levels should not be considered as primary endpoints of pain studies. Age-dependent differences in hormonal levels as well as age-dependent differences in circadian rhythm are important confounders. Especially in postoperative patients the extent and duration of the so-called hormonal stress response are highly determined by age.[58] However, salivary cortisol could be a substitute marker for pain or stress in severely cognitively impaired children. Remarkably, RCTs in this vulnerable patient group have not yet been performed despite the fact that co-medication, such as anticonvulsants, could influence opioid use during surgery, as reported in a single study from 1990, which so far has never been replicated.[59]

Brain activity related parameters

Experimental approaches involving the use of fMRI and PET scans have been tested in the research setting only.[60,61] PET scans performed solely for pediatric research reasons may, however, meet with ethical and practical obstacles as they involve administration of radioactive labeled drugs. As a non invasive procedure, fMRI is more promising for (semi)clinical evaluation and can be combined with quantitative sensory testing.[62]

Neurophysiological measurements such as EEG and somatosensory response have so far not identified a specific pain signal that could be useful in daily clinical practice. There is direct EEG evidence of specific noxious-evoked neural activity in the infant brain.[63] Somato-sensory responses have been demonstrated in young infants but as yet cannot serve as endpoints; we first need to establish normal values of voltage, frequency and duration.

Time to first (rescue) analgesia and analgesic consumption

As many postoperative patients will receive preemptive analgesic drugs, time to first rescue analgesia may serve as a clinical endpoint together with the total analgesic consumption over the first 12, 24 or 48 hours. Consumption should be expressed in microgram or mg per kg per hour or per 24 hours so as to enable comparison. Ideally these endpoints should be combined with scores obtained from validated pain assessment instruments.

Safety/adverse effects

Documentation of drug safety is highly important, especially in pediatric drug trials. There is some debate on whether it is better to have a pre-defined list of possible adverse events to be taken into account, or to resort to an unstructured approach in which researchers, parents or other individuals report any suspected adverse events.[22] This latter approach may carry the risk of underreporting of adverse events.

Safe and effective pain treatment in neonates and young infants requires thorough understanding of various developmental aspects of drug disposition and metabolism. In general, the phenotypic variation in drug disposition and metabolism is based on constitutional, genetic and environmental factors. The clearance rate of most drugs is lower in neonates than in adults and older children. Neonates still show immature renal function, i.e. decreased glomerular filtration rate and less effective tubular reabsorption and/or excretion. Moreover, they have a lower capacity of drug metabolizing enzymes. Furthermore, as reviewed by both Weinshilboum[64] and Evans and McLeod,[65] the disposition and action of many drugs are polygenetic determined events. Polymorphisms in drug metabolizing enzymes, transporters and receptors determine to a larger extent the spectrum of drug response (i.e., ranging from no effect to drug toxicity).

Long-term effects of analgesic treatment

The short and long-term consequences of prolonged opioid use in newborns and infants are largely unknown. Studies in animals suggest potential adverse long-term effects of morphine. Morphine administration to neonatal rats produces long-term changes in behavior and brain function[66] and impairs the adult cognitive functioning,[67] in particular spatial recognition memory.[68] Basic science has shown that the opioid system modulates neural proliferation in vivo.[69] Thus, it may well be that morphine treatment harms the neurogenesis of newborn babies. Mechanistically, morphine induces apoptosis of human microglial cells[70] and stimulates red neuron degeneration in the rat brain, which may lead to cerebral dysfunction.[71] Boasen et al recently showed in rodents that either neonatal stress and morphine treatment produced long-lasting behavioral effects to a degree sufficient to alter learning, while the combination of neonatal stress and morphine did not.[72]

Endpoints in human studies should therefore include cognition, neuropsychological tests, a chronic pain questionnaire, and pain and detection thresholds.

The latter thresholds may be assessed with quantitative sensory testing (QST), for which normal values are available.[73]

Finally, we should realize behavioral assessment instruments reveal other aspects of the phenomenon pain than do neurophysiological evaluation or the use of biomarkers. Moreover, no single parameter covers the whole spectrum from a nociceptive stimulus to behavior. It would seem essential, therefore, to also evaluate the fate of drugs in the body (pharmacokinetics) as well as the response of the body (pharmacodynamics).

Pharmacokinetics of the parent drug and (active) metabolites in relation to pharmacodynamics.

It has become easier to measure plasma levels of drugs in children. Sophisticated analytical methods (e.g. LC-MS-MS) and statistical analyses (e.g. population pharmacokinetics-pharmacodynamics, such as NONMEM) require smaller and fewer samples.[74] A possible relationship between therapeutic plasma ranges and pharmacodynamic parameters has not yet been found. Mutation analysis can provide answers to individual aberrant responses although tailoring of analgesic dosing is still a long way to go.[75]

Efforts to improve pain therapy, for example by means of RCTs, should be developed within the context of regulatory initiatives. American legislation ('Food and Drug Administration Modernization Act' in 1997, 'Best Pharmaceuticals for Children Act' in 2002 and 'Pediatric Research Equity Act' in 2003) has come into force to promote drug development and authorization of medicines for use in pediatric patients. Similar legislation was introduced in the European Union in January 2007 ('The Pediatric Regulation') (Full text on www.fda.gov and www.emea.europe.eu). These legislations and clinical trial registers (http://clinicaltrials.gov) provide essential information on ongoing studies in other centers and prevent duplication of studies in this vulnerable age group.

Summary

Tools to measure pain are being used as primary endpoints in studies on the effects of analgesic drugs. Nevertheless, further research is needed to develop more objective pain measurements, to identify causes of variation in pain intensity and

responses to pain treatment (both non-pharmacological and pharmacological PK-PD), and to develop age and disease specific pain treatment protocols.

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PART 2

Assessment of Pain

Insanity is doing the same thing over and over again and expecting a different outcome

Albert Einstein

CHAPTER 2.1

Protocolized postoperative pain management in infants; do we stick to it?

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Submitted

Abstract

Background
The American Academy of Pediatrics states that ongoing assessment of pain is essential for adequate pain treatment. Pain assessment by means of the COMFORT behaviour scale and the Numeric Rating Scale is therefore an important component of the postoperative pain treatment protocol for neonates and infants in our ICU.

Aim
To determine degrees of staff compliance with this protocol.

Patients and Methods
This retrospective chart review concerned postsurgical patients under the age of 3 years admitted to our level III ICU over a one-year period. The degree of compliance to the postoperative pain protocol was measured by the frequency of deviations from protocol-dictated drug treatment and pain assessments.

Results
Records of 200 children with a median age at surgery of 98 days (IQR 6-320) were analyzed. A mean of 11 assessments in the first 72 hours postoperatively per patient had been recorded. A total of 2103 pain assessments were retrieved of which 1675 (79.7%) suggested comfort. Compliance to the protocol (reassessment and correct medication) was provided in 66 (15.4%) of the 428 assessments suggesting pain or distress.

Conclusion
The postoperative pain protocol applied in our ICU appears to be effective, however full compliance to the protocol was marginal, possibly leading to under treatment of pain.

Introduction

Untreated pain may lead to physical complications, prolonged recovery time and long-term behavioural changes.[1-4] Physicians used to fear that opioids administration might have adverse effects, and the misconception that young infants cannot feel pain was widespread. Potential pain in infants was therefore often not treated. In recent years, however, medical institutions worldwide have implemented pain management protocols.

Reliable pain assessment is typically the first step in the protocol. The International Association for the Study of Pain (IASP) considers self-report the gold standard for the report of pain.[5] Self-report has been applied from the age of 4 years onwards with the limitation that it is not possible to test its reliability.[6,7] The 3-year-olds and younger comprise two thirds of our PICU population and are the most challenging with regard to pain and distress management. First because we have to rely on behavioural assessments with the risk of misinterpretation; second because most drugs are given off-label and unlicensed and optimal dosing guidelines are often lacking. The COMFORT-B scale was validated for postoperative pain in 0 to-3-year-olds. In older children we often can rely on self-report or parents' proxy report. Pain assessment tools based on observation of behavior are applied in younger and non-verbal patients.[8] The second step is effective pain treatment.[9] The Society of Critical Care Medicine guidelines specifically recommend that the effects of therapy should be systematically assessed because efficient pain treatment enhances recovery after surgery.[10] Assessment as part of pain treatment protocols is important to recognize pain and enable the management of pain.[11]

Grol and Grimshaw[12] showed that implementation of and compliance to new guidelines is difficult in general; pain management protocols are no exception to this rule.[13]

The aim of the study was to determine the degree of compliance with a postoperative pain management protocol for under 3-year-olds admitted to our ICU after surgery. We further evaluated whether any patient's characteristics or time of assessment would influence compliance.

Methods and materials

Setting

The setting of this study was the surgical ICU of the Erasmus MC- Sophia Children's Hospital, Rotterdam, the Netherlands. This 8-bed level-3 and 6-bed High Care unit admits patients from 0 to 16 years of age, mainly newborns with major congenital anomalies, postoperative patients, ECMO patients, and neurotrauma patients. In view of the strictly observational and non-invasive nature of the study, the institutional review board waived the need for informed consent.

Study design

We retrospectively determined to what extent nurses and physicians had complied with the unit's postoperative pain management protocol for all under 3–year-old admitted to our unit postoperatively during one year in a 72 hours postoperative period.

Procedure

The following patient data were retrieved from the computerized Patient Data Management System (PDMS): age at surgery, sex, duration of surgery, use and duration of mechanical ventilation, number and level of COMFORT-behaviour (COMFORT-B) scores and Numeric Rating Scale (NRS-11) pain scores, and sedative/analgesic medication given. Ventilation parameters, medication administration, and pain scores had been recorded prospectively. Data were exported automatically to SPSS. If reassessment should have taken place but was not done, we consulted the nursing notes in the PDMS for information on non-pharmacological and pharmacological interventions.

COMFORT 'behaviour' scale (COMFORT-B)

The COMFORT-B scale is an adaptation of the COMFORT scale introduced in 1992 by Ambuel et al.[14] as a non-invasive assessment of distress in patients on the PICU. In 1999 the COMFORT-B scale was validated to assess postoperative pain in under 3–year-olds.[15] The COMFORT-B scale asks observers to consider intensity of six behavioral items: Alertness, Calmness, Respiratory response (for ventilated children) or Crying (for spontaneously breathing children), Body movements, Facial tension and Muscle tone. For each of these items, five descriptions are provided reflecting

increasing intensity of the behavior in question; these are rated from 1 to 5. Summating the six ratings leads to a total score ranging from 6 to 30. COMFORT-B scores from 17 to 30 are thought to suggest pain or distress; these scores in combination with NRS pain of 4 or higher suggest pain.[15]

Numeric Rating Scale (NRS-11)

The NRS-11 is a validated scale which asks to rate pain intensity by number (0= no pain and 10= worst pain).[16] It expresses the nurses' expert opinion of the patient's level of pain – taking the patients' circumstances (disease-related, treatment related, environmental and patient specific) into account. The NRS-11 shows good inter-rater reliability[17] and has been correlated to other postoperative pain instruments.[18]

Postoperative pain protocol

Our postoperative pain management protocol (Figure 1)[19] was described in two randomized controlled trials we performed earlier.[20, 21] It dictates that nurses assess pain with both the NRS-11 and the COMFORT-B scale at least three times every

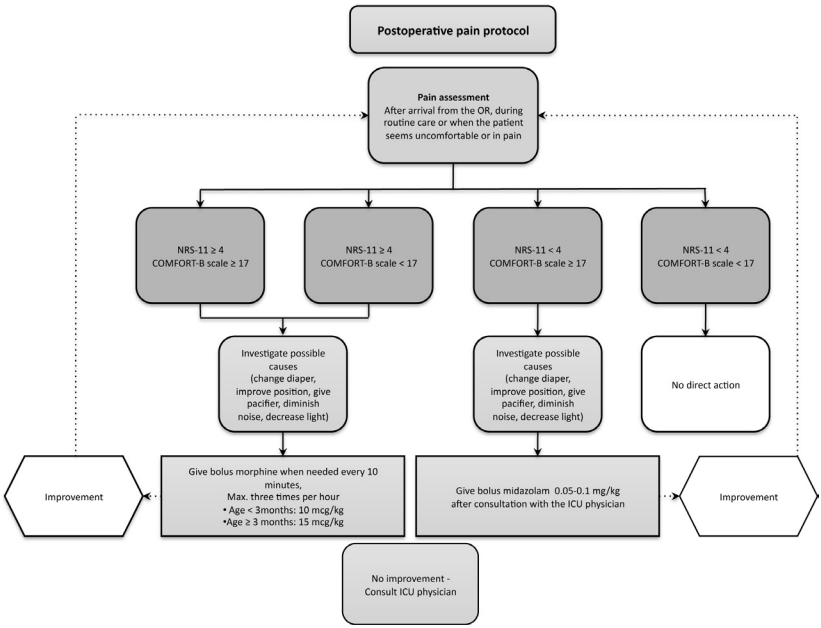

FIGURE 1. Postoperative pain protocol ICU Erasmus MC-Sophia Children's Hospital.

24 hours. The combined scores determine whether treatment should be started, maintained, increased or tapered off.

Two specific combinations suggest pain: NRS-11 score 4-10 with COMFORT-B score 17-30; and NRS-11 score 4-10 with COMFORT-B score 6-16. The combination NRS-11 score 0-3 with COMFORT-B score 17-30 suggests distress. The combination NRS-11 score 0-3 with COMFORT-B score below 17 suggests comfort and is the treatment target.

If scores suggest pain or distress, the first remedy is the use of non-pharmacological interventions, e.g. consolation, posture change, heat or cold-pack, or diaper change. These need to be followed by reassessment within one hour. If indicated, a further intervention is to administer systemic analgesia in preset dosages, i.e. morphine to treat pain and midazolam in case of distress.

All nurses on the unit are trained and certified to apply the COMFORT-B scale and the NRS-11.[15] The postoperative pain protocol was introduced in 1999 and has not been changed since that time.

Compliance

We first present the data on the assessments and confounders (such as age, time of day of scoring and mechanical ventilation); next the treatment-related data, and finally data on overall compliance to the postoperative protocol. Overall compliance was defined as pain assessment at least once every shift, reassessment following a high score within the hour, and correct medication administration (notably in case of high pain scores) or non-pharmacological actions (Figure 1). Pain assessment by only one of the two pain scores (either COMFORT behaviour scale or NRS-11) did not qualify as compliance.

Data analysis

Patient characteristics are presented using descriptive statistics. We distinguished two age groups: neonates, aged 0 to 28 days, and older children (1 mo-36 mo). Unit of analysis was assessment. The effects of age (neonates vs. older patients), sex, mechanical ventilation or not, and time of assessment (day, afternoon/evening, night) on compliance were determined using Chi Square tests. Statistical analyses

were performed with the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA). A p-value of 0.05 was set as statistically significant.

Results

In the study period 586 patients were admitted to the surgical ICU, 387 under the age of three years. Two hundred of these were surgical patients and constituted the study group (Figure 2).

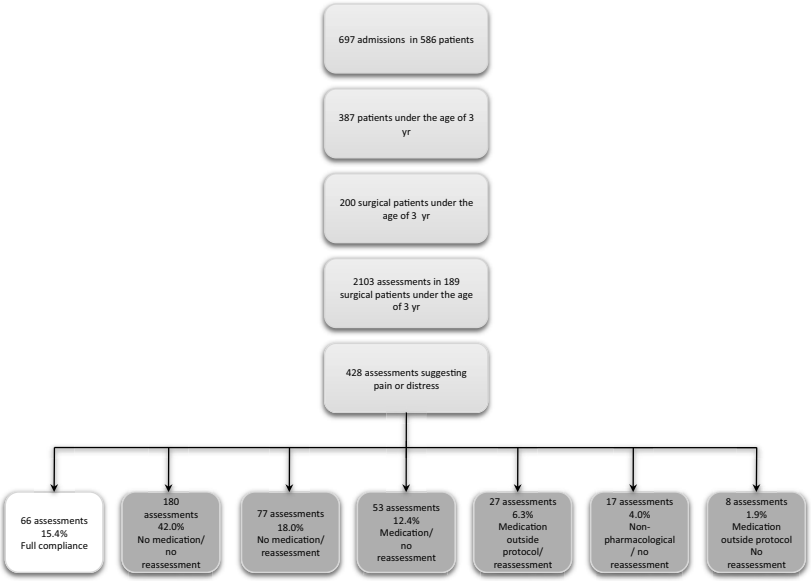

FIGURE 2. Flow chart of scores obtained in patients under the age of 3 years, postoperatively

These patients had a median age at surgery of 98 days (IQR 6-320); see Table 1 for other patient characteristics.

Assessments

The mean number of pain assessments (NRS-11 plus COMFORT-B) per patient during the first 72 hours after surgery was 11 (SD 6); the total was 2103. Low pain scores (NRS-11 <4 and COMFORT-B <17) were assigned in more than three-quarter (79.6%) of the 2103 assessments. Only 35.7% of the 428 other assessments (those

	Surgical patients under the age of 3 (n=200)
Boys/girls, n (%)	126 (63.0)/74 (37.0)
Duration ICU stay (in days), median (IQR)	5 (2 to 13)
Age at surgery (in days), median (IQR)	98 (6- 320)
Neonates, n (%)	65 (32.5)
Duration surgery (hours:minutes), median (IQR)	2:55 (1:54- 4:10)
Type of surgery, n (%)	
Gastro-intestinal tract	53 (26.5)
Craniofacial	48 (24.0)
Cardiac	28 (14.0)
ECMO cannulation	26 (13.0)
Lung and ENT	14 (7.0)
Neurology	8 (4.0)
Malignancies	7 (3.5)
Diaphragmatic hernia repair	6 (3.0)
Miscellaneous	10 (5.0)
Patients ventilated/non ventilated, n (%)	107 (53.5)/93 (46.5)
Duration mechanical ventilation in days, median (IQR)	7 (3 to 12)

TABLE 1. Patient characteristics.

suggesting pain or distress) had been followed by the stipulated reassessment. Compliance to reassessment during the evening shift (47.1%) was significantly better than during the day (24.8%) and night shifts (30.3%) (Chi-square test p=0.01). Age group (neonates vs. older patients), and ventilatory support (yes/no), did not significantly influence compliance to reassessments (p=0.15; 0.19; 0.69, respectively).

Treatment

Combined scores suggesting pain or distress were not followed by pharmacological intervention in 64.0% of cases; another protocol violation was substituting morphine by other medication, e.g. paracetamol or fentanyl, which occurred in 8.2% of cases. In 27.8% the correct medication was given. Medication (according to protocol or outside the protocol) was more often given during ventilation (43.4% vs. 30.8% in non ventilated patients, p=0.008). There were no statistically significant differences for shift and age group (p=0.31 and p=0.49 respectively).

Compliance (assessment and treatment)

Full compliance with the protocol (including correct pharmacological treatment and timely reassessment) occurred in 66 of the total 428 (15.4%) paired high scores suggesting pain or distress. Full compliance was not statistically significantly associated with shift, age group, and ventilation (p=0.12, p=0.16, and p=0.79 respectively). Reassessment without any pharmacological treatment occurred in 18.0% (77 cases) of all assessments. In 27 cases (6.3%) reassessment was followed by pharmacological treatment outside the protocol. Pharmacological treatment without reassessment occurred 53 times (12.4%). In 180 (42.0%) cases neither (non)-pharmacological treatment nor reassessment had been performed. Finally, non-pharmacological interventions were reported 17 times (4.0%) all without reassessment (See Figure 2).

The PDMS provided justifiable reasons for non-compliance with the postoperative pain protocol in the case of 4 patients whose pain was due to a procedure (nausea for which a stomach tube was inserted, insertion of a venous cannula) and 1 patient whose discomfort dissolved spontaneously.

Discussion

In almost 85% of all episodes of pain, the postoperative pain protocol was violated indicating poor compliance. The patient's sex, age, and mechanical ventilation had no significant influence on full compliance. Assessments made during the evening shift were positively related with compliance however. A possible explanation is that during the day shift the nurses have many additional tasks, such as taking the child for diagnostic tests; attend the rounds etc., which might distract them from protocol compliance. During the night time when children are often asleep nurses will try to avoid handling of the patients and therefore withhold scoring. Therefore the afternoon, without managing tasks is positively related with compliance.

Medication was more often given in ventilated patients. This could be explained by the fear for respiratory depression due to opiods in non ventilated children.

Moreover, only rarely these violations were documented as justifiable. On the other hand, most pain assessments in the present study suggested comfort.

The question arises to what extent non-compliance to pain assessments may be harmful. Although many organizations and authors recommend the use of pain

assessment and/or pain protocols in neonates and children, the scientific evidence to support this practice is low.[22-24] On the other hand pain in children matters and should be treated in the best possible way.[11] A survey of practices in a single Canadian pediatric hospital showed that pain is not standard assessed, across all age groups and services, when standardized pain protocols are lacking.[25] For example, in a US study of emergency room practices in general and children's hospitals, pain scores were documented in only 44.5% of the children seen.[26]

Franck and Bruce[23] explored possible reasons for poor compliance with protocolized pain protocols in 14 studies over two decades. They concluded that factors such as age and sex of patients influence protocol compliance and that these are hard to control. Furthermore they concluded that good-quality evidence is lacking for the efficacy and cost-benefit effectiveness of the protocolized pain assessment and the tools used in pediatric patients, especially in the ICU setting.

Barriers to compliance with clinical pain management guidelines may be related to lack of knowledge,[27] low priority given to pain management; time constraints and insufficient physician orders.[13] Facilitators to enhance compliance are the availability of 'local champions', a multidisciplinary pain committee;[28] and one-on-one coaching.[27]

There may be other reasons for not following the protocol. For example, it can be legitimate not to administer morphine when patients are expected to be extubated soon. These kinds of reasons cannot be retrieved from the PDMS and we suggest adding a field for such information.

We recently evaluated compliance with our unit's sedation protocol for non-surgical patients. The non-compliance rates are similar to those found in the present study (28% no medication given when needed).[29] In contrast, we found much better protocol compliance (> 90%) in the context of a pharmacokinetic-pharmacodynamic study on midazolam for sedation in critically ill infants.[30] In that study, however, the principal researcher was to be contacted by the nurse if an assessment indicated over sedation. The researcher then guided next protocol steps.

To counteract for the absence of such an investigator, protocols may dictate reassessment to evaluate actions taken. Bucknall et al.[31] found that nurses hardly ever re-assessed pain after the administration of analgesics to postoperative adult patients. In the context of a clinical trial comparing empiric with protocol-based sedation, protocol compliance was much higher (83.7%) than in our study.[32]

As suggested by Czarnecki et al.,[13] we offered refresher courses in pharmacological pain treatment, NRS-11 and COMFORT-B scoring, to improve protocol compliance on our ICU. These are very time consuming, however, and – as others have concluded – affect only a part of the medication administration and (re-) assessment.[33] We therefore feel that protocol compliance could be improved by monthly feedback to the nurses and physicians on numbers of pain scores, reassessments and protocol violations, in line with the recommendations of Ellis et al.[28] Furthermore, physicians should be educated to prescribe rescue medication only on the basis of high pain scores.[34] Finally, visibility of multidisciplinary pain teams on the floor could be improved for instance by frequent walk rounds providing for one-on-one coaching.[27]

With respect to research recommendations; we still lack scientific evidence for the effectiveness of pain guidelines.[22-24] Randomized controlled trials on implementation of pain guidelines vs standard care can not be executed if pain assessment is both the outcome and the intervention. Moreover, most PICUs will have some type of pain protocol in place and a control condition is therefore often not available. The second best option would be to use a before-after design.

One limitation of our study is the retrospective nature which is illustrated for example by the lack of information on non-compliance with the protocol. Finally, underestimation of patients in pain could be due to limited reassessments of patients unresponsive to the used analgesics.

Conclusion

The postoperative pain protocol applied in our ICU appears to be effective, as judged from the fact that no more than 20% of all scores exceeded cut-off scores suggesting pain or distress. However, in case of such high scores, full compliance to the protocol (reassessment and medication) was marginal, possibly leading to under treatment of pain. The optimal way to manage pain in postoperative pediatric patients encompasses adequate pain treatment guided by pain assessments according to protocol while leaving room for occasional protocol violations for justifiable reasons.

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PART 3

Treatment of Pain

There is no pharmacologic equivalent of human compassion.

Movius and Martin

CHAPTER 3.1

Intravenous paracetamol reduces morphine requirements in neonates and young infants after major non-cardiac surgery: results of a randomized controlled trial

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Submitted

Abstract

Background

Continuous morphine infusion as standard postoperative analgesic therapy in neonates and infants is associated with side effects such as respiratory depression. We aimed to assess whether intermittent intravenous paracetamol administration would significantly (>30%) reduce morphine requirements.

Methods

In this single-centre prospective, randomized double-blind study, infants under the age of 1 year were randomized to receive either continuous morphine or intermittent intravenous paracetamol after major abdominal or thoracic, non-cardiac surgery. Infants in both study groups received morphine (boluses and/or continuous infusion) as rescue medication on the guidance of the validated pain assessment instruments COMFORT behaviour scale and Numeric Rating Scale. Endpoints in the first 48 hours postoperatively were: 1) cumulative morphine dose (study and rescue dose) (mcg/kg); 2) morphine rescue dose (mcg/kg); 3) morphine-related side effects. Analysis was by intention to treat. This trial was registered with www.trialregister.nl, number NTR1438.

Findings

Between March 2008 and July 2010, 71 of 74 patients were included in the primary analysis (paracetamol (P), n=33 vs. morphine (M), n=38). Patients in the paracetamol group received 66% less morphine than patients in the morphine group in the first 48 hours postoperatively [121 (IQR 99-264) vs. 357 (IQR 220-605) mcg/kg, p< 0·001]. The median rescue dose of morphine (P; 25 (0-164) mcg/kg vs. M; 20 (IQR 0-226), p=0·99), incidences of morphine-related side effects (P; 27·3% vs. M; 34·2%), RR 1·4, 95% CI 0·5-3·8) and levels of pain scores did not differ between study groups.

Interpretation

Intravenous paracetamol reduces morphine requirements in neonates and young infants after major surgery, thereby potentially reducing the risk for opioid-related side effects with similar validated pain scores demonstrating identical pain levels.

Funding

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Introduction

The treatment of pain in young children has improved after the landmark publications by Anand et al. in 1987 that made clear that neonates have well-developed nociceptive pathways and therefore are capable of experiencing pain.[1,2] Because untreated pain may lead to suffering and even adverse consequences in the long run,[3-6] opioids were introduced, and have been used ever since.[7] Opioid therapy, however, is associated with side effects, in particular respiratory depression thereby limiting its widespread use.[8] Researchers, therefore, are in search for alternative analgesic regimens in neonates and young infants that are as effective and safer as opoid therapy.[9]

Paracetamol has been proposed as an alternative. No more than two studies have evaluated the opioid-sparing effect of paracetamol as add-on medication in postoperative neonates and young infants. One, a randomized controlled trial on rectal paracetamol in neonates aged 0-2 months undergoing major non-cardiac thoracic or abdominal surgery failed to show such an effect.[10] The other, however, demonstrated a fentanyl-sparing effect of intravenous paracetamol in infants aged 6-24 months after ureteroneocystostomy.[11] The discrepancy between these studies may be explained by the different paracetamol formulations. Neither study directly compared the analgesic effect of morphine with that of paracetamol as primary analgesic. It could be argued that intravenous paracetamol with an option for rescue morphine boluses may further reduce postoperative opioid consumption.[12]

We performed a randomized controlled trial in infants who had undergone major abdominal and non-cardiac thoracic surgery. Patients were randomized to receive either intravenous paracetamol or morphine postoperatively, with the possibility of rescue morphine doses in both groups. The aim of this trial was to determine if intermittent administration of intravenous paracetamol would reduce the cumulative morphine dose needed to provide adequate analgesia by at least 30%.

Methods and Materials

Patients

In this single-centre prospective, randomized double-blind study, all children under the age of 1 year undergoing major thoracic, non-cardiac, or abdominal surgery between March 2008 and July 2010 at the Erasmus MC-Sophia Children's Hospital in Rotterdam, the Netherlands, were eligible for inclusion. Exclusion criteria were: 1) postconceptual age younger than 36 weeks; 2) body weight less than 1500 grams; 3) Extra Corporeal Membrane Oxygenation (ECMO) treatment; 4) neurological, hepatic dysfunction or renal insufficiency; 5) pre- or postnatal administration of opioids or psychotropic drug (antiepileptics, benzodiazepines, antidepressants) for more than 24 hours; 6) known allergy or intolerance for paracetamol or morphine; 7) administration of opioids in the 24 hours prior to surgery.

The study was approved by the Erasmus MC ethics review board, and was registered in the trial register under the code NTR1438. Patients were included in the study not until after informed consent from parents or legal representatives had been obtained.

Study arms

Patients were randomized to receive either morphine or paracetamol postoperatively. Patients were stratified for age in two groups; 0-10 days and 11 days-1 year. When randomized for paracetamol (30 mg/kg/day in 4 doses) a placebo infusion of normal saline was administered continuously at the same rate as an equivalent morphine infusion. When randomized for morphine (patients aged 0-10 days 2.5 mcg/kg$^{1.5}$/hour and patients aged 11 days-1 year 5 mcg/kg$^{1.5}$/hour)[13,14] normal saline was administered 4 times daily as placebo in a similar volume as the intravenous paracetamol dose. Placebos could not be distinguished from the actual study drug in color, odor, or viscosity.

In both study arms, rescue morphine (0-10 days 10 mcg/kg, 11 days-1 year 15 mcg/kg) was administered whenever COMFORT-behaviour scale (COMFORT-B) or Numeric Rating Scale-11 (NRS-11) scores indicated pain (Figure 1). Rescue doses were administered every 10 minutes when needed, with a maximum of three per hour. If pain persisted a continuous morphine rescue infusion was started at 1.25 mcg/kg$^{1.5}$/hour (0- 10 days) or 2.5 mcg/kg$^{1.5}$/hour (11 days- 1 year). When patients then still needed rescue morphine three times per hour, the infusion dose was

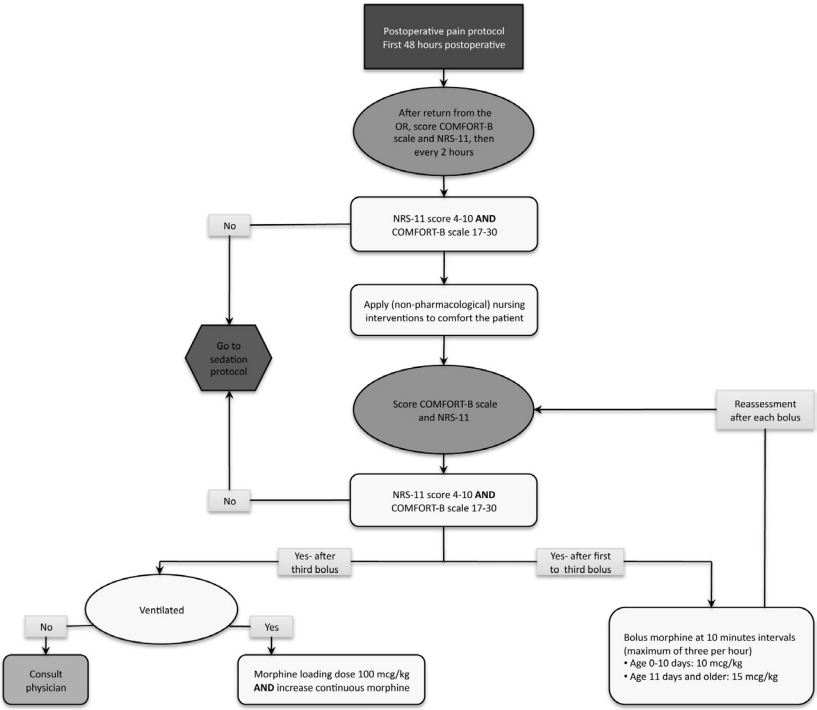

FIGURE 1. Postoperative pain protocol Erasmus MC-Sophia Children's Hospital

doubled. Eventually, if pain persisted in spite of the rescue morphine boluses and the continuous morphine infusion at a maximum dose, fentanyl was started. If pain decreased, as documented by NRS-11 scores below 4 for more than 12 hours, morphine dosage was reduced by 50%.

In case of discomfort (COMFORT-B score ≥ 17 and NRS-11<4) midazolam was started.

Assessments

The patient's nurses performed pain assessments with the COMFORT-B scale and the NRS-11 according to the unit's postoperative pain protocol (Figure 1). [10,15] Pain is indicated by two different score combinations: NRS-11 ≥4 and COMFORT-B<17 or NRS-11 ≥4 and COMFORT-B≥17. Discomfort is indicated by the score combination COMFORT-B ≥17 and NRS-11<4. All nurses had been trained to apply these scales. Inter-rater reliability had been established on the basis of ten paired ob-

servations with an already trained nurse. A linear weighted Cohen's kappa of 0.65 was deemed acceptable; this was the case for all nurses. The median scored linear weighted kappa for the COMFORT-B scale was 0·79 (IQR 0·72-0·86).

The Surgical Stress Score was computed by the surgeon, classifying the surgical procedures in terms of minor, moderate, or severe surgical stress.[16]

Randomization and masking

Patients had an equal probability of assignment to study groups. Stratified randomization was used in combination with random permuted blocks. Initially, we stratified for 4 age groups, i.e. (a) 0-10 days, (b) 11 days-3 months, (c) 3-6 months and (d) 6-12 months. A hospital pharmacist carried out computer randomization in advance, and codes were safely stored. Inclusion numbers for groups b, c and d were falling behind after 9 months' inclusion: 18 in group (a); 2 in group (b); 11 in group (c); and 3 in group (d). We then decided to randomize into two age groups; 0-10 days and 11 days-1 year, as major changes in pharmacokinetics of morphine are to be expected in the first 10 days of life, with relatively minor changes thereafter.[13] A new randomization schedule was computer-generated by the same pharmacist. Only the pharmacist had access to deblinded data during the study period, for preparation of study medication.

To evaluate nurses' blinding, we asked the nurses' opinion on the treatment arm the patient was assigned to.

Standardized anesthesia

Anesthesia was induced by thiopental 3-5 mg/kg or by inhalation with sevoflurane in air/oxygen mixture. Fentanyl 2-5 µg/kg was administered before tracheal intubation with a cumulative total dose of 5 µg/kg before the surgical procedure. Tracheal intubation was facilitated with cis-atracurium 0·15 mg/kg, except for rapid sequence inductions, when succinylcholine 2 mg/kg was administered. Anesthesia was maintained with oxygen/air and isoflurane, titrated to an end tidal concentration of 0·8-1·2%. Extra doses of fentanyl (2 µg/kg) were administered when heart rate and/or mean arterial blood pressure was 10% or more above baseline values. Peroperative fluids were given in a standardized way, and normoglycemia was maintained alongside normothermia (35·5-37°C).

All patients received a loading dose of morphine (100 µg/kg) 30 minutes before the anticipated end of the surgical procedure. Postoperatively they were directly

transferred to the ICU, where study medication was started within 5 minutes after arrival.

Study endpoints

The primary endpoint was the cumulative morphine dose in mcg/kg during the first 48 hours postoperatively, i.e. the sum of the intra-operative loading dose, the morphine study dose and the rescue morphine doses.

Secondary endpoints were morphine rescue dose in mcg/kg in the first 48 hours postoperatively, number of extra rescue morphine doses and infusions (rescue doses and rescue dose in combination with a rescue infusion start/increase counted as one), number of patients receiving rescue doses, based on COMFORT-B and NRS-11 scores, and morphine-related side effects.

Morphine-related side effects were defined as follows:

1) Mechanical ventilation and/or reintubation,
2) Apnea: SpO2 <94% or respiratory rate <20/min longer than 30 seconds
3) Naloxone administration
4) Bradycardia: heart rate <100/min neonates or <80/min for older infants and >30 seconds per episode other than due to or directly related to the disease or operation
5) Hypotension: vaso-active medication or additional fluid boluses
6) Seizures: when other causes could be ruled out
7) Gastro-intestinal adverse effects: antiemetics or laxatives administration; ileus signs
8) Urinary retention

Clinical data collection

Clinical data collected were sex, age at surgery, bodyweight, duration and type of surgery (thoracic or abdominal), co-medication, mechanical ventilation postoperatively, severity of illness scores (PRISM, PIM).[17,18]

Statistical methods

Power analysis

We considered a 30% reduction in cumulative morphine dose (as based on previous data)[19] in the intravenous paracetamol group compared with the morphine group clinically relevant. To be able to estimate this, the number of patients required in each group equaled 32, as shown by a power analysis in which the alpha level of significance was fixed at 0·05 (2 tailed) and the beta level was fixed at 0·20. Considering a dropout rate of 15%, 37 patients per group were needed.

Interim evaluation

The pharmacist and the statistician performed an interim evaluation after inclusion of 20 patients while the investigators remained blinded. The study was to be discontinued when more than 18 patients would have needed a rescue morphine infusion (i.e. three doses of morphine and start of background morphine).

Statistical analysis

Descriptive statistics served to compare clinical characteristics. The Kolmorgorov-Smirnov test served to assess distribution of the variables. Groups were compared using t-test or Mann-Whitney test. Proportions were compared by using Chi-squared tests with continuity correction, or Fisher's exact test when appropriate. The relative risk was calculated in a logistic regression analysis. For each patient we calculated the percentage of correct nurses' opinions on whether this patient was randomized for morphine or paracetamol. If at least 75% was correct, this was set at 'opinion correct'. The mean COMFORT-B and median NRS scores per patient were calculated and compared between the two groups with the unpaired t-test and Mann-Whitney test respectively. Level of significance was set at 0·05.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 17·0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

We initially enrolled 74 patients. However, the parents of one withdrew the informed consent before start of the study procedure; one eventually did not undergo major surgery (no intussusception present at laparoscopy); and blood tests just before surgery revealed abnormal liver function in one (Figure 2).

The characteristics of the remaining 71 patients did not differ significantly between the paracetamol and morphine groups (Table 1). The most frequent

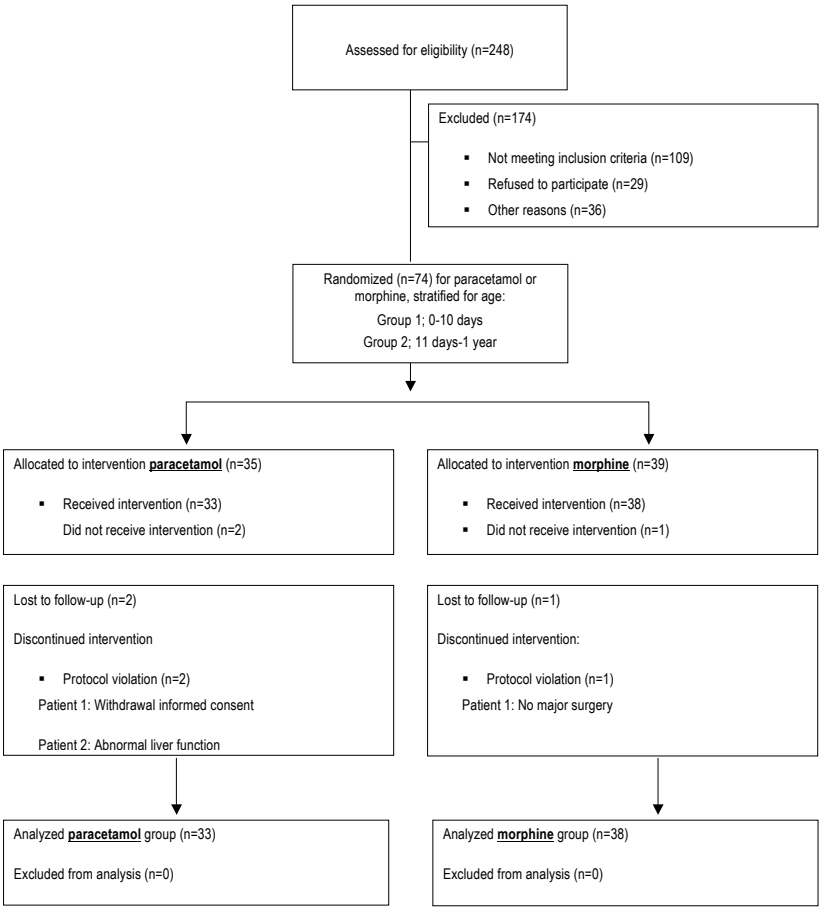

FIGURE 2. Inclusion diagram

		Morphine	*Paracetamol*	*p-value*
No. of patients	N=	38	33	
Male /Female	N/N	26/12	18/15	0·23
Age at surgery (days)	Median (IQR)	20 (1·8-87·5)	5 (1·5-64·5)	0·50
Weight (kg)	Mean (SD)	4·4 (2·0)	3·8 (1·3)	0·17
Duration of surgery (min)	Mean (SD)	156·6 (87·9)	172·1 (83·7)	0·45
Surgical procedure				
• Thoracic	N =(%)	11 (28·9%)	5 (15·2%)	0·17
• Abdominal		27 (71·1%)	28 (84·8%)	
Postoperative mechanical ventilation	N= (%)	14 (36·8%)	15 (45·5%)	0·46
Duration of postoperative ventilation (hours)	Median (IQR)	23 (16-45)	34 (15-45)	0·43
Surgical Stress Score	Median (IQR)	10 (9-11)	10 (9-11)	0·75
PRISM2	Mean (SD)	8·97 (5·14)	8·61 (6·47)	0·79
PRISM3	Mean (SD)	3·50 (3·95)	3·39 (4·16)	0·91
PIM	Mean (SD)	-4·23 (1·20)	-4·33 (1·35)	0·75
PIM2	Mean (SD)	-4·24 (0·97)	-4·44 (1·11)	0·42

TABLE 1. Patient characteristics. PRISM; The Pediatric Risk of Mortality score, PIM; Pediatric Index of Mortality

surgical procedures were closure of congenital diaphragmatic hernia, and repair of intestinal atresia and esophageal atresia.

One patient with gastroschisis in the paracetamol group underwent additional surgery for bowel necrosis. This patient postoperatively received vecuronium, on account of which the NRS-11 and the COMFORT-B could not be applied, and therefore the study medication was terminated and replaced by morphine after 19 hours, and cumulative morphine dose was calculated for the first 48 hours postoperatively (intention to treat).

Study endpoints

The cumulative morphine dose in the paracetamol group was 66% lower than that in the morphine group [121 (IQR 99-264) mcg/kg vs. 357 (IQR 220-605) mcg/kg, p< 0·001] (Table 2). Box plots of cumulative morphine doses are depicted in Figure 3. Considering the two stratified age groups separately, the cumulative morphine dose in the paracetamol group was 49% lower than that in the morphine group for the neonates (0-10 days of age) [111 (IQR 96-169) vs. 218 (IQR 186-294) mcg/kg, p=0·002] and 73% lower for the older infants (11 days-1 year) [152 (IQR 112-346) vs. 553 (IQR 361-765) mcg/kg, p< 0·001].

The total morphine rescue dose did not differ significantly between the paracetamol and morphine groups [25 (IQR 0-164) mcg/kg vs. 20 (IQR 0-226) mcg/kg, p=0·99]. Neither did the number of rescue morphine interventions (bolus or infusion start/increase) differ nor the total number of patients receiving rescue medication (Table 2).

Side effects are listed in Table 3, showing no significant differences between percentage side effects in both groups (27·3% (P) vs. 34·2% (M), RR 1·4 95% CI 0·5-3·8). Similarly, evaluating the respiratory side effects together (need for reintubation, apnoea and need for naloxone) no significant difference was found (15·2% (P) vs. 26·3% (M), RR 2·0, 95% CI 0·6-6·6). Naloxone was given three times in the morphine

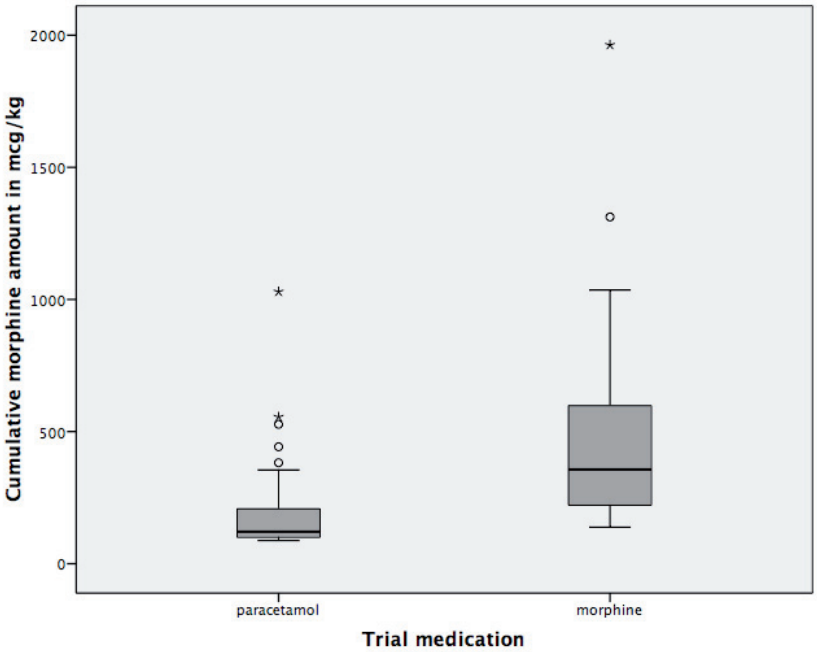

FIGURE 3. Cumulative morphine dose for both morphine and paracetamol study groups over 48 hours postoperative. Asterisks depict outliers, in the paracetamol group we identified two: the first a boy, 68 days old, who underwent surgery for a long gap esophageal atresia and subsequently needed a chest tube for a pneumothorax. The second is a boy, newborn, with a gastroschisis for which a silo was placed. In the morphine group one outlier is identified, a girl, 355 days old, who underwent surgery for a recurrence of a Congenital Diaphragmatic Hernia (CDH).

Endpoints in the first 48 hours postoperative		**Morphine N= 38**	**Paracetamol N=33**	p-value
Cumulative morphine dose (in mcg/kg)	Median (IQR)	357 (220- 605)	121 (99- 264)	< 0·001
Rescue dose morphine (in mcg/kg)	Median (IQR)	20 (0- 226)	25 (0- 164)	0·99
Number of rescue morphine doses and infusions	Median (IQR)	2 (0-5)	2 (0-6)	0·97
Patients receiving rescue morphine	N (%)	23 (60·5%)	22 (66·7%)	0·59
Co-medication	N=			
• Midazolam	(%)	3 (7·9%)	5 (15·2%)	0·34
• Fentanyl	(%)	1 (2·6%)	0	0·35
• Vecuronium	(%)	0	1 (3·0%)	0·28
• Locoregional block	(%)	3 (7·9%)	0	0·10

TABLE 2. Morphine requirements and co-medication.

		Morphine (n=38)	***Paracetamol (n=33)***	p-value
Reintubation	N(%)	2 (5·3%)	1 (3·0%)	0·64
Apneu	N(%)	10 (26·3%)	4 (12·1%)	0·13
Naloxone	N(%)	3 (7·9%)	-	0·10
Bradycardia	N(%)	7 (18·4%)	6 (18·2%)	0·98
Urinary retention	N(%)	- (31 patients had a CAD)	1 (26 patients had a CAD)	0·28

TABLE 3. Side effects.

group and not at all in the paracetamol group (p=0·10). Seizures, hypotension, or gastro-intestinal side effects did not occur.

The median NRS-11 scores in the paracetamol group did not differ from those in the morphine group [1 (IQR 0-1) vs. 1 (IQR 0-2), p=0·17]. The mean COMFORT-B scores in the paracetamol group did not differ from those in the morphine group (13·0 (SD 2·0) vs. 13·1 (SD 2·1), p=0·80).

For 63 patients, 299 nurses' opinions on treatment arm assignment were available (1-13 per patient). For 23 patients, the nurses' opinion on treatment arm was correct in at least 75% of the observations. Percentage correct opinions were not related to number of opinions per patient (Mann Whitney, p=0·46).

Discussion

In this randomized controlled trial, we showed that young infants who received intravenous paracetamol as primary analgesic after major surgery consumed significantly less morphine than those who received a continuous morphine infusion. Judged from the rescue morphine doses, a similar level of analgesia was obtained in either group. These results suggest that intravenous paracetamol may well replace opoid therapy as primairy analgesic in neonates and young infants following major surgery. Administration of opioids to infants under the age of 3 months should always be monitored as a safety measure, but in many parts of the world monitoring facilities are not available.

The opioid-sparing potential of paracetamol was shown in older children and adults as well. Hong et al. found a fentanyl-sparing effect of intravenous paracetamol in infants aged 6-24 months using parent-/nurses-controlled analgesia after ureteroneocystostomy.[11] In older children, Korpela et al. showed that a single dose of 40 or 60 mg/kg of rectal acetaminophen has a clear morphine-sparing effect in day-case surgery for older children, if administered during the induction of anesthesia.[20] A recent systematic review showed a morphine-sparing effect of paracetamol (oral, rectal or intravenous) in adult patients receiving morphine as postoperative patient-controlled analgesia. The reduction of morphine requirements was lower than in our study (14% vs. 66%).[21]

In contrast, other studies did not find a morphine-sparing effect of rectal paracetamol, neither in young infants (0-2 months)[10] nor in older children.[22-24] We speculate that type of study design may (partly) explain the contrasting findings. In most studies (10, 11, 24) baseline standard opioid infusions were given in both study arms,[10,11,24] potentially blurring the actual effect of paracetamol. In our study, apart from the intra-operative morphine loading dose, paracetamol was given as primary analgesic with morphine rescue possibility. Furthermore, differences in paracetamol formulations used may result in variable absorption and plasma concentrations, explaining the lack of an opioid-sparing effect in other referred studies. More specifically, surgery may further contribute to unpredictable absorption of both rectal and oral formulations. These limitations are overcome by the intravenous administration in our study and may explain the efficacy of intravenous paracetamol in our study.

Paracetamol did not induce respiratory depression, a side effect observed in three patients in the morphine group. Despite a lack of statistical significance for this and other side effects, this observation does suggest a potential reduction in respiratory depression by using paracetamol. A systematic review in adults by Maund et al. neither found a significant reduction in morphine-related side effects, despite a reduction in cumulative morphine dose postoperatively.[21] This phenomenon may be explained by a lack of power as most studies were designed to detect a difference in efficacy, but not in side effects. Also, in many studies, side effects are not systematically reported.[21] Therefore the potential advantage of paracetamol over morphine in terms of preventing respiratory depression deserves further study.

Finally, the question remains whether paracetamol is safe in young infants. Its general safety in children has been widely documented,[25] but the evidence on safety of intravenous paracetamol in young neonates is scarcely investigated.[26] Neonates have a lower risk of paracetamol-induced hepatotoxicity than have older children and adults: the enzymes (e.g. CYP2E1) involved in the formation of NAPQI, the hepatotoxic metabolite, are still immature.[27] Nevertheless, we excluded patients with pre-existing liver abnormalities, to reduce the risk of hepatotoxicity. Ethical constraints prevented us from taking additional blood samples to assess liver function. Future research using for instance metabolomic approached might increase our level of understanding and could predict the development of hepatotoxicity. A systematic analysis of hepatotoxicity as side effect in pediatric paracetamol trials could not confirm paracetamol-related toxicity when dosed therapeutically.[28] In contrast, we recently described three cases of liver failure with recommended doses of paracetamol in children with myopathies, who likely are at high risk.[29] Other case reports also suggest that this phenomenon may occur, but data are often lacking to determine a definitive causal relationship.[28] The evaluation of safety is also complicated by the fact that the mechanism of action of paracetamol is still unclear.[25]

Some limitations of our study need to be addressed. First, this is a single-centre study in a strictly defined patient population. This may potentially limit external validity of the findings.[30] Second, as discussed above, this study was not powered to detect a difference in side effects, nor were we able to monitor liver function in

the paracetamol group. This limits our ability to determine which treatment arm was safest.

In conclusion, our results suggest that intravenous, regularly-dosed paracetamol can be used as primary analgesic in neonates and infants under the age of 1 year after major, non-cardiac thoracic or abdominal surgery, provided that treatment is guided by validated pain assessment instruments, and adequate rescue medication. Regarding its safety, future studies should aim to follow-up liver function before and after treatment.

Research in context

Systematic review

We searched PubMed and Cochrane Library databases up to May 20, 2011, without language restrictions for articles reporting randomized trials, systematic reviews, and meta-analyses with the search terms "paracetamol or acetaminophen", "morphine or morphine-sparing", "opioid or opioid-sparing" with the limits "newborn and infants". We included articles on major abdominal, non-cardiac thoracic surgery, articles were otherwise excluded.

Our search identified two randomized trials.[10,11] When the search was extended for adult meta-analyses we identified multiple papers, of which we used the most up-to-date version.[21]

Interpretation

The results of the two RCTs were not consistent between both studies. The routes of administration of paracetamol were rectal and intravenous, respectively. In the study using intravenous paracetamol, an opioid sparing effect was found.[11] In the other study no effect of rectal paracetamol was found.[10] In adults a morphine sparing effect was described in the meta-analyses for reduction of opioid requirements.

However, in no study paracetamol was used as primary analgesic for postoperative pain after major non-cardiac surgery.

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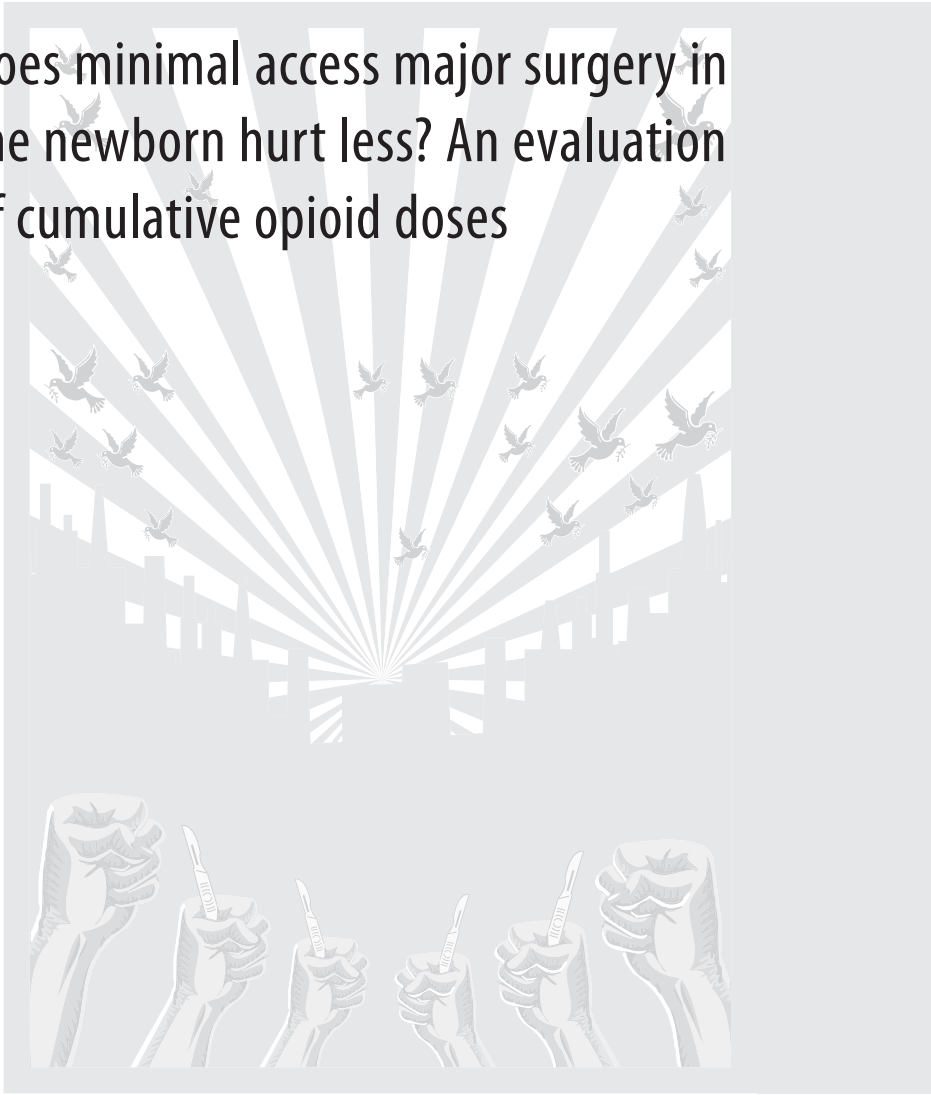
CHAPTER 3.2

Does minimal access major surgery in the newborn hurt less? An evaluation of cumulative opioid doses



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Abstract

Background
Minimal access surgery (MAS) in adults is associated with less postoperative pain in comparison to conventional 'open' surgery. It is not known whether this holds true for neonates as well. Less pain would imply that opioid consumption can be reduced, which has a beneficial effect on morbidity.

Aim
To evaluate potential differences in' opioid consumption between neonates undergoing thoracoscopic minimal access surgery or conventional surgery of esophageal atresia (EA) and congenital diaphragmatic hernia (CDH).

Methods
In this retrospective cohort study we included two controls for each MAS patient, matched on diagnosis, sex and age at surgery. Opioid dose titration was based on validated pain scores (VAS and COMFORT behaviour), applied by protocol. Cumulative opioid doses at 12, 24, 48 hours and 7 days postoperatively were compared between groups with the Mann-Whitney test.

Results
The study group consisted of 24 MAS patients (14 EA; 10 CDH). These were matched to 48 control patients (28 EA; 20 CDH). At none of the time points cumulative opioid (median in mg/kg (IQR)) doses significantly differed between MAS patients and controls, both with CDH and EA. For example at 24 hours postoperative for CDH patients cumulative opioid doses were [0.84(0.61- 1.83) MAS vs. 1.06(0.60- 1.36) p=1.0] controls, For EA patients at 24 hours the cumulative opioid doses were [0.48(0.30- 0.75) MAS vs. 0.49(0.35- 0.79) p=0.83] controls. This held true for the postoperative pain scores as well.

Conclusions
Minimal access surgery for the repair of esophageal atresia or congenital diaphragmatic hernia is not associated with less cumulative opioid doses.

Introduction

Several randomized controlled trials (RCTs) and meta-analyses indeed have demonstrated beneficial effects of minimal access surgery (MAS) in adults, i.e. less postoperative pain and morbidity and shorter hospital stay in comparison to open surgery.[1,2] There is little such evidence with regard to children. Findings for adults are not transferable to children, however, in view of their characteristic anatomical and physiological features as manifested, for example, by insufflation-induced hypothermia and hypercarbia.[3] A systematic review identified only six level-one RCTs (1.46% of all studies) on pediatric MAS for the period 1995-2006, demonstrating low levels of evidence.[4]

Two RCTs in older children for various surgery indications showed no beneficial effect of MAS on postoperative pain.[5,6] On the other hand, one study in 4 to 15-year-old children indeed found significant decreases in pain and analgesics use after laparoscopic appendectomy.[7] Data on the effect of MAS on postoperative pain in neonates are lacking. We hypothesized that newborns undergoing MAS consume significantly fewer postoperative analgesics compared to those who undergo conventional 'open' surgery and tested this hypothesis in a retrospective cohort study with matched controls. Two types of major surgical interventions for significant congenital anomalies were considered: correction of esophageal atresia (EA) and correction of congenital diaphragmatic hernia (CDH). Patients with these conditions form more homogeneous groups than those with other birth defect such as intestinal atresia or malrotation. The primary outcome was the total amount of opioids received in the first week postoperatively.

Materials and Methods

Subjects and setting

The study was approved by the hospital's medical ethics review board.

We identified all patients under the age of 2 months who underwent MAS for EA or CDH in our hospital and were subsequently admitted to the Intensive Care Unit (ICU), i.e. from January 1st, 2006 to January 1st, 2009. Patients receiving extracorporeal membrane oxygenation and patients participating in an ongoing trial comparing IV paracetamol and IV morphine were excluded. Our ICU is a 28-bed

level-3 ICU in a university children's hospital admitting all categories of patients including direct postoperative cardiopulmonary bypass patients following cardiac surgery.

Each eligible patient was matched with two control patients who underwent conventional 'open' surgery on the same diagnosis from January 1st 2004 to January 1st 2009. Patients were further matched on sex, age and weight at surgery, consecutively, whenever possible. During this period neither the surgical team nor the ICU team, nor the postoperative pain management protocol changed significantly. Until recently, intra-operative analgesics, sedatives and muscle relaxants were not fully standardized in our hospital. The patients in this study received four different intravenous analgesics, three sedatives and four muscle relaxants – in different combinations. Hence, it is not feasible to include intra-operative medications in the analyses.

The main criteria for performing minimal invasive surgery were hemodynamic and respiratory stability as well as the availability of an experienced MAS surgeon.

Neither gestational age, nor weight at birth, nor the need for immediate ventilatory support at birth was considered a contraindication for MAS as long as the patient was stabilized before surgery.

Procedure

Administered doses of morphine and fentanyl were retrieved from the computerized patient data management system (PDMS). Secondary outcomes, such as COMFORT behaviour scores and VAS, duration of ventilatory support, need for re-intubation, duration of surgery and length of stay on the ICU, were retrieved from this system as well.

Doses of morphine and fentanyl were summed after fentanyl had been converted to a morphine equivalent by the following rule: 0.1 mg of fentanyl is equivalent to 10 mg of morphine.[8] We calculated total amounts over the first 12, 24, 48 hours and 7 days. Patients discharged within one week were assigned the amount until discharge. The rationale for selection of the above time frame is the following: in the first 12 hours opioid doses are most frequently adjusted; the first 24 hours are often the most painful; after 48 hours analgesics are usually decreased or stopped and mechanical ventilation is often withdrawn except in CDH.[9] Finally, the 7-days calculation covers longer term opioids administration.

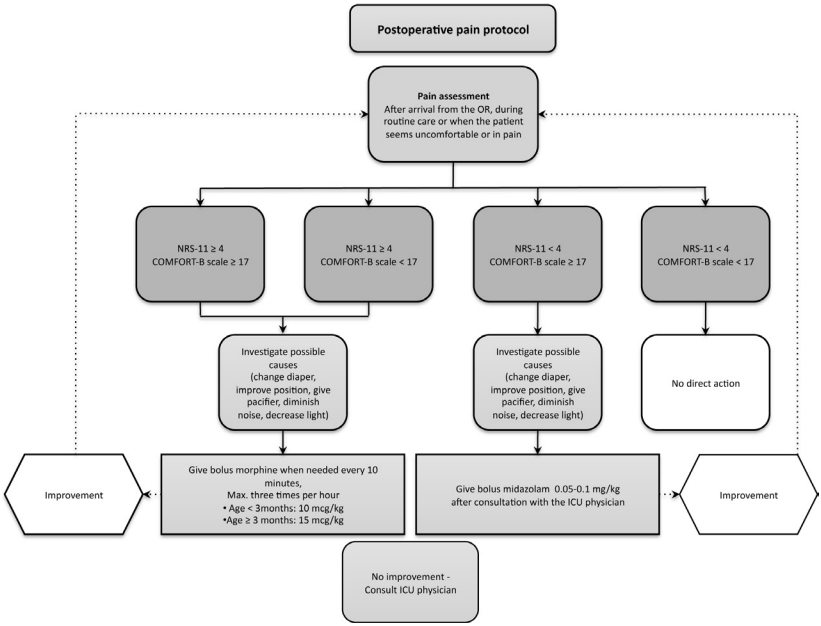

FIGURE 1. Postoperative pain decision-tree as used on the ICU of the Erasmus MC-Sophia Children's Hospital.

A nurse-led postoperative pain and distress management protocol[10] is in place in our unit (Figure 1). Nurses assess the children's pain at regular predefined intervals and when clinically needed. For children up to the age of three years they will use the Visual Analogue Scale[11,12] in combination with the 'COMFORT behaviour scale".[10,13] The COMFORT-B scale is a validated tool for the evaluation of pain in this age group [14]. The observational VAS has been validated for the assessment of acute pain in infants.[15] The protocol was implemented in 1999, and experiences with the postoperative pain protocol were used in several RCTs on the ICU.[9,16,17]

All nurses in the unit are routinely trained to apply these scales and are allowed to do so after sufficient interrater reliability has been established. Their median linear weighted kappa for the COMFORT-B scale was 0.70.

Since a score-based decision tree determines next steps in pain treatment, we evaluated the scores in all patients for the first 12, 24, 48 hours and 7 days post-operative, and counted the total numbers of scores exceeding the cut-off points (COMFORT≥ 17; VAS≥ 4). At these scores patients receive rescue morphine after

non-pharmaceutical measures have proven insufficient. Within 15 minutes after administration of medication, patients are re-assessed and when necessary further action is taken.

The pharmacological pain management protocol provides for decrease of morphine dosing and finally discontinuation when pain scores are lower. After cessation of morphine, paracetamol is given according to need, to a maximum of 60 mg/kg/day (rectally) and 30 mg/kg/day (intravenously).

The protocol provides for administration of midazolam in case of discomfort, as reflected by a VAS score <4 in combination with a COMFORT-B score of 17 or higher. Since the use of midazolam can influence a patient's pain perception, we have chosen to monitor the amount of midazolam to avoid bias.

Because the severity of illness could play a role in the decision whether to use MAS or open surgery, especially in patients with CDH, we calculated the paediatric logistic organ dysfunction (PELOD) score for the 24 hours prior to surgery.[18] This score ranges from 0 (no organ dysfunction) to 71. In the original validation study, the PELOD score for non-survivors was significantly higher (mean 31.0 SE 1.2) than that for survivors (mean 9.2 SE 0.2).[18]

Data analysis

Patient characteristics are presented using descriptive statistics. The mean cumulative opioid dose for each set of matched controls was compared with the cumulative opioid dose for the MAS patient in question for the first 12, 24, 48 hours and 7 days postoperatively. Variables were compared with the t-test for the normally distributed variables and with the Mann-Whitney test for skewed variables. The Chi-square test or Fisher exact test was used for the comparison of nominal data.

As summary measures, mean COMFORT–B and VAS pain scores per patient per time interval were calculated of all available assessments, and compared using analysis of variance (ANOVA). This approach of summary measures will allow for a different number of assessments per patient.[19] Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Inclusion

We identified 31 eligible MAS patients. Five of them were excluded as they participated in an ongoing analgesic RCT. Furthermore, one patient (CDH, male, age at surgery 34 days) was excluded because no matching controls could be identified. Another patient was excluded because the MAS procedure had been converted to a conventional 'open' procedure. The remaining 24 patients (14 EA; 10 CDH) were matched to 48 control patients (28 EA; 20 CDH).

Patient characteristics

Patient characteristics, for the EA and CDH groups separately, are shown in Table 1. In line with previous reports, duration of MAS was significantly longer than that of open surgery (p=0.002 for EA and p= 0.017 for CDH).

Postoperative ventilation duration did not differ significantly between the MAS patients and the control surgery groups. Proportions of patients still ventilated after 48 hours did not differ between the MAS group and the controls, for both the EA and the CDH patients. (See Table 1)

Administration of regional and local anesthetics did not significantly differ (EA MAS n= 0 and control group n= 3 (p= 0.54); CDH MAS n= 2 and control group n= 0 (p= 0.10)).

The median number of pain scores, for the first 48 hours, were 8 (IQR 7 to 9) and 10 (IQR 8 to 12) respectively for MAS and controls. The mean COMFORT-B scores per patient per time interval did not differ between MAS and controls for EA and CDH (Table 2). Two patients (one 'open' EA and one 'open' CDH) did not have digitally documented pain scores, because they were transferred to the NICU. At that time the PDMS was not yet introduced at the NICU, but the pain protocol was. Furthermore, other patients were only scored during one or two of the three time intervals.

Opioid consumption

Regarding both EA and CDH patients, median cumulative opioid doses at all postoperative time points did not significantly differ between patients who underwent MAS and the controls (Table 3 and Figure 2). One outlier in the first time interval concerned a patient with CDH who underwent MAS. This patient needed more

	EA			CDH		
	MAS	Conventional surgery	*p-value*	MAS	Conventional surgery	*p-value*
	n=14	**n=28**		**n=10**	**n=20**	
Male/ Female	7/7	14/14	-	5/5	10/10	-
Weight at surgery (in kg) Mean (SD)	2.62 (0.52)	2.79 (0.75)	*0.45*	3.36 (0.73)	3.25 (0.67)	*.69*
Initial length of stay at ICU (in days) Median (IQR)	10.5 (7-13.3)	18.5 (12.3-32.0)	*0.10*	23 (10.3-28.8)	21 (13.3-34.3)	*.57*
Duration surgery (in min) Mean (SD)	260 (39)	204 (59)	***0.002***	219 (53)	171 (47)	***.02***
Age at surgery (in days) Median (IQR)	2.0 (1.8-2.0)	1.0 (1.0-2.0)	***0.001***	4.0 (2.0-5.0)	3.5 (3.0-6.0)	*.45*
Time from ICU admission to surgery (in hours) Median (IQR)	29.5 (20-38.3)	18.0 (12.0-25.8)	***0.01***	76.4 (44.5-103.8)	83.5 (58-120.5)	*.36*
Duration initial ventilation after surgery (in hours) Median (IQR)	19.5 (16.3-41.8)	32.5 (17.5-46.8)	*0.22*	141.0 (48.3-217.5)	135.0 (49.8-253.3)	*.86*
No. (%) of pts not on ventilatory support postoperative	1 (7.1%)	1 (3.6%)	*1.00*	0 (0%)	0 (0%)	-
No. (%) of pts still on ventilatory support 48 hours postoperative	2 (14.3%)	6 (21.4%)	*0.70*	8 (80%)	15 (75%)	*1.00*
No. (%) of pts re-intubated in the first week after surgery	0 (0%)	2 (7.1%)	*0.55*	0 (0%)	3 (15%)	*.53*
PELOD score in						
No. of pts (%) with PELOD score 0 to 1	6 (42.9%)	10 (35.7%)	*0.83*	0 (0%)	1 (5%)	*1.00*
No. of pts (%) with PELOD score 10 to 11	8 (57.1%)	18 (64.3%)		10 (100%)	19 (95%)	
No. of pts receiving additional sedatives and analgesics:						
- Paracetamol	7 (50%)	7 (25%)	*.17*	8 (80%)	14 (70%)	*1.00*
- Midazolam	5 (35.7%)	6 (21.4%)	*.46*	6 (60%)	8 (40%)	*.44*

TABLE 1. Patient characteristics.

	EA,MAS (N=14)	EA, open surgery (N=28)	CDH MAS (N=10)	CDH open surgery (N=20)	p-value
No. of patients with scores Mean COMFORT scores 0-12 hours after surgery	N=14 10.9 (1.4)	N=26 10.3 (1.8)	N=10 9.9 (1.2)	N=17 9.7 (1.6)	.17
No. of patients with scores Mean COMFORT scores >12 to 24 hours after surgery	N=13 10.3 (1.5)	N=26 10.8 (1.3)	N=10 10.2 (1.8)	N=17 9.9 (1.7)	.30
No. of patients with scores Mean COMFORT scores >24 to 48 hours after surgery	N=14 11.1 (1.7)	N=24 11.4 (1.3)	N=10 11.4 (1.8)	N=18 10.5 (1.3)	.18
No. of patients with scores Mean COMFORT scores >48 hours to 7 days after surgery	N=14 12.0 (.90)	N=24 12.4 (1.4)	N=9 11.8 (.72)	N=19 11.5 (.90)	.07
% of VAS pain 4 or higher 0-12 hours after surgery	5.3	6.7	5.0	3.6	
% of VAS pain 4 or higher >12 to 24 hours after surgery	-	-	-	2.1	
% of VAS pain 4 or higher >24 to 48 hours after surgery	-	2.9	2.6	-	
% of VAS pain 4 or higher >48 to 7 days after surgery	1.4	2.0	.7	3.5	

TABLE 2. Mean COMFORT–B and VAS pain scores per patient per time interval.

EA	MAS	Conventional surgery	*p-value*
Time point	**N=14**	**N=28**	
12 hrs postop	0.30 (0.18- 0.44)	0.33 (0.21- 0.42)	*.63*
24 hrs postop	0.48 (0.30- 0.75)	0.49 (0.35- 0.79)	*.83*
48 hs postop	0.79 (0.37- 1.10)	0.77 (0.35- 1.11)	*1.0*
7 days postop	0.83 (0.37- 1.10)	0.86 (0.36- 1.11)	*1.0*
CDH	**N=10**	**N=20**	
12 hrs postop	0.45 (0.39- 0.61)	0.64 (0.31- 0.81)	*.95*
24 hrs postop	0.84 (0.61- 1.83)	1.06 (0.60- 1.36)	*1.00*
48 hrs postop	1.57 (0.78- 1.93)	1.39 (0.82- 2.35)	*.76*
7 days postop	2.27 (0.78- 5.44)	2.22 (1.06- 5.32)	*.54*

TABLE 3. Median (IQR) opioid doses (mg/kg) in EA and CDH patients operated on with MAS and conventional 'open' surgery

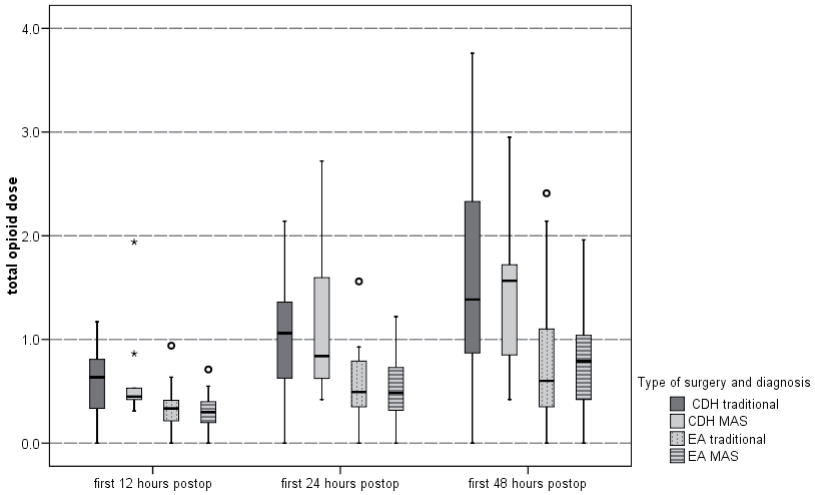

FIGURE 2. Boxplot of the postoperative opioid dose (in mg/kg)

opioids due to (postoperative) pulmonary hypertension, aiming to decrease any stress as trigger for pulmonary hypertensive crises. Amounts of midazolam and paracetamol did not significantly differ between MAS patients and controls.

Discussion

To our knowledge this is the first study to evaluate the effect of MAS on neonates' postoperative pain after correction of a major congenital anomaly. We found no significant differences in postoperative opioid consumption between patients operated on with MAS and those who underwent conventional 'open' surgery. Thus we must reject our a priori hypothesis that newborns undergoing MAS would consume less postoperative analgesics.

Studies including older children report contradictory findings on postoperative pain reduction after MAS. Two RCTs showed no beneficial effect of MAS. One is a single-blinded study on laparoscopic inguinal hernia repair in 89 patients aged from 4 months to 16 years.[5] Rescue analgesics and pain scores on the second day postoperatively did not differ from those after open surgery. The second is a single-blinded study as well, on appendectomy in 63 children aged from 8 to 15 years.[6] Laparoscopy did not reduce analgesic consumption. In contrast, a single-blinded

trial found a significant decrease in postoperative pain and postoperative analgesics use in 61 patients aged from 4 to 15 years after laparoscopic appendectomy.[7]

Around the world pedatric surgical centres use MAS for a wide variety of indications. Advantages of the thoracoscopic approach for CDH are the following: lower insufflation pressure, more working space as the intestines are replaced, and a gentle replacement technique for the intestines, all of which may reduce postoperative pain.[20] Thoracoscopic EA repair seems to have a similar safety and efficacy (e.g. recurrence rate) as the open approach.[21] Advantages of the thoracoscopic approach in general are a better visualisation of the thoracic cavity and the potential reduction of musculoskeletal sequelae that frequently develop after a thoracotomy.[22] Also, in adults, sternotomy using thoracotomy can cause significant postoperative but also chronic pain.[23] In general it is assumed that a smaller incision, as in MAS, is less painful. On the other hand, in thoracoscopic surgery the cavity is insufflated with CO_2, which may be painful. The prolonged duration of surgery in the MAS patients may therefore give rise to postoperative pain.

Our study has several limitations. For one, sample sizes are small, even though our unit is one of the major referral centres in the Netherlands for newborns with congenital anomalies. Furthermore, retrospective evaluation and matching of patients has its drawbacks, although we retrieved reliable data on prescribed medication from the electronic patient data management system. To minimize the risk of selection bias we matched each MAS patient to two control patients. There were no significant differences between groups except duration of surgery, suggesting that matching was acceptable. As a possible limitation, CDH control patients were operated on through a laparotomic approach, whereas a thoracoscopic approach was used in all MAS patients.

Another limitation of our study is that we only focused on one outcome parameter, i.e. pain relief. We focused only on the cumulative opioid dose, which was partly based on the observational VAS. This observational VAS has not been sufficiently validated in it's own right for neonatal postoperative pain.[24,25] Other clinically important outcomes are length of stay, time on ventilator and adverse outcomes such as infection, wound dehiscence, or anastamotic leaks. To our knowledge, prospective randomized trials or well-designed retrospective analyses of these outcome measures in the neonatal population are lacking.

Furthermore, as far as we know of, prospective randomized trials or well-designed retrospective analyses of postoperative wound infections are lacking.

Adult data, however, suggest a lower infection rate for MAS.[26] Also, case studies in neonatal surgery do not suggest an increased risk of infection after scopic surgery.[27,28] Re-evaluation of our patient data revealed no signs of postoperative wound infections.

Conclusions

MAS is a technique that promises to improve patient care through reduced morbidity, shorter hospital stay and less postoperative pain. Our data, although retrospective, do not support a reduction of postoperative pain as reflected by postoperative opioid consumption, seeing that this did not differ between MAS and conventional 'open' surgery in newborns with major congenital anomalies.

Acknowledgement

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PART 4

Safety issues

If we don't get lost we'll never find a new route

Joan Littlewood

CHAPTER 4.1

Morphine-induced muscle rigidity in a term neonate

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Abstract

Objective

To describe a potentially fatal adverse drug event (ADE) of morphine in a term neonate which before has been reported for fentanyl and similar opioids, but not for morphine.

Case Summary

Recently, a term neonate experienced generalized muscle rigidity and laryngeal spasm resulting in acute respiratory failure on two separate occasions after morphine administration. On the first occasion a bolus of morphine was administered in the operating theatre; when muscle rigidity occurred, propofol was administered which resulted in relief of symptoms. On the second occasion in the ICU the patient received continuous infusion of morphine. The patient experienced generalized muscle rigidity with respiratory compromise. The opioid antagonist naloxone was administered which immediately resulted in a patent airway and spontaneous breathing. An objective causality assessment using the Naranjo Probability Scale revealed that the ADE was highly probable to definite.

Discussion

We searched the literature for previous reports of morphine-related muscle rigidity and/or laryngeal spasm in Pubmed and Embase. Sudden onset of muscle rigidity and laryngeal spasm is described in the literature as a rare serious adverse event after infusion of fentanyl and similar opioids in both adults and young infants. However, there are no reports of this potentially fatal adverse event after administration of morphine. To our knowledge this is the first case in humans of life-threatening muscle rigidity and laryngeal spasm after therapeutic doses of morphine.

Conclusion

Generalized muscle rigidity and laryngospasm is a serious adverse event that can occur after bolus administration of morphine but also during continuous infusion. Increased vigilance while using this drug seems to be warranted.

Introduction

Numerous case reports exist in the literature describing muscle rigidity and/or laryngeal spasm after administration of synthetic opioids, such as fentanyl. This adverse effect is described in all age groups, including children. Pediatric cases have been reported mainly in neonates, both term and preterm.[1-4]

We describe a case of a term neonate who twice developed muscle rigidity and laryngeal spasm. One instance occurred after bolus doses of morphine and fentanyl and another during a continuous infusion of morphine only.

Case report

A 2 day-old, 3.1 kg term male neonate underwent colostomy for anorectal malformation without associated VACTERL anomalies. He developed generalized muscle rigidity and laryngeal spasm after administration of morphine and fentanyl as bolus doses in the operating theatre and a few hours later on the pediatric intensive care unit while receiving a continuous morphine infusion.

Drugs used to induce anesthesia were thiopental, fentanyl (5 µg/kg) and cisatracurium. Anesthesia was maintained with oxygen/air and isoflurane. During surgery, two additional bolus doses of fentanyl (2 µg/kg) were given when the heart rate and/or the mean arterial blood pressure were 10% or more above baseline values. The last dose was given 45 minutes before extubation. Forty minutes before extubation intravenous (IV) morphine (100 µg/kg) was given as loading dose for postoperative analgesia. Shortly after extubation, thoracic muscle rigidity and laryngeal spasm occurred which compromised air entry, and led to rapid oxygen desaturation. The patient promptly received propofol 2mg/kg IV, which relieved muscle rigidity, but necessitated re-intubation due to apnea. Within an hour the patient could be successfully extubated and was transferred to the intensive care unit (ICU). Upon arrival at the ICU, a continuous morphine infusion was started at 4.4 mcg/kg/h according to our ICU's postoperative pain protocol. The patient was somnolent, but could be easily aroused and breathed spontaneously without additional oxygen need. Ninety minutes after start of the continuous morphine infusion, the patient suddenly became rigid with rapidly declining oxygen saturations. Again air entry was restricted and mask-bag ventilation was not possible. Muscle

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.	Yes	No	Do not Know	**Score in OR**	**Score in ICU**
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	**0-1**	**0-1**
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	**2**	**2**
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	**0**	**1**
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	**0**	**2**
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	**-1**	**2**
6. Did the reaction reappear when a placebo was given?	-1	+1	0	**0**	**0**
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	**0**	**0**
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	**0**	**0**
9. Did the patients have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	**0**	**1**
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	**0**	**1**
Total Score				**1-2**	**9-10**

OR = operating room; ICU = intensive care unit

NARANJO PROBABILITY SCALE

rigidity and laryngeal spasm as adverse drug reaction to opiates was suspected. Naloxone (30 µg/kg IV) was administered within 60 seconds. The continuous morphine infusion was discontinued at the same time. Almost immediately after administration of naloxone the general muscle rigidity resolved, the patient started to breathe spontaneously and woke up with crying. Intravenous acetaminophen (30 mg/kg/day divided q6h) was administered as alternative analgesia. Muscle rigidity did not recur. The patient remained alert, breathing spontaneously. He was discharged without any sequelae to the pediatric surgical ward the next morning.

Discussion

In this case muscle rigidity and laryngeal spasm occurred 40-45 minutes after bolus administration of fentanyl and morphine, and also a few hours later during continuous infusion of morphine. The first episode responded favourable to propofol,

the second to naloxone. The favourable response to naloxone supports a causal relationship between morphine and muscle rigidity. As clinicians, we were not aware of such reports for morphine in the literature, which gave reason to further study this possible causal relationship.

First, we performed a literature search using Medline and Embase, using the following search terms: (muscle rigidity OR chest rigidity OR laryngeal spasm) AND (morphine OR fentanyl OR opioid).

As expected, we identified multiple reports of muscle rigidity and laryngeal spasm in adults in relation to high-doses of fentanyl and other synthetic opioids, such as meperidine and sufentanil. The same response has been reported in response to low doses of fentanyl (2-6 mcg/kg) in preterm and term infants.[1] The reported incidence of this phenomenon is between 0.3% and 9%. The mechanism of the opiate-induced muscle rigidity appears to involve the basal ganglia and the nuclei raphe pontis. In rat studies a reversal of opiate-induced muscle rigidity was attained by stimulating pre-synaptic α_2-adrenoceptors, but also serotonergic receptors have been implicated.[5]

In contrast, we could not identify any report in humans on life-threatening muscle rigidity in relation to morphine use. In a pharmacokinetic study of continuous morphine infusion in premature neonates, in one patient transient hypertonia without respiratory compromise was observed.[6] In rat, supra-therapeutic doses of morphine (>2.5 mg/kg) led to increased muscle tone, but not to respiratory compromise.

Adverse effects of pharmaceuticals are common and usually well documented in adults. We used the Naranjo Probability Scale to determine the likelihood the life-threatening muscle rigidity was causally related to the administration of morphine in a term infant (see table).[7] The Naranjo score ranges from -4 to 13 and indicates the strength of the causal relationship as follows: definite ≥ 9; probable 5 to 8; possible 1 to 4; and doubtful ≤ 0.

We first evaluated the first occurrence of muscle rigidity. The first occurrence is not a clear case of morphine induced muscle rigidity (total score 1-2 = possible causal relationship), since both morphine and fentanyl were administered 40-45 minutes prior to the incident and the incident could have been due to fentanyl alone. Also, this could have been an extubation laryngospasm.

For the second incident a causal relationship between morphine administration and muscle rigidity with laryngeal spasm was highly probable to definite (score

9-10). This incident occurred more than two and half-hours after the last fentanyl dose, while the patient was on continuous morphine. We did consider the possibility that the second incident occurred due to remaining fentanyl in the body and a subsiding effect of the propofol bolus dose given two hours previously. In contrast to adults, in newborn infants, fentanyl is not a fast-clearing drug (mean elimination half-life around 5 hrs). However, as our patient breathed spontaneously and was arousable upon ICU admission, a remaining significant fentanyl or propofol effect at that time is not probable. Also, we could not identify other causes (e.g. co-medication, underlying neurological disease) that might explain the muscle rigidity. Finally, the morphine doses prescribed and prepared were correct and in line with clinical practice.

In our patient, muscle rigidity at two occasions resolved after propofol and naloxone, respectively. The opioid antagonist naloxone is lipid-soluble and enters the brain rapidly. Reversal of respiratory depression is evident within 3-4 minutes after IV administration. The reported half-life is 1.1 hrs in adults, but the activity of a bolus dose disappears clinically after 45 minutes. Disappearance of muscle rigidity and acute awakening of our patient almost immediately after naloxone administration further supports an opioid as cause for the observed symptoms. Hence, as a full opioid antagonist, this drug seems the preferred drug of choice to not only antagonize opioid respiratory depression but also muscle rigidity. A word of caution is needed, as acute cardiac arrest has been reported after naloxone administration in a preterm infant, but also in adults.[8] Alternatively, in anesthetic practice, postextubation laryngeal spasms are treated successfully with propofol. The muscle relaxing effect of propofol may be due to reduced calcium influx in muscle cells and/or a decrease in sympathetic activity.[9]

Conclusion

To our knowledge this is the first report of muscle rigidity and laryngospasm in a neonate in relation to morphine use. This finding implies that an increase in vigilance for respiratory compromise is necessary for neonates or infants, but possibly also for adults, receiving morphine.

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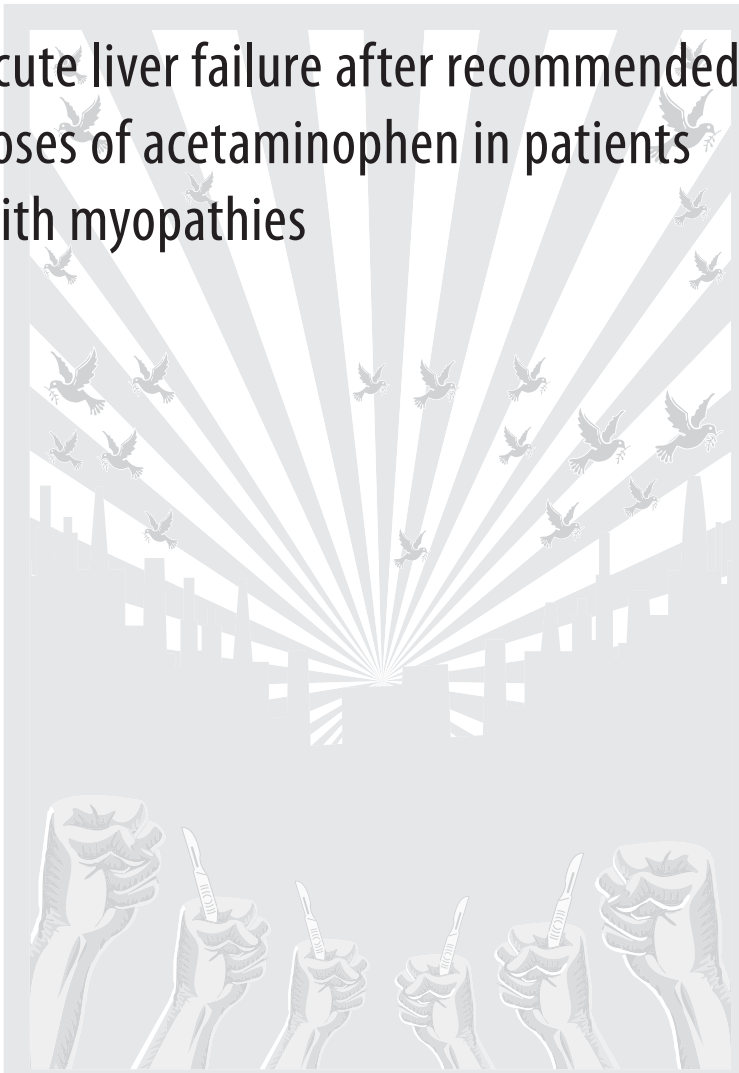
CHAPTER 4.2

Acute liver failure after recommended doses of acetaminophen in patients with myopathies



Ceelie I, James LP, Gijsen V, Mathot RA, Ito S, Tesselaar CD, Tibboel D, Koren G, de Wildt SN

Critical Care Medicine. 2011 April;39(4):678-82.

Abstract

Objective
To determine the likelihood that recommended doses of acetaminophen (APAP) are associated with acute liver failure (ALF) in patients with myopathies.

Design
Retrospective analysis.

Setting
Level III pediatric intensive care unit.

Patients
Two pediatric patients with myopathies and acute liver failure.

Clinical Investigations
We determined acetaminophen protein adduct levels, in combination with a literature review and systematic evaluation of the cases, using the Roussel Uclaf Causality Assessment Method (RUCAM) for drug-induced liver injury (DILI) to assess causality between recommended acetaminophen dosing and acute liver failure in two children with myopathies.

Main Results
The serum adduct levels were consistent with the values previously reported in children with acute liver injury following APAP overdose. We found four similar cases of ALF in pediatric and adult patients with myopathies following recommended APAP doses in the literature (n=3) and personal communication (n=1).The RUCAM suggested a probable relationship between APAP use at recommended doses and ALF in our myopathy patients.

Conclusions
Our data suggest that some patients with myopathies receiving recommended doses of APAP may be at increased risk for the development of toxicity resulting in ALF. More studies are needed to corroborate these findings. In the meantime, we would advise physicians to be alert in these patients while taking APAP, especially when critically ill or postoperative.

Introduction

Acetaminophen (N-acetyl-paraaminophenol (APAP)) is a commonly used analgesic and antipyretic agent, which is generally safe at recommended therapeutic doses. Overdosing may result in acute liver failure (ALF) however, and thus constitutes a serious public health concern, notably in children.[1,2] Data from the US suggest that up to 50% of all pediatric patients experiencing ALF die or require liver transplantation.[3]

Most of a single dose (>90%) of APAP is metabolized to non-toxic metabolites by glucuronidation or sulphation. Approximately 5% of a therapeutic dose is metabolized to N-acetyl-p-benzoquinone (NAPQI) by cytochrome P450 2E1, CYP2E1 (to a lesser extent by CYP1A2 or CYP3A4).[4,5] NAPQI is rapidly detoxified by interaction with glutathione to form cysteine and mercapturic acid conjugates. When glutathione is depleted, NAPQI binds to cysteine groups on protein, forming APAP-CYS adducts. Adduct formation correlates with toxicity in experimental models of APAP toxicity and in APAP overdose patients.[6,7] Recently, quantitative assessment of APAP adduct concentrations in patient sera has been shown to be a highly sensitive and specific biomarker of suspected APAP toxicity, even in the absence of toxic APAP blood concentrations.[8-10]

We describe two children with underlying myopathies who developed ALF after having received therapeutic doses of APAP. Furthermore, we report the use of adduct measurements in these patients, so as to raise clinicians' awareness of therapeutic doses of APAP as a possible cause of ALF in children with myopathies.

Patients and methods

Patients

Two patients admitted to the Erasmus MC-Sophia Children's Hospital in Rotterdam, the Netherlands developed acute liver failure, as defined by the Pediatric Acute Liver Failure Study Group.[3] The Institutional Review Board of the Erasmus MC Sophia Children's Hospital approved of this study and waived the need for informed consent. Plasma AST and APAP levels in relation to APAP dosing are shown in Figures 1 and 2, respectively. All prescribed drugs and their doses in relation to clinical events, acute liver failure and other diagnostic tests can be found in the supplementary files.

Patient 1

A 12-year-old, 40-kilogram girl with spinal muscular atrophy (SMA) type II underwent spinal fusion surgery for the correction of scoliosis under general anesthesia with sevoflurane and remifentanil. Liver function tests at pre-operative screening were normal. Postoperative analgesics consisted of hydromorphine, diclofenac and APAP rectally (69 mg/kg/d for 4 days).

Three days postoperatively, the patient developed a hematothorax. Pre-procedure screening by anaesthesiology showed increased hepatic transaminases that were greater than 2 times above normal values. A chest drain and central venous catheter were placed under general anesthesia after a difficult intubation. Ventilatory support was continued post-procedure under propofol sedation (2.5 mg/kg/h for 17 hours). Propofol and APAP were discontinued after laboratory findings showed liver injury (Figure 1). The patient ultimately developed ALF with encephalopathy and required prolonged ventilatory support. N-acetylcysteine (150 mg/kg bolus IV in 15 minutes, followed by 50 mg/kg/dose IV every 4 hrs for 17 doses) was started on day 4. The ALF resolved with supportive measures; on day 6 she was extubated and on day 8 she was transferred to the referring hospital.

Patient 2

A 17-year-old, 55-kilogram girl with congenital muscular dystrophy, carnitine deficiency and home ventilator dependency was admitted to the intensive care unit due to respiratory insufficiency and pneumonia. Liver function tests obtained at the last regular outpatient clinic visit were normal. Initially, pneumonia was treated with amoxicillin-clavulanic acid. When the clinical signs did not improve, antibiotics were switched to cefuroxime, in addition to clarithromycin. She received APAP rectal pro re nata (on average 40 mg/kg/d, max 90 mg/kg/d). On day 10, tracheotomy, under propofol, fentanyl and rocuronium, was performed and invasive ventilation was initiated. On day 11 she developed icterus, abdominal pain, nausea and vomiting. Liver tests showed ALF (Table 1 and Figure 1). Acetaminophen was discontinued immediately and N- acetylcysteine was started (150 mg/kg bolus IV in 15 minutes, followed by 50 mg/kg/dose IV every 4 hrs for 17 doses). Despite supportive therapy, she developed multiple organ failure with severe hypotension and died of refractory shock on day 14.

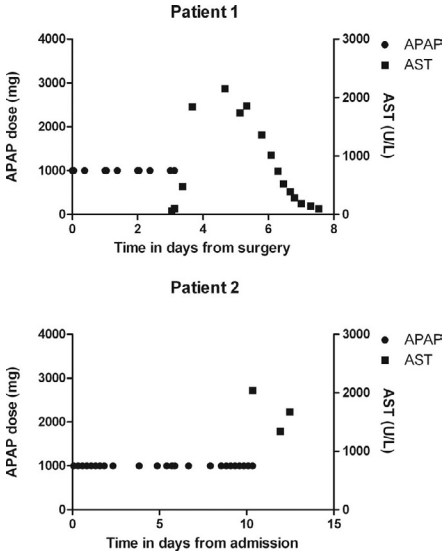


FIGURE 1. AST levels and APAP doses after surgery in patient 1 and after admission in patient 2

Laboratory analysis

Serum samples (0.5 mL) were obtained and stored at -80C until analysis. APAP protein adducts in serum were quantified by means of a previously reported assay for determination of APAP protein adducts (APAP-CYS) in serum.[8,10]

Literature search

We performed a literature search using PubMed and Embase databases from inception - July 2010. We used the following search terms: [(acetaminophen OR paracetamol) AND (myopathy OR muscle dystrophy)]. Papers were evaluated by two authors (IC, SNW) for relevance. Literature references of identified papers were checked for additional references.

To determine 'recommended' dosage of APAP, we used the Dutch national formulary (www.fk.cvz.nl, accessed July 6, 2010) and the Dutch national pediatric formulary (www.kinderformularium.nl accessed July 6, 2010). For adults, the recommended oral dose is 4 g/d (2.5 g/d for chronic use). For children, the oral and rectal recommended dose is 60-90 mg/kg/d, with a maximum of 4 g/d.

Causality assessment

The causality assessment of our cases was based on the standard liver-specific Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method scale for DILI [11]. The RUCAM consensus was developed in 1993, based on international consensus meeting with hepatology and pharmacovigilance experts. The method has a high reproducibility and validity for drug-induced liver injuries.[11,12] The method was validated using reported cases with positive re-challenge. Despite the shortcomings of all existing causality assessment scales, we chose this scale as it appears the best validated scale to date.[13] The RUCAM is based on seven components including time to onset and clinical course of the reactions, risk factors, concomitant drugs, screening for other causes, previous information of hepatotoxicity of the drugs and response to re-administration, toxic concentration or validated laboratory test. To determine if concomitantly prescribed drugs were potential hepatotoxins, we searched the Dutch National Formulary for serious hepatotoxicity listed as reported adverse event. Theoretically the scale has a range from -9 to +15, but in reality only scores between -5 and +13 are found. The classification of the degrees of DILI diagnosis was as follows: score <0: 'relationship excluded'; 1–2: 'unlikely'; 3–5: 'possible'; 6–8: 'probable'; and above 8: 'highly probable'.

Results

APAP protein adduct levels

The serum APAP protein adduct levels for our two cases were consistent with the values previously reported in children with acute liver injury following APAP overdose (Figure 2).[9] Previous receiver operator curve analysis determined that APAP protein adduct levels in serum of > 1.1 nmol/mL had a sensitivity of 96.8% and a specificity of 95% for patients with ALT values > 1000 IU/L.[10]

Literature search & personal communication

Of the 98 papers retrieved using the predefined search terms, only one was of interest. This report described two adult patients with muscular dystrophies who developed acute liver failure after receiving APAP (3g and 4 g, daily respectively) for treatment of pulmonary infections associated with end stage neuromuscular

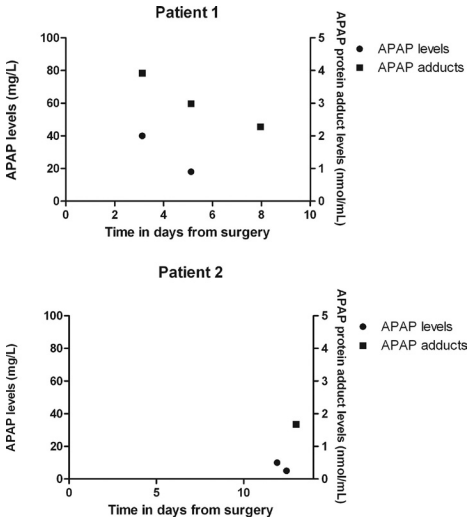


FIGURE 2. APAP serum levels and APAP protein adduct levels in days after surgery in patient 1 and after admission in patient 2.

respiratory failure.[14] A second report was identified, from reference list search, in which a 12-year-old patient with Duchenne's muscular dystrophy developed hepatotoxicity in association with doses of APAP ranging from 70 to 108 mg/kg/day that were administered after posterior spinal fusion surgery.[15] These three patients had full recovery after APAP was discontinued and supportive care and N- acetylcysteine treatment were initiated.

In addition to the three previously reported cases of APAP toxicity in patients with existing muscular disorders described in the literature, we identified another child with a myopathy who developed ALF requiring liver transplantation after the use recommended doses of APAP (personal communication, Dr S. Ito). This 12-year, 60-kilogram boy, with SMA type II underwent spinal fusion surgery for scoliosis repair and received on average APAP 23 mg/kg/day for 5 days. The highest measured APAP level was 248 mg/l for this patient but APAP protein adduct analysis was not performed.

Causality assessment

Using the RUCAM scale, we found a probable relationship between APAP and acute liver failure for both patients (RUCAM +6 and +8 for patient 1 and 2, respectively).

Based on the criteria of the RUCAM, both patients developed acute liver injury (ALT >2N = ALT 872 U/l and 4173 U/L, respectively). *The time to onset* was compatible for patient 1 (<5 days from onset of drug and <15 days after cessation) and highly suggestive (5-90 days from onset of drug and <15 days after cessation) for patient 2. For patient 1, the *course of reaction* was highly suggestive as ALT levels decreased >50% within 8 days. The course of the reaction was inconclusive for patient 2, as the patient died within two days of liver failure and ALT levels did not decrease <50% in that time window. There were no *known risk factors* (age>55yr, ethanol use or pregnancy) for either patient. Other *drugs with compatible time of onset and known hepatotoxins* were sevoflurane for patient 1 and clarithromycin and amoxicillin-clavulanic acid for patient 2. We ruled out hepatitis, biliary obstruction, alcoholism, acute hypotension episode as *non-drug causes*. Abdominal ultrasound excluded biliary obstruction. Inspection of surgery and ICU charts did not reveal hypovolemic episodes. We could not rule out ALF as complication of myopathy for either patient. The specific drug reaction in this context (therapeutic dose in myopathy patients) has been *published in this context, but is unlabelled*. *A validated test* (APAP protein adducts) was positive for both patients. When we also applied RUCAM for the other potential hepatotoxic drugs, we found a possible relationship (RUCAM + 4) between each drug and ALF.

Discussion

Overall, the available data involving six patients (two clinical cases, three in the literature and one personal communication) with underlying myopathies and the development of ALF following the administration of manufacturer recommended doses of APAP suggest that some of these individuals may have increased susceptibility to APAP. This in an interesting finding in the light of a recent meeting held by the US Food and Drug Administration to address the public health problem of liver injury related to the use of acetaminophen in both over-the-counter (OTC) and prescription (Rx) products. The risk to the individual patient of developing liver injury after use of APAP at doses recommended by the manufacturer is very low. However, the agency recognizes that acetaminophen containing products are used extensively making the absolute number of liver injury cases a public health concern [16].The cases reported herein may represent a specific patient population

at risk for acute liver failure with the use of doses of APAP recommended by the manufacturer. Our findings suggest that inter-individual variations in the metabolism of APAP may predispose certain subpopulations of patients to a higher risk for developing this serious adverse event.[1]

Although APAP levels in our two patients were below the reported toxic range (Figure 2), the probability that ALF was APAP-induced is supported by the high levels of APAP protein adduct levels in both patients. Earlier studies reported a range of levels of APAP protein adducts in serum between 1 to 40 nmol/mL in patients with acute APAP overdose.[9,10] In addition, strong correlations were noted between peak adduct measurements and peak AST and ALT values.[9,10] While adducts have been detected in healthy adult volunteers receiving a seven day course of APAP at 4 grams/day, the mean C_{max} for adducts in serum was 0.3 nmol/mL.[17] Importantly, no adducts were observed in control patients who received placebo. Thus, the high levels of adducts in the two patients reported herein suggest a causal relationship between APAP consumption and the development of ALF. To the best of our knowledge, this is the first time that APAP protein adduct measurements were used in clinical care to assess the role of recommended APAP doses in the development of ALF.

Although we found a probable association between APAP exposure and acute liver failure in our two patients, we cannot exclude that other drugs also contributed to the liver failure. Patient 1 received sevoflurane twice, first during scoliosis surgery, next during chest tube and central venous line placement. Although sevoflurane is generally considered safe in comparison with other halogenated anesthetics, cases in the literature suggest that sevoflurane can lead to severe life-threatening hepatic necrosis in at-risk individuals.[18] For patient 2, we identified amoxicillin-clavulanic acid and clarithromycin as possible other serious hepatotoxins.

For both these drugs serious hepatic failure has been reported rarely, most often in patients with serious underlying disease or in combination with other drugs. In addition, both patients received propofol, which has been associated with propofol transfusion syndrome. The limited doses and durations of treatment with propofol (2.5 mg/kg/h for 17 hours and 6 mg/kg/h for 2 hours, respectively) were less than that previously associated with the development of propofol infusion syndrome.[19] In addition, the most striking symptoms of propofol transfusion syndrome, i.e.

cardiac failure combined with lipemic plasma, fatty liver enlargement, metabolic acidosis with negative base excess >10 mmol/l, rhabdomyolysis or myoglobinuria were not present in our patients.[19]

Despite the fact that we cannot exclude a possible role of other drugs in the development of acute liver failure, the causality between APAP and ALF appears more probable in our patients, as supported by the high APAP adduct levels.

The underlying mechanism in the development of APAP toxicity in patients with myopathies is unknown. Glutathione depletion and increased CYP 2E1 activity in relation to relative malnutrition may contribute to increased APAP toxicity.[20,21] Although both our patients had age-adequate weights, an undernourished status may have been present.[22,23] Second, as critically ill patients often receive multiple drugs concurrently, drug interactions at the level of APAP metabolism, e.g. induction of CYP2E1 or inhibition of alternative pathways, may contribute to increased APAP toxicity in this setting.[24-26] Patient 2 also received clarithromycin, which is a cytochrome P450 3A substrate and inhibitor.[27] Theoretically, it may change metabolic disposition of acetaminophen by blocking its CYP3A metabolic pathway, resulting in higher compensatory CYP2E1 metabolism, which in turn may increase the risk of APAP induced liver injury. However, as the main metabolic pathways of acetaminophen are sulphation and glucuronidation, we do not expect a significant effect of CYP3A inhibition on the formation of APAP adducts.[4,5] In addition, we could not find reports of clarithromycin and acetaminophen interaction in the literature. To our knowledge our patients did not receive any drugs, in addition to clarithromycin, that are known to interact with the metabolism of APAP. Third, inflammation has been shown to play a role in the mediation of APAP toxicity in experimental models but its relevance to the underlying muscular disorders in these children is unclear.[28]

In addition, the adduction of mitochondrial proteins appears to trigger mitochondrial dysfunction,[29] and may contribute to the development of liver cell death after APAP exposure.[30] The 12 year old patient referenced above (personal communication, Dr Ito) showed clinical signs and symptoms of severe mitochondrial derangement, including ALF. This patient ultimately required emergency liver transplantation. Also, animal studies suggest a protective role of L-carnitine in APAP-induced liver failure, which may hint to the underlying reason why the patient with carnitine deficiency developed ALF.[31] In addition, a recent report found that patients with myopathies have evidence of increased oxidative stress in

cells isolated from peripheral blood.[32] Oxidative stress is a known mechanism in the pathogenesis of APAP toxicity in laboratory mice.[33] Thus, further study is needed to understand the relative role and contribution of mitochondrial derangement and anti-oxidant status in patients with myopathies as these mechanisms may have relevance to understanding the potential for increased sensitivity to APAP.

Conclusion

Our data suggest that some children with myopathies receiving recommended doses of APAP may be at increased risk for the development of toxicity resulting in ALF. Despite a possible relationship between therapeutic APAP use and ALF in myopathic patients, we do not recommend dose adjustment of APAP at this time. Further research is needed to validate our findings and to reveal the underlying mechanisms, underlying the interactions between myopathy and potential sensitivity to APAP toxicity.

In the meantime, we would advise physicians to be alert in these patients while taking APAP, especially when critically ill or postoperative.

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CHAPTER 4.3

Evaluation of drug formularies for pediatric intensive care

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Abstract

Objectives
Most drugs used in the pediatric intensive care unit (ICU) are prescribed off-label, often on the guidance of limited information from commonly used drug formularies. The aim of this study was to evaluate availability and reliability of pediatric drug dosing guidelines for intensive care patients in selected formularies.

Design
Availability of dosing information on prescribed drugs in a Dutch ICU from January 1st 2005 to December 31st 2006 was compared among four selected formularies (Micromedex®, LexiComp®, Drug Formulary for Children, Drug Doses). Reliability of dosing guidelines was assessed by evaluating labeling status and literature data for the three most (midazolam, acetaminophen and amoxicillin/ clavulanic acid) and the three least (bosentan, ketanserin and iloprost) prescribed drugs.

Measurements and Main Results
The selected formularies covered 68-86% of all 257 prescribed drugs. Guidelines differ widely on daily doses per kilogram, dose description, dosing regimen and age ranges. For the three most prescribed and one of the least prescribed drugs (bosentan), dosing guidelines adequately reflected labeling status and existing (but scarce) literature. No dosing guidelines were available for iloprost, and only one for ketanserin.

Conclusions
This study shows that four commonly used drug formularies give few and widely differing dosing guidelines for drugs prescribed in the ICU. If guidelines exist, they seem to reflect labeling status (if present) and limited literature available. Findings from this study likely reflect the scarcity of drug studies in this population. Physicians should be aware of the limitations of these formularies for daily practice in this group of vulnerable patients.

Introduction

Reducing medication errors is an important means to improve patient safety, for which clinicians are expected to follow the 'the five rights': the right drug, the right dose, the right route, the right time and the right patient.[1] Getting the dose right is especially challenging in pediatric patients, as it needs to be age-appropriate. Also, off-label (outside the terms of the product license) and unlicensed (not licensed for the use in children) use of drugs in pediatric ICUs is a reason for concern, as these patients' lives often depend on adequate treatment. A 2002 study in general practices and general pediatric wards and ICUs in the Netherlands showed, however, that 30% to 68% of drugs prescribed to children were off-label or unlicensed.[2,3]

Both staff and trainees prescribe such drugs on the guidance of dosing guidelines from drug formularies. Although widely used all over the world, the availability and reliability of these sources of information have received little attention in the current debate on drug prescription in children. Yet, 'getting the dose right' depends on the availability of adequate dosing guidelines.

The objective of the present study was to determine the availability and reliability of drug dosing guidelines for pediatric intensive care patients in selected drug formularies.

Materials and Methods

Availability of information

Two pediatric residents independently searched four drug formularies for dosing guidelines on all drugs prescribed in the ICU of the Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands in 2005 and 2006, excluding intravenous fluids and feeds. This 28-bed, level-3 ICU admits all pediatric categories of patients except direct postoperative cardiopulmonary bypass. Information on the drugs used was retrieved from the Patient Data Management System. The four study formularies were selected from hundreds of formularies as a convenience sample as they are often used on our ICU. Selection criteria were easy accessibility/user-friendly format, different geographic origin (the Netherlands, USA and Australia) and different funding sources (commercial vs. public). The selection includes Drug Doses [4], Drug Formulary for Children [5], Lexi-Comp® (http://www.utdol.com/home/

	Drug Doses	Drug Formulary for Children*	Lexi-Comp	Micromedex
Country of origin	Australia	The Netherlands	USA	USA
Consulted version	Booklet	Booklet	Online- via UptoDate®	Online
Target patient group	Pediatric intensive care	Office pediatrics	General Medicine + Pediatrics	General Medicine
Information sources (as presented in the actual formulary)	Practice based	N/A	Literature references	Literature references
Book/online/PDA	Book/online/pda	Book/pda*	Online/pda	Online/pda
Costs	?≈15 USD (PDA) <10 USD (book) Free:online	≈ 20 USD	Institutional subscription	Institutional subscription

TABLE 1.* As of March 2008, after we performed the actual study, the Drug Formulary for Children formulary dosing guidelines are incorporated in the Dutch National Formulary, which is available free online (www.kinderformularium.nl).
N/A not available

index.html) and Micromedex® (http://www.micromedex.com/products/hcs/). Characteristics are given in Table 1.

All information retrieved by the two residents was counter-checked to ensure no errors were made in copying the data. If a formulary recommended a more than 100% higher daily dose per kilogram than the lowest dose recommended in the other formularies, the drug in question was tagged as 'different dosing per kilogram'. A drug was tagged as 'different description' on the basis of differences in e.g. mg/kg in 'x'doses vs. mg/kg/day, in 'x' doses or every 'x' hours, mg/kg/hour vs. mcg/kg/min and amount per kg vs. amount per square meter (m^2). 'Differences in regimen' refers to e.g. bolus vs. not bolus, bolus-dosing vs. continuous, and differences in the number of doses per day and differences in routes of administration. 'Differences in age range' refers to differences in recommended age ranges or the absence of age ranges. Finally, 'lack of pediatric data' was assigned when there was no guideline at all, or no pediatric dosing guideline available in any of the formularies. These 'tags' were dichotomized (0 or 1) so that percentages could be calculated.

The list of all prescribed drugs was divided into quartiles with respect to number of prescriptions. Quartile 1 referred to the most frequently prescribed drugs; quartile 4 to the least frequently prescribed drugs. Number of prescriptions (following

the quartiles) was related to both the availability of dosing guidelines and variation of drug doses.

Reliability of information

Since the availability of information on pediatric drug doses is only a quantitative measure to determine a formulary's usefulness, we assessed quality of the dosing guidelines for the three most and the three least prescribed drugs. To that end we performed exploratory literature searches in PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez) and EMBASE (http://www.embase.com). The search strategies were similar.

The initial search consisted of drug name, followed by the limits Humans, English and Child (0-18 year). For the three most prescribed drugs, the search was further limited to Newborn, Infant, Preschool child and Child, AND (clinical trial or pharmacokinetics or pharmacodynamics). To reduce the number of initial, less relevant hits, the search was repeated using extensive MeSH terms in PubMed; drug name, restricted to administration and dosage, pharmacokinetics, pharmacology, therapeutic use and the previously mentioned limits (Humans, English and Newborn, Infant, Preschool child and Child) for each drug. Extended EMBASE search was performed with limits randomized clinical trial, humans, English, Newborn, Infant, Preschool child and School child for all years. Relevance of the hits was evaluated by the availability of used drug doses as described in the abstract; when of interest, 'related articles' were searched. Dosing information was preferably obtained from randomized controlled trials (RCTs) that supported the efficacy and safety of the drug in question. If RCTs were not available, dosing information from pharmacokinetic studies, case series, etc. was used.

Information regarding Food and Drug Administration labeling status was retrieved from the website http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm (last accessed December 1st, 2008), to evaluate if approval status was reflected in the availability of dosing guidelines. Drug doses reported in studies and drug labels were compared with the dosing guidelines from the formularies.

Statistics

Availability of dosing guidelines of the formularies was compared for all prescribed drugs, by calculating the percentage of covered drugs for each formulary. Similarly, percentages for the other variables (differences in doses/kg, regimen, administration age range, lack of pediatric data) were calculated.

The relationship between number of prescriptions (following the quartiles) and availability of dosing guidelines was tested by Kruskall Wallis-test. The variation of drug doses per kilogram in relation to the number of prescriptions was also tested by Krukall Wallis-test.

The calculations were performed using Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Availability of information

A total of 257 unique drugs had been prescribed during the study period. For 9.4% of all drugs, none of the four formularies provided a paediatric dosing guideline. For 34.7% of drugs the guideline for the daily dose differed more than 100% compared to the formulary with the lowest daily dose. For 61.0% of drugs dose descriptions differed between formularies in, while for 53.4% the dosing regimen guidelines differed. Finally, for 34.5% of drugs recommended age ranges differed.

For each drug formulary the availability of dosing guidelines significantly correlated with prescription frequency in our ICU (p=0.033).

We did not find a relationship between prescription frequency and dose variation (p=0.293).

Availability of information for the three most and the three least prescribed drugs

The three most prescribed drugs were acetaminophen (14330 prescriptions), midazolam (1646 units for multiple use), and amoxicillin/ clavulanic acid (5174 units). The least prescribed drugs were bosentan, iloprost and ketanserin (each prescribed only once). Table 2 shows the dosing guidelines for these drugs in the four studied formularies. The dosing guidelines for the three most prescribed

Drug	*Drug Formulary for Children*	*Micromedex*	*Drug Doses*	*Lexi-Comp*
Acetaminophen	Oral 60-90 mg/kg/ day in 4-6 doses, first doses double dose Rectal 60-90 mg/kg/d in 3 doses	Oral 10-15 mg/kg/ dose every 4-6H Rectal (1-3y) 80 mg every 4H	Oral 20 mg/kg stat then 15 mg/kg/ dose 4H rectal 40 mg/kg stat then 30 mg/kg/dose 6H	Oral 10-15 mg/kg/ dose every 4-6H Rectal 10-20 mg/ kg/dose every 4-6H
Acetaminophen dose calculated per mg/kg/ day (mg/kg/d)	*Oral 60-90 mg/kg/d Rectal 60-90 mg/kg/d*	*Oral 40-90mg/kg/d Rectal 30-50 mg/kg/d*	*Oral 90 mg/kg/d Rectal 120 mg/kg/d*	*Oral 40-90 mg/kg/d Rectal 40-120 mg/ kg/d*
Midazolam	0.05-0.2 mg/kg/h	0.06-0.12 mg/kg/ hour	1-4 mcg/kg/min	0.4-6 mcg/kg/min
Midazolam dose calculated per mg/ kg/day	*1.2-4.8 mg/kg/d*	*1.44-2.88 mg/kg/d*	*1.44-5.76 mg/kg/d*	*0.58-8.64 mg/kg/d*
Amoxicilin/ Clavulanic Acid	Oral 50/12.5-100/25 mg/kg/d in 3 doses	Oral 25-45 mg/kg/ day divided every 12H (child <40 kg ascertain appropriate formulation)	Amoxi component 10-25 mg/kg/dose 8H iv im oral	Oral (child <40 kg) 20-40 mg/ kg/day every 8H (amoxicillin component)
Amoxicillin/ Clavulanic acid dose calculated per calculated per mg/ kg/day	*50-100 mg/kg/d*	*25-45 mg/kg/d*	*30-75 mg/kg/d*	*20-40 mg/kg/d*

TABLE 2A. The 3 most prescribed drugs in 2005/2006 on the ICU and their dosing guidelines following the four studied formularies. For each drug the recommended dose was converted to a dose for 24 hours for easier comparison.

drugs were provided in all formularies and were largely in agreement. In contrast, only two formularies provided dosing guidelines for bosentan, none for iloprost, and one for ketanserin.

Reliability of information

For the three most prescribed drugs, the dosing guidelines in the formularies adequately reflected the FDA labeling guidelines (www.fda.gov). The literature search results are shown in Table 3. The doses of midazolam[6,7] acetaminophen[8-10] and amoxicillin/ clavulanic acid[11,12] used in clinical trials or PK/PD studies (>20 for each drug) also corresponded to the drug dosing guidelines in the formularies.

Drug	*Drug Formulary for Children*	*Micromedex*	*Drug Doses*	*Lexi-Comp*
Ketanserin	0.5-5 mcg/kg/min Max 150 mg/day	Not available	Not available	Not available
Ketanserin dose calculated per mg/kg/day	*0.72-7.2 mg/kg/d max 150mg/day*	Not available	Not available	Not available
Bosentan	Not available	Not available	Oral; 1 mg/kg/ dose 12H for 1-4 wk then 2 mg/kg/ dose 12H Iv half oral dose	Oral <10 kg 15.6 mg daily to 15.6 twice daily 10-20 kg 31.25 mg daily to twice daily >20-40 kg 31.25 mg twice daily to 62.5 mg twice daily >40 kg 62.5 mg twice daily to 125 mg twice daily
Bosentan dose calculated per mg/kg/day	Not available	Not available	*2-4 mg/kg/d*	*1.6-4 mg/kg/d*
Iloprost	Not available	Not available	Not available	Not available
Iloprost dose calculated per mg/kg/day	Not available	Not available	Not available	Not available

TABLE 2B. The 3 least prescribed drugs in 2005/2006 on the ICU and their dosing guidelines following the four studied formularies. For each drug the recommended dose was converted to a dose for 24 hours for easier comparison. When no dosing guideline was available this was noted as such.

The amoxicillin/clavulanic acid dosing guidelines can be potentially confusing and are prone to error. In the Micromedex®, LexiComp® and Drug Doses formularies the daily dose of amoxicillin/ clavulanic acid is only based on amoxicillin properties and not on the combination. As the formulation in the USA and Australia differs from the formulation prescribed in the Netherlands amoxicillin/ clavulanic acid ratio in the Netherlands 4:1 versus 7:1 elsewhere) recommendations on dosing differ. These differences disappear once the dose is corrected for clavulanic acid.

In contrast to the frequently used drugs, no FDA approval for pediatric use has been granted for ketanserin, bosentan and iloprost. For bosentan, dosing guidelines in two formularies reflected similar doses used in a small number of retrospective reports and open label studies.[13] This only provides limited evidence for dosing; we did not find PK-PD studies or randomized clinical trials. Similarly, for iloprost a number of relevant papers for use in children are available, but these do not include clinical trials.[14,15] Finally, the only study ketanserin study provided

Medication	Pubmed (01-04-08)	+ limits (humans, english, all child 0-18 yr)	+ limits (human, English,newborn, infant, preschool child, school child) + (clinical trial, or pharmacokinetics or pharmacodynamics	+ MeSH (administration and dosage, pharmacokinetics, + limits)	Embase (02-05-08) all years	All years + human	+ limits (RCT, English, human, all years, newborn, infant, preschool child, school child)	Number of formularies that agree with literature
Midazolam	7859	1109	829	24	20576	17864	109	4 of 4
Augmentin	2242	368	206	2	16000	13065	76	4 of 4
Acetaminophen	12517	1340	1021	43	40513	29680	111	4 of 4
Ketanserin	4374	23	18	0	6978	2614	1	0 of 0
Bosentan	1235	44	31	31 (substance name + limits)	2652	1292	1	2 of 2
Iloprost	1949	44	31	1	3721	2705	0	0 of 0

TABLE 3. Number of hits following the literature search as performed in PubMed and EMBASE.

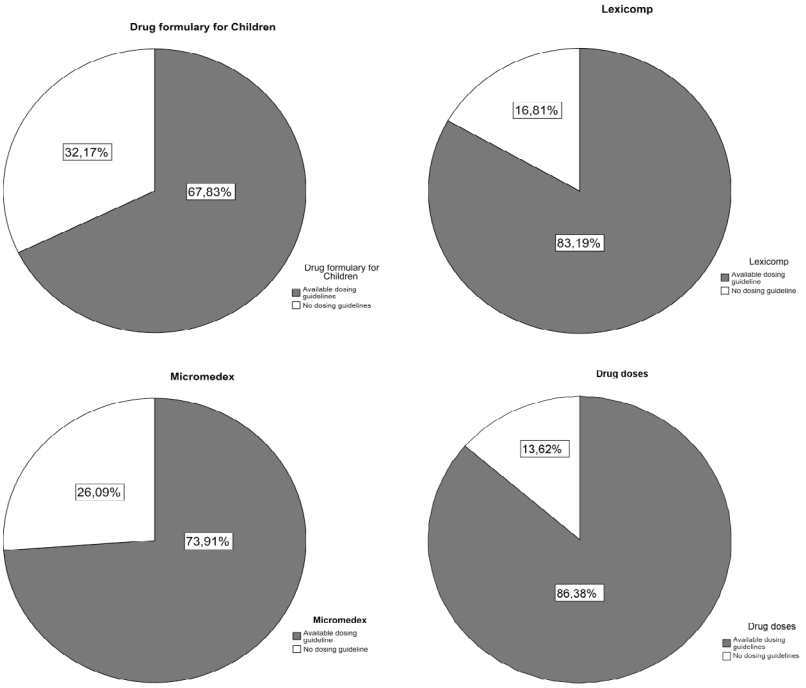

FIGURE 1. Availability of dosing guidelines of the 257 prescribed drugs on the ICU, in the four used formularies.

information only on transplacental passage of the drug to the fetus and no data on pediatric use (Table 3).[16]

Discussion

This study shows that the four selected drug formularies give dosing guidelines from 67.8% to 86.4% of the 257 drugs prescribed in our ICU. These guidelines diverge widely on various aspects. They reflect FDA status for the most and least frequently prescribed drugs. The coverage of drugs was associated with the number of prescriptions, with more information available for more frequently prescribed drugs and less variation between drug formularies with respect to the drug doses.

An important limitation is however, that not all studies that are used as basis for drug dosing guidelines are performed in the (sub) population of patients admit-

ted on the ICU. For example, the dosing guidelines of the FDA on midazolam are based on a study performed in pediatric patients undergoing CT scans[6], a different population than the critically ill patients admitted to the ICU.

In addition, even for frequently used drugs there are few pediatric studies. For example, analgesics have been evaluated by no more than one or two randomized clinical trials, which often lack power.[17,18] While it has been recognized that further research is needed, pediatric drug research still faces financial, regulatory, practical and scientific challenges.[19]

In recent years, both American and European legislation has aimed to stimulate the study of medicines for use in children. Still, one cannot expect that the information gap will be closed soon. In this context, we believe that specific pediatric formularies, based on the latest evidence and expert opinions, are mandatory.

They will enable physicians to provide the most effective and safe drug therapy in children. They may also serve to protect physicians legally when prescribing urgently needed drugs to children.[20]

The formularies studied were developed for different user groups. The focus of the Drug Formulary for Children is office-based pediatrics, whereas Drug Doses focuses on ICUs. This may perhaps explain the larger differences between these two as well as the higher total doses per 24 hours in Drug Doses. Micromedex® and Lexi-Comp® were not specifically developed for pediatric use, although both now have a large pediatric component. The geographical origin of the formularies differs as well, resulting in different marketing and labeling strategies as well as different 'culturally-determined' prescribing preferences (e.g. rectal formulations are less common in North America than in Europe). Also, the formularies differ with regard to evidence supporting the dosing guidelines. The Drug Formulary for Children and Drug Doses do not provide literature references at all.

A partial solution to this issue could be setting up a database of the literature references on which the dosing guidelines are based. It should be freely accessible, preferably online. The content would also allow physicians to create a personal formulary as advised by the World Health Organization (WHO) in their Guide to Good Prescribing.[21]

In addition to literature references, the rationale for the dosing guidelines should be given, as well as contact information to facilitate information sharing. Further

needed research could then be anticipated according to evident knowledge gaps. It would also reduce the need for individual hospitals to perform time- and money consuming literature search and to schedule Drug & Therapeutic committees meetings. Recently, the Dutch Knowledge Centre for Pediatric Pharmacotherapy (NKFK) launched a government sponsored, free online pediatric formulary in the Netherlands, largely based on these principles (www.kinderformularium.nl/search/index.php). Dosing guidelines are initially derived from the Drug Formulary for Children. In the near future, they will all be verified against existing evidence, adjusted if needed and provided with the relevant literature references. In case of absence of evidence to support the guidelines, expert opinion is used to decide on dosing guidelines. Currently, general consensus is reached in face-to-face meetings with a panel of experts (e.g. pediatric subspecialists, pharmacists, clinical pharmacologists and epidemiologists). Alternatively, Delphi surveys could aid this process of decision-making.[22]

Similarly, the British National Formulary for Children (BNFC) is a collective publication by the Royal College of Paediatrics and Child Health (RCPCH), British Medical Association, Neonatal and Paediatric Pharmacists Group and the Royal Pharmaceutical Society of Great Britain.[20] As the BNFC explicitly states that its main focus is not tertiary care, we did not include it in our analysis.

Even when FDA or other government labeling is available based on sufficient pediatric data, age restrictions are not always mentioned. Thus there is a risk that drugs are prescribed to children younger than the age group they are intended for. Pediatric data used to label drugs in children, may not be applicable to the patient population that is to receive the drug, such as critically ill patients. Furthermore, physicians should realize that data on less commonly used drugs often have been derived from retrospective case series or open label studies.

Our study may be limited in that we only searched four formularies. Nevertheless, as our selection represents a wide variety of properties (e.g. pocket book vs. digital, international coverage, commercial vs. academic, referenced vs. 'experience-based', pediatric-specific vs. non-pediatric specific) we believe that our findings may be generalized to other formularies. Another possible limitation is that we determined reliability of dosing guidelines for only the three most and three least prescribed drugs. Also we did not perform a complete systematic review for these six drugs. We do believe, however, that this exploratory search provides a relevant

overview of reliability of dosing guidelines in these formularies. To our knowledge no systematic reviews or randomized controlled trials have been published that unequivocally determine optimal drug dosing for drugs used in pediatric intensive care covering all ages. Our search more or less reflects what a physician could do in limited time, while juggling all other demands in a busy clinical practice.

Conclusions

In conclusion, this study points at challenges in the availability and reliability of pediatric drug dosing guidelines in present drug formularies. Physicians should be aware of the limitations of the use of these formularies in daily practice.

The lack of adequate and evidence-based dosing recommendations for pediatric intensive care patients reflects the lack of drug studies in this population. Many others have made a plea, too, for studies in this population that might improve the current practice of off-label and unlicensed prescription.

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Drug dosing in pediatric intensive care and in pediatrics in general
Authors reply

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We thank Drs. Degraeuwe and Van der Zanden for their response to our recent paper.[1] We appreciate their suggestions for possible solutions to some of the problems we identified.

As they argue, the 'different description' (e.g. mg/kg in 'x' doses vs. mg/kg/day, in 'x' doses or every 'x' hours, mg/kg/hour vs. mcg/kg/min and amount per kg vs. amount per square meter (m^2)) was discussed marginally. These differences in itself are indeed confusing and we believe that one consistent way of providing descriptions for children should be used. However, current state of evidence for pediatric drugs often can not lead to a clear choice in dosing frequency and therefore the Dutch pediatric formulary committee still chose to use mg/kg/d in 'x' doses whenever possible. In most English-language formularies the notation mg/kg/d q'x'h is used. As in many CPOE systems doses need to be entered as mg 'x' times per time unit, this also requires an additional calculation step (24/'x'h) in addition to the mg/kg calculation. We agree with authors that a 'mg/kg every 'x' hrs' notation needs less calculation and may thus be the safest.[2]

The issue of combination preparations with different compound ratios such as amoxicillin- clavulanic acid is addressed by Degraeuwe and van der Zanden by their suggestion that the full compound ratio should be used and is written down rather than the dose of only one of the compound. We fully agree to their proposed way of prescribing which not only clarifies the compound ratio but also reduces the risk of administration of only the prescribed compound (e.g. solely amoxicillin instead of amoxicillin- clavulanic acid).

We agree with the authors, that computerized physician order entry (CPOE) and prescription-writing tools have shown success in decreasing the number of prescriptions and orders written incorrectly. Nevertheless, they do not prevent dosing errors in pediatrics without significant pediatric-specific dosing logic.[3] A recent study looking at ambulatory pediatric prescriptions confirmed that a "computerized prescription writer" without dosing logic provided no prescription error reduction advantage over completely manual prescriptions.[4] Furthermore, CPOE will not prevent errors due to incorrect entry of a patient's weight: human error and software inadequacy can combine to make drug doses calculated by CPOE unreliable.[5]

To accept changes and have them assimilated into clinical practice, it is essential that strong evidence be available as a starting point. Hence, the decision, in the Netherlands to first develop evidence based pediatric dosing guidelines before adding a calculating tool. This is a very labor-intensive process. First, all available literature evidence for individual drugs is collected and a dosing proposal is prepared. Next, in a consensus meeting with up to 20 experts the dosing proposal for each drug is discussed and finalized. As of February 2010, evidence-based dosing guidelines are available for 420 (of 583 drugs). Although the dosing guidelines, together with references, are presented on the website as free text-based information in Dutch, a database containing all information is the source-document. Hence, technically, the combination of these data with a dosing calculator or CPOE system should be feasible, not only for the Dutch language area, but also more globally. We strongly support collaborative international efforts to provide evidence-based dosing guidelines in a safe prescribing environment for children. We wish that these efforts eventually result in safe and effective drug therapy for our most vulnerable children.

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PART 5

Future Perspectives

Our lives end as soon as we start being silent

about things that mean something to us

Martin Luther King

CHAPTER 5.1

General Discussion

Ceelie I, de Wildt SN, van Dijk M, Tibboel D

Introduction

This thesis concerns the question how to optimize pain treatment in young children. In this general discussion we give future perspectives on pain, assessment, treatment, pharmacovigilance and genetics in pain. In the final conclusion we propose a concept for future pain research.

Perspectives on pain have shifted over time. In ancient Greece, Plato thought that pain and pleasure arose from within the body, an idea that later became the concept that pain is an emotional experience rather than a localized body disturbance. In 1664 Rene Descartes combined the previous conceptions about pain into the 'bell theory'. He described the pain system as the 'bell' ringing mechanism in a church: when the bell-ringer tugs on the rope the bell high up in the tower will ring. This biological theory is now known as the specificity theory – it suggests that pain is caused by injury or damage to body tissue and that there is a link between pain and injury, and that the severity of the injury determines the amount of pain. In 1874 Wilhelm Erb challenged the specificity theory by stating that a pain signal can be generated by stimulation of any sensory receptor, if the stimulus is intense enough. His point of view is now known as the pattern theory. The pattern of stimulation, hence the intensity over time and the area, and not the receptor type determines the nociception. It has been recognized that neither the specificity theory nor the pattern theory fully grasps the experience of pain including its psychological aspects. In 1965 Wall and Melzack launched their 'Gate Control Theory' in which pain perception is influenced by several factors, which begin at the spinal cord.[1] In this theory, non-painful input can compete with painful impulses to reach the brain. This theory was the first to take physiological factors into account.[2,3]

The ancient Egyptians used both hemp and poppy juice to induce drowsiness – thereby facilitating surgery. It was not until 1846, however, before the first 'modern' anesthetic was introduced, i.e. ether. Chloroform was introduced in 1847. The founding father of anesthesiology, Snow, was one of the first physicians to calculate dose of chloroform and ether for surgery and published his book on chloroform administration in 1858. Postoperative pain was treated with opium and derivates. The German pharmacist Sertürner isolated morphine from opium in 1806. Cocaine was introduced in 1884 and soon thereafter used as local anesthetic. Harmon Northrop Morse synthesized paracetamol, as early as 1877, but it was not until 1887 that the pharmacologist Von Mering tested paracetamol on patients. He published

the results in 1893, concluding that paracetamol causes methemoglobinemia. It was not until 1948 that this conclusion was refuted, after which paracetamol could gained its present-day popularity.[3,4]

Thus, having reached a situation in which pain could be more efficiently treated, it seemed that only adults benefitted from the progress made. In 1985, the medical world was shocked by the death of a young premature neonate, Jeffrey Lawson, who was operated on for a patent ductus arteriosus, without analgesia during or after surgery. It was not until 1987 when the publication of Anand and Hickey made physicians aware that neonates are capable to experience pain and should be given pain killers a s a matter of course.[5]

Definition of pain

The International Association for the Study of Pain (IASP) has defined pain as follows '*Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain is always subjective*'.

Each individual is confronted with pain through injury in early life involving actual or potential tissue damage. It is unquestionably a bodily sensation, but also tends to be an unpleasant emotional experience.[6] Two types of psychological factors related to the adjustment to pain are important in the experience of pain. The first type includes factors associated with increased pain, such as pain catastrophizing, pain-related anxiety, and helplessness. The second includes factors associated with decreased pain, such as self-efficacy, pain coping strategies, readiness to change, and acceptance.[7]

Pain is a protective biological system essential for survival. However, once the physiological role of pain as a warning system has been fulfilled, it may become a very unpleasant symptom up to the degree of gaining disease character by itself. After tissue damage the following processes take place:

nociception → receptor activation → signal transduction → pain → pain behavior.

Loeser has graphically represented in a model the following four dimensions of pain: nociception, pain, suffering, and pain behaviour (see Figure 1).[8] The multifac-

eted nature of pain experience and treatment implies that interpretation of pain behaviour is not directly related to nociceptive stimuli.

Conclusion
In children, variability due to developmental changes in physiology, pharmacology and the expression of pain play a role in the existence and treatment of pain. In this thesis we studied several aspects of pain assessment and treatment in post-surgical neonates and infants.

1. Pain assessment

In 2001 The American Academy of Pediatrics pronounced on the relevance of pain assessment as follows: 'to treat pain adequately, ongoing assessment of the presence and severity of the pain and the child's response to the treatment is essential.'[9]

Compliance to behavioural pain instruments
The use and especially the compliance to pain management guidelines remain troublesome in daily practice, as we show in this thesis (Chapter 2.1). On our ward we use a postoperative pain protocol, designed to act on pain identified by validated pain scores (COMFORT-behaviour scale and the NRS-11) in several treatment steps. Almost 80% of all scores obtained in a one-year period indicated absence of pain or distress. But on the other hand, follow up of scores indicating the presence of pain or distress after surgery, complies to the protocol in only 15% of cases. These findings are in line with previous research by Grol and Grimshaw, who reported an average 10% effect of change with an intervention.[10] Various studies have identified facilitators and barriers for pain management protocols. Possible faciliators are one-on-one coaching, education, use of 'local champions' and monthly feedback to nurses and physicians on the number of assessments.[11,12]

Franck and Bruce found marginal evidence of reduced pain intensity after implementation of pain protocols.[13,14] This suggests that efforts to improve compliance to a pain protocol could not only reduce painful experiences but also improve clinical outcomes.

Next, the authors suggest one would do well to motivate caregivers and family members to recognize and to act on pain in others. Standardized pain protocols

might be useful in this respect. Health care professionals could less accurately identify infants' pain expressions than could non-professionals or parents.[15,16] However, empathic recognition of pain by health care professionals does not necessarily lead to better pain management.[17]

"Objective" measurement tools

A golden standard for pain assessment in non-verbal patients is lacking. Future research should focus on finding objective pain measuring tools – preferably physiological measures.[18] As early as 1959, Beecher phrased this as follows; 'there is a very great and understandable desire on the part of many people for objective indicators for subjective phenomena.' [19] Promising results have been reported of the use of noninvasive electroencephalography and neuroimaging techniques to measure somatosensory and frontal cortex activation.[20,21] One of these techniques, Near Infrared Spectroscopy (NIRS), detects subtle changes in oxygenation and deoxygenation of the hemoglobin in the brain. It is based on the assumption that increased tissue oxygenation represents an increase in regional cerebral blood flow. This is in turn associated with an increase in neuronal activity as seen in noxious events.[22,23] NIRS studies in premature infants indicated that painful stimuli cause circulatory and metabolic changes in specific cortical and subcortical regions.[20,23] Slater et al. found that infants with low behavioral pain scores do show corticol activities in response to acute painful stimuli. They suggest, therefore, that pain may be processed at the cortical level without producing detectable behavioural changes.[24] Bowsher stated that noxious stimulation activates cortical areas in the preterm newborn brain.[25] However, increased oxygen consumption and altered EEG are not necessarily the same as nociceptive response. Human infants can display distinctive behavioural and physiological spinal cord and brainstem responses to noxious stimuli. It is not clear, however, whether cortical neurons are specifically activated by these stimuli. Slater et al., using a new approach to time-lock an EEG recording to a heel lance, found a nociceptive-specific potential in newborn infants (35–39 weeks postmenstrual age) and suggested that these infants are capable to discriminate the sensory-discriminative aspects of pain experience.[21]

Another promising tool is the skin conductance algesimeter (SCA). It is based on the mechanism by which changes in emotions produce neurophysiologic arousal with increased activity in the sympathetic nervous system, causing a release of acetylcholine that acts on muscarine receptors, leading to a subsequent burst of

sweat especially in the palm and sole, and thus increased skin conductance. An increase of the activity can be used as a surrogate measure of stress.[26] The SCA reacts immediately and is not influenced by hemodynamic variability or neuromuscular blockade.[27] Recent research, however, showed several limitations. Increased perspiration through the skin may result in inadequate readings – suggesting pain when other assessments show no signs of pain. Furthermore, skin conductance may be correlated to skin temperature in all subjects. A study in infants suggested that sympathetic neural activity in order to maintain homeostasis (such as autoregulation of skin temperature) results in skin conductance peaks. Real-time evaluation of the sympathetic nervous system could be valuable for pain assessment. However, the technique should be better defined to increase both sensitivity and specificity for the measurement of pain before use in daily practice can be advocated.[28]

The bispectral index monitor (BIS) has been used to monitor the level of consciousness, mostly in children above the age of 1 year.[29] Research has shown that BIS values obtained during sedation or anaesthesia using the software based on adult electroencephalogram should be interpreted with caution in infants under the age of 1 year. Until new software becomes available, based on the electroencephalogram of infants, the use of BIS on the ICU in infants under the age of 1 year should be discouraged.[30]

Another device named accelerometer allows for continuous measurement of peripheral motor parameters through body-fixed sensors to discriminate between pain and no pain in hospitalized nonverbal infants. It was tested in a feasibility study on procedural (heel lance) and postoperative pain.[31] It was found that for both procedural and postoperative pain, the accelerometry-based pain indicators appeared better discriminators between pain and no pain than EMG-based pain indicators.

Alternative objective pain measures are pain imaging techniques such as fMRI and PET scans away from the bedside. PET scans performed solely for research reasons may, however, meet with ethical and practical obstacles, as they involve administration of a radioactive labelled drug, which is not allowed in young children. The visualization of pain by functional MRI (f-MRI) will be used in research setting mainly. Hohmeister et al. stated that due to maturation-related plasticity of the developing nociceptive system, neonatal nociceptive input induced by medical procedures may cause long-term alterations in pain processing. They used fMRI in

three different, but small, groups of school-aged children and adolescents (11–16 yr). Two groups had been hospitalized as newborns: patients born preterm (<31 weeks gestational age, N=9) or at full term (37 weeks gestational age, N=9). A control group consisted of full-term born children without early hospitalization experience (N=9). In response to tonic heat stimuli, the preterm but not the full-term earlier hospitalized children exhibited significant activations. In a number of brain regions such as thalamus, anterior cingulate cortex, cerebellum, basal ganglia, and periaquaeductal gray, preterm born children showed increased activity compared to controls. The preterms showed significantly higher activations than controls in primary somatosensory cortex, anterior cingulate cortex, and insula. This increased brain response was pain-specific.[32]

Conclusion

Up to now, hospitalized young infants' pain is typically assessed with behavioural pain instruments. The search, for objective tools that can easily be used in daily practice is ongoing. Pain assessment, (re-) assessment, and treatment if necessary have been implemented in postoperative pain protocols. Compliance to protocol dictated treatment has proven difficult in daily practice.

2. Pain treatment

Non-pharmacological treatment

When pain is suspected in preverbal patients, the first goal is to exclude other sources of discomfort such as a soiled diaper, and postural discomfort. A number of non-pharmacological therapies have been proven effective to treat mild to moderate pain and should precede pharmacological interventions. These therapies include non-nutritive sucking (with or without sucrose)[33,34]; kangaroo care[35]; music therapy[36], massage[37]; and multi-sensorial stimulation.[38] Other effective measures include noise control in the PICU; control of lighting to maintain the day and night pattern and the sleep-wake cycle; and massage.[39]

Pharmacological treatment

The major disadvantages of morphine are its often serious adverse events including hypotension,[40-43] and respiratory depression,[44,45] possibly resulting in protracted

clinical course. Hence, there is a need to find new approaches to reduce opioid exposure, while maintaining adequate analgesics. [46]

We have explored how we could minimize morphine use in postoperative patients aged 0-3 years by optimizing dosing guidelines.[47] We also studied the potential morphine sparing effect of paracetamol, as adult studies found a morphine sparing effect of the use of multimodal (or balanced) analgesics.[48] In our randomized controlled trial[49] patients were randomized to receive either rectal paracetamol or placebo on top of a morphine loading dose and continuous morphine infusion. We found no significant difference in total morphine consumption (p=0.60) due to the limitations of a high dosage background morphine infusion in all patients, which by protocol could only be decreased after the first 24 hours. A new intravenous paracetamol formulation (Perfalgan®) allows greater dosing accuracy and more rapid effect of onset than do oral or rectal formulations. [50-52] Multimodal approach combines smaller doses of opioids with non-opioids such as paracetamol, NSAIDs, NMDA antagonists (e.g. ketamine), α_2 adrenergic agonists (e.g. clonidine).[48, 53, 54]

In this thesis we present a study (Chapter 3.1) that found a 66% morphine sparing effect of intravenous paracetamol in neonates and infants under the age of 1 year following major non-cardiac surgery – without a significant increase in adverse side effects. [55] The results of our study are important as a reduced morphine dose potentially reduces the risk for opioid-related side effects. More importantly, intravenous paracetamol can be used as a primary analgesic instead of morphine, thereby inducing a worldwide alteration in postoperative pain management.

Dosing of analgesics

In the study reported in Chapter 3.1 we used the dosing guidelines for intravenous paracetamol available at the time the protocol was written (e.g. 30 mg/kg/day in 4 doses). Since then, new guidelines based on new pharmacokinetic and safety data dictated higher dosing (< 1 month 40 mg/kg/day in 4 doses; >1 month-1 year 60 mg/kg/day in 4 doses).[56] This means higher doses of intravenous paracetamol, without an increased risk of paracetamol-related hepatotoxicity. There is a real possibility for even further reduced morphine requirements – with the increased dose of 10 mg/kg (being slightly more than the equivalent of 1 dose) for patients under the age of 1 month, but 30 mg/kg (double the amount!) for patients over 1 month old.

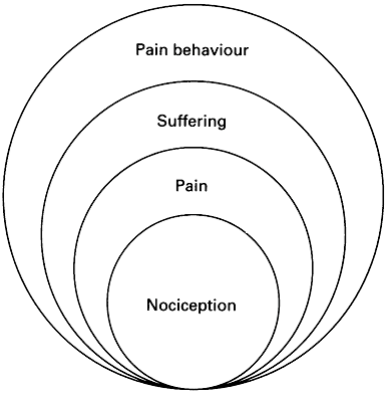

FIGURE 1. Loeser's multifaceted model of the components of pain.

Most drug doses for children have been established by extrapolating from adult doses, but need to be optimized.[57] This could be done with the use of sophisticated models using sparse samples such as NONMEM and new equipment for the detection of drug levels in little amounts of blood (such as the liquid chromatography, LC-MS).[58] Also, new legislation provides an elongation of manufacturer patent term of six months.[59]

Population pharmacokinetic–pharmacodynamic (PK–PD) models and simulations serve to develop more accurate pediatric dosing guidelines (see Figure 2). Simulations consist of; '(i) optimization of clinical trial designs based on preliminary data; (ii) development and internal validation of population PK–PD models using sparse data; (iii) external validation using independent data; and (iv) prospective clinical evaluation'.

The use of a multidisciplinary infrastructure for data-sharing minimizes the strain on individual patients but still gives maximum results especially when combined with modeling of effect (PD) pathways.[60]

For example, combining morphine doses and blood levels obtained in previous studies in one population pharmacokinetic model has resulted in a new dosing schedule, with age appropriate doses reflecting maturation of the main metabolic pathway glucuronidation.[58] As a proof of principle we performed a study using this dosing schedule in 0-10–day-old neonates (2.5 mcg/kg$^{1.5}$/hour) and older infants up to 1 year of age (5 mcg/kg$^{1.5}$/hour) The drug effect outcomes; e.g. the total

amount of morphine needed and rescue doses based on pain scores, still need to be evaluated. We anticipate that this schedule will optimize analgesic effects and will reduce side effects.[57,58]

Loco-regional techniques

Multimodal approach combines smaller doses of opioids with non-opioids to ensure maximal pain relief and minimal chance on adverse events although drug-drug interactions are possible.[48,53,54] Moreover, local and regional anesthesia have gained popularity, for use both in adults and children.[61]

Single-shot caudal epidural analgesia is the most used pediatric regional block, for its ease of performance, reliability, and safety especially in patients weighing over 10 kg.[62] Single shot caudal analgesia is relatively safe compared to general anesthesia. Under caudal (or spinal regional) anesthesia, children's hemodynamics are much less affected than under general anesthesia, postoperative ventilatory support is generally not required, oral intake starts earlier, stress hormones are not or marginally released, and additional postoperative analgesia is not needed in minor surgery.[63]

The ideal local anesthetic for pediatric epidural analgesia should have a rapid onset and an easily titratable duration of action with a reversible and selective blockade of sensory nerve conduction without risks of toxicity (both local (neurotoxic and myotoxic) or systemic (neurological and cardiovascular)).

Bupivacaine has been widely used to this aim. It exerts a comparatively long analgesic effect, but on the other hand may cause toxicity. Notably the younger age group is at risk for toxicity since large volumes are used in epidural infusions and decreased protein bindingcould delay its elimination.[64] Furthermore, accumulation due to hepatic immaturity may occur.[65] Regional blocks carry a high risk of intravascular insertion, even in the case of negative aspiration for blood [66] or when using ultrasound control[67].

The single-shot caudal epidural block is also not optimal because of its limited duration of action (90–120 minutes with bupivacaine).[68] Adding adjuvant may lead to side effects [68]. Furthermore, insufficient evidence is available on the safety of non-opioid adjuvants.[68,69]

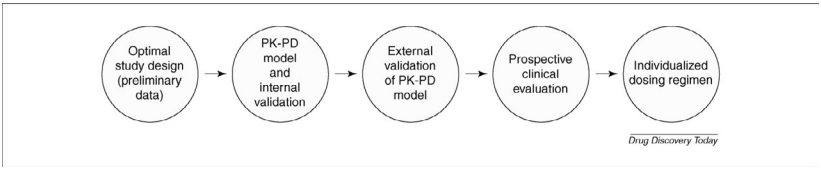

FIGURE 2. Proposed multi-step approach for modeling and simulation using nonlinear mixed effects modeling for the optimization of drug dosing in children. The four steps that are proposed are (1) optimization of clinical trial designs based on simulations using preliminary data; (2) development and internal validation of population
PK–PD models using sparse data; (3) external validation of the population PK–PD models using independent data; and (4) prospective clinical evaluation of the PK–PD model based dosing regimen. PK, pharmacokinetics; PD, pharmacodynamics.[60]

There is every reason, therefore, to further study epidural blocks in postoperative pain treatment. The pharmacokinetics in neonates is different compared to older children, however, and it is a challenge to find optimal doses with the least toxicity.

Developments in surgical techniques

In adults, type of surgical techniques proved to be associated with extent of postoperative pain: minimal access surgery (MAS) produced less pain than 'open' surgery. Similar trials in pediatric patients seem to contradict each other.[70] In our own retrospective cohort study (Chapter 3.2) in neonates undergoing either MAS or 'open' surgery – for congenital diaphragmatic hernia or esophageal atresia repair – postoperative opioid consumption did not significantly differ between type of operation.[71] We suspect, however, that patients in both groups might have been over treated, seeing that the then doses for postoperative morphine were higher than the doses currently used. Possible differences in opioid requirements might therefore have been obscured. However, MAS offers other benefits such as smaller scars and better visualization during surgery.[72] Validation of the advantage of MAS in repair of esophageal atresia in a multicentre cohort study seems feasible. A pilot study on the effects of MAS on NIRS, stress hormone profiles and analgesia consumption is ongoing. Furthermore, MAS is eminently suited for additional use of loco-regional techniques, which have not yet been fully integrated in standard practice for neonates.

Conclusion

Treatment of pain should always start with non-pharmacological measures. Then, if re-assessment documents the presence pain, pharmacological treatment is the next step. Dosing should be geared to the actual need of infants instead of using extrapolated data from adults. New models and sophisticated techniques such as the LC-MS offer the possibility to adjust dosing guidelines. Furthermore, multimodal analgesic treatment has proven to be effective, e.g. in the case of the morphine sparing potential of intravenous paracetamol. Next steps in pediatric analgesia should be to incline loco-regional steps and eventually the use of adjuvant therapy in loco-regional techniques. As the use of new surgical techniques, the opioid consumption was found not to differ between MAS patients and conventional surgery. The opioid consumption in these patients could benefit from the use of new analgesic regimens and the use of loco-regional techniques.

3. Pharmacovigilance

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[73] Pharmacovigilance is the process of identifying, monitoring, and effectively reducing ADRs on the short- and long term. Especially children are at risk to develop ADRs as dosing guidelines for much of the drugs used in children widely vary or are lacking at all.[74] All health-care professionals have a responsibility to inform their colleagues about clinically important ADRs that they detect; first by reporting them, and secondly by publishing case reports of suspected ADRs, even if a causal link is uncertain.[73,75]

ADRs are reported in national formal surveillance systems (Lareb in the Netherlands, MedWatch in the USA), which report back to the international service (WHO Uppsala Monitoring Centre). It is strongly suspected that not all ADRs are reported. As early as 1979 Dr Inman described possible reasons as the 'Seven deadly sins': ignorance ('I am unsure how to report'), diffidence ('I may appear foolish about reporting a suspected ADR'), fear ('I may expose myself to legal liability by reporting an ADR'), lethargy ('I am too busy to report ADRs'), guilt ('I am reluctant to admit I

- Only 26% knew which ADRs to report.
- 93% thought the reaction was too well known.
- 75% thought the reaction was trivial.
- 72% were uncertain whether a drug caused the reaction.
- 38% did not have enough time.
- 36% thought that reporting was too bureaucratic.
- 22% did not know how to report.
- 18% were not aware of the requirement to report ADRs.

FIGURE 3. Results of an attitudinal survey among Dutch physicians (general practitioners and specialists) regarding the voluntary reporting of ADRs and the contributing factors why ADR were not reported.[77]

may have caused harm'), ambition ('I would rather collect cases and publish them') and complacency ('only safe drugs are marketed').[76] Efforts have been directed at improving this situation but a 1999 survey among Dutch general physicians and specialists) revealed that the 'deadly sins' are still there (Figure 3).[77] Edwards and Aronson have proposed several methods to improve detection and prove associations (see Figure 4).[75] Nevertheless, health care professionals still have trouble recognizing and preventing these calamities.[78-80] Among the tools for identifying ADRs are objective causality assessment such as the Naranjo Probability Scale,[81] and the liver-specific Council for International Organizations of Medical Sciences / Roussel Uclaf Causality Assessment Method (RUCAM) scale for drug-induced liver injury (DILI).[82] The best way of identifying an ADR seems to be the resolving of symptoms after discontinuation of the suspected drug and recurrence of symptoms when restarting the drug (re-challenge). However, re-challenger may clash with ethics, and then the scoring lists such as the Naranjo and the RUCAM are of great value

Method	Advantages	Disadvantages
Anecdotal reporting (eg, in journals)	Simple; cheap	Relies on individual vigilance and astuteness; may only detect relatively common effects
Voluntary organized reporting* (doctors, pharmacists, pharmaceutical companies)	Simple	Under-reporting; reporting bias by "bandwagon" effect
Intensive event monitoring	Easily organised	Selected population studied for a short time
Cohort studies	Can be prospective; good at detecting effects	Very large numbers required; very expensive
Case-control studies	Excellent for validation and assessment	Will not detect new effects; expensive
Case-cohort studies	Good for studying rare effects with high power	As for cohort and case-control studies; complex calculations
Population statistics	Large numbers can be studied	Difficult to coordinate; quality of information may be poor; too coarse
Record linkage	Excellent if comprehensive	Time-consuming; expensive; retrospective; relies on accurate records
Meta-analysis	Uses data that have already been obtained	Need to obtain unpublished data; heterogeneity of different studies

FIGURE 4. Surveillance methods for ADRs and methods of proving associations[75] *Involving computerized systems

despite their limitations. Hence, other supporting evidence is very useful to determine the causality of an adverse drug reaction. The scientific study of chemical processes involving metabolites (metabolomics) reveals more and more specific biomarkers, for example for paracetamol intoxication, as shown in this thesis. Most institutions are using the Rumack-Matthews normogram to predict the chance of clinical toxicity. This normogram, however, is based on a single administration of paracetamol in adults.[83] It is useless when time of ingestion is unknown or when multiple doses are taken at different times. Paracetamol protein adducts, as novel biomarker for paracetamol toxicity, can shed light on those cases not complying with the Rumack-Matthews nomogram, resulting in a better prediction of hepatotoxicity and the need for NAC (N-acetylcysteine). Even in cases where ingestion has been over 12 hours ago, the protein adducts can be measured and in case of high levels treatment with NAC can be started.[84,85] We were able to identify paracetamol as a very probable cause for hepatoxicity in two children with myopathies using paracetamol adducts. We recommend, therefore, monitoring paracetamol use in children with myopathies more diligently. Valid biomarkers confirming ADRs are not available yet for all drugs. As proteomics is expected to yield such biomarkers, we recommend drawing blood and storing it for future determination in case of suspected ADRs.

A new promising technique in the field of drug research is fibroblast-derived induced pluripotent stem cells (iPSC). Instead of initially testing of drugs on animals, drugs can be tested on cells grown from iPSC. Those drugs that appear to be tolerated and safe can then progress to testing on animals and finally, humans.[86]

Reducing medication errors is an important mean to improve patient safety and to avoid ADRs. To reach this goal, clinicians are expected to follow the 'the five rights': the right drug, the right dose, the right route, the right time and the right patient.[87] Getting the dose right is especially challenging in pediatric patients. For many drugs, the right dose at different ages is unknown, moreover calculations including size, e.g. body weight or body surface area, are prone to mistakes.

Off-label (outside the terms of the product license) and unlicensed (not registered for use in the respective country at all) use of drugs in pediatric ICUs is a reason for concern, as these patients' lives often depend on adequate treatment. A 2002 study in general practices and general pediatric wards and ICUs in the Netherlands showed, however, that 30% to 68% of drugs prescribed to children were off-label

or unlicensed.[88] To prevent errors in dosing, guidelines must be available. We found that for patients on the pediatric ICU dosing guidelines widely differ between drug formularies, if dosing guidelines even exist at all.[74] It is therefore imperative that guidelines be derived from existing data from investigator-initiated and industry studies in children and made available in easily accessible drug formularies. Such an approach has been taken in the case of the Dutch pediatric formulary. The use of this formulary internationally should be encouraged.

Conclusion

For medication safety it is essential that ADRs be reported, even if a causal link is uncertain. Several tools have been developed to determine the cause of an ADR, but they are still being underreported. New methods to prove causality between ADRs and drugs are found- biomarkers can be helpful as shown with the paracetamol protein adducts in paracetamol induced hepatotoxicity. Collecting blood samples from patients with suspected ADRs for future detemination should be promoted.

4. Genetics in pain and pharmacogenetics

We showed that most of the postoperative neonates and infants in our ICU are adequately treated and are pain free. However, there are exceptions; some are over sedated or still in pain using the standard dose and need additional drugs. A higher or lower intensity of pain is very likely to require higher or lower doses of analgesics for efficacious therapy. Pain thresholds, perception and processing are genetically controlled and are therefore likely to modulate analgesic therapy. The clearest example of genetic control of pain is the presence of mutations that cause congenital insensitivity to pain.

Genetics of pain

Six distinct rare hereditary syndromes causing congenital insensitivity to pain have been identified. One is the 'channelopathy-associated insensitivity to pain' syndrome caused by variants in the *SCN9A* gene coding for the α-subunit of the voltage-gated sodium channel. The five others are the hereditary sensory and autonomic neuropathy (HSAN) syndromes I–V.[89] These are characterized by various mutations in several genes causing pathologic changes in peripheral nerves.

It remains unclear how the *SCN9A* gene functions, although it appears to serve as a universal amplifier for nociceptive pain. This gene could be of interest in the development of analgesics, since people with complete knock out of the gene are healthy but are incapable to experience pain. This means that if a drug could be developed that blocks the activity of *SCN9A* or its protein product, Nav1.7, it would not have any side effects. One confusing aspect of the gene is that while humans without a functioning *SCN9A* gene are essentially healthy, apart from the inability to sense pain and to smell, mice that have been engineered to lack the *SCN9A* gene die soon after birth.[90] So far it has been very difficult to develop drugs—small molecule blockers or specific antibodies—that target only *SCN9A* and do not block the other proteins.[91,92]

To enhance further research in the pain genetics field, the Pain Genes Database gives access to all published pain-related phenotypes of mutant mice, as transgenic knockout mice are a tool for pain researchers to examine the function of genes of interest. The information is useful to generate novel hypotheses regarding the roles of genes and their protein products in pain processing and modulation.[93] (http://paingeneticslab.ca/4105/06_02_pain_genetics_database.asp)

Pain in the average population is controlled by fairly frequent genetic variants (allelic frequencies 10–50%). Each of them, however, modifies the pain phenotype to only a modest degree, and most information so far has been derived from experimental pain models.[94]

Pharmacogenetics

Inter-individual variation in response to opioids is a well-known phenomenon. Variation occurs in the required dose, the analgesic efficacy, and also in the occurrence of ADRs. No clinical factor has been identified that can predict this variation. Data on modulating SNPs is available, but results are not reproducible or conflict with one another. For example, SNPs in COMT (catechol-O-methyltransferase) MC1R (melanocortin-1 receptor) OPRM1, are believed to alter nociception and pharmacodynamics.[94]

The COMT gene codes for catechol-O-methyltransferase, an enzyme involved in the metabolism of catecholamines such as adrenaline, noradrenaline and dopamine.

COMT haplotypes associated with higher COMT activity were associated with a lower pain sensitivity in adults[95,96], although this association was not reproduced in another study.[97] The most commonly studied polymorphism in this gene is Val158MetMDR-1, also known as ATP-binding cassette B1 (ABCB1), which is responsible for p-glycoprotein, which regulates the transport (efflux) of morphine from the brain into the blood across the blood-brain barrier.

Seventy-five percent of the persons with a red-head-pale-skin phenotype carry two or more inactivating variants of the melanocortin-1 receptor gene (MC1R). These result in loss of function MC1 receptors due to impaired G-protein coupling. One study in adults holds that these carriers have a 1.3 times higher tolerance to electrical pain stimuli than controls with functional MC1Rs.[98] However, this association was not found in another study.[99] Women with two nonfunctional variant alleles of the MC1R displayed significantly greater opioid analgesia than women carrying only one or none MC1R variant.[98]

OPRM is the gene that codes for μ-opioid receptor, and therefore a natural candidate gene in pain research, as morphine and other opioids exercise their effects primarily through this receptor. The clinical relevance of OPRM A118G is difficult to interpret at this point. There are a number of inconsistencies in the results of studies in this area.

Genetic factors act via pharmacodynamic interferences that may cause decreased effects of analgesics. The μ-opioid receptor is the clinically most relevant target of opioid analgesics.[100] From the fact that the OPRM1 gene is highly polymorphic[101], one would expect that opioids should be almost ineffective in carriers of those polymorphisms. However, ineffectiveness was not shown due to the very low allele frequency. Only the OPRM1 variant 118A>G SNP, which causes an amino acid exchange of the aspartate with an asparagine, was found to influence the μ-opioid receptor in that it may decrease μ-opioid receptor expression or signaling.[102,103]

The glucuronidation of morphine is mainly mediated by the UDP glucuronosyl transferase (UGT) 2B7 [104,105], for which a couple of genetic polymorphisms have been described. Polymorphisms of the UGT2B7 gene are functional and have been

associated with altered plasma concentration ratios of opioids and their glucuronide metabolites.[106]

Genetic research

The pharmacogenetic studies of opioids highlight two of the main concerns in this field: (1) clinical phenotype definition and (2) sample size. The heterogeneity in the classification of study outcomes in these studies makes it almost impossible to compare data.

Pain and its genetic profile are a complex trait. Genes involved in this complex trait have the following characteristics:

- The chance that multiple genes are involved is high since single genes will make a relatively small contribution to the overall likelihood of pain development
- Gene variants will be common polymorphisms rather than rare mutations
- Complex, gene-environment interactions will be the rule rather than the exception
- Other genetic variances are hard to find due to the complex trait.

It is recommended to perform future studies in large groups of patients with the same subtype of pain (e.g. chronic, acute or neuropathic) and as less biased as possible – for example patients on the ICU, who mostly will have postoperative pain. It is a problem, however, to obtain the correct sample sizes as indicated by power calculations. We therefore suggest collecting DNA samples from all postoperative patients receiving analgesics. Bias should be limited by using validated pain assessments in a postoperative pain protocol for rescue medication and/or tapering. DNA samples of patients in whom ADRs occurred, and of non-responders or fast-responders to analgesics can be used for epigenetic research. This involves modifying the activation of certain genes but without modifying the basic structure of DNA. Furthermore, the chromatin proteins associated with DNA may be activated or silenced. This explains why the differentiated cells in a multi-cellular organism express only the genes that are necessary for their own activity. Epigenetic changes are preserved when cells divide and can be inherited.[107] Additional data on disease severity should be obtained, as recent papers showed a possible relation between disease severity and drug requirements.[108] Finally, collaborations with other hospitals should be formed to ensure sufficient sample sizes.

Conclusion

Genetic aspects of pain partly explain insensitivity to pain syndromes and may serve as a starting point for the development of new analgesics. Pharmacogenetics can help understand why certain patients need more or less analgesics than most others. However, we are still far away from determining individualized optimal analgesic dosing based on genetic constitution.

5. Conclusion

In this thesis we showed that he assessment and treatment of pain in non-verbal children is a challenging task but with room for improvement. Assessment relies on validated pain tools, implemented in pain protocols. In the absence of objective pain measurement tools, these remain the standard in clinical use. Further evidence to optimize guidelines on pain protocols is needed, also to improve adherence to pain protocols.

Progress has been made in the pharmacological treatment of neonates and infants. More evidence has become available on multimodal pain treatment, such as the morphine sparing potential of intravenous paracetamol. The use of epidural analgesics in neonates is expected to be a further step in progress, enabling optimization of opioid doses.

The main reason why pediatricians are searching for alternatives to opioids is the frequent occurrence of adverse drug events. In this thesis we describe such events noted after administration of morphine and paracetamol. These examples make clear that adverse drug events need to be reported and preferably also published to increase awareness. We recommend that in all (suspected) cases blood samples should be taken for evaluation of biomarkers, now or in the future. This could also apply to pharmacogenetics. Large numbers of blood samples are needed to evaluate genetic profiles in relation to analgesic drug concentrations and their effects.

There is still much to be done to elucidate the whole process of pain and its treatment. Analgesic RCTs with enough power are necessary to establish optimal dosing guidelines, and these should include a critical appraisal of possible side effects.

Moreover, the long-term effects of (prolonged) pain and the use of opioids should be further studied, as well as withdrawal effects. Ideally, pain research should make use of standard clinical parameters. These are;

- Validated population-specific pain assessment tools, incorporated in a pain protocol that dictates both assessment and treatment.
- Stress markers such as cortisol and (nor-) epinephrine blood levels
- DNA sampling for genetic constitution in pain as well as pharmacogenetic profiles
- Drug metabolism; plasma drug levels and excretion products. In cases of (suspected) adverse drug events, blood samples should be obtained for biomarkers.
- Neurophysiological measurements such as EEG and somatosensory responses.

Considering there is no golden standard for the optimal treatment of pain in non-verbal patients, we dare say that the research presented in this thesis adds at least a thin layer of gold in the way of achieving better pain treatment – and preferably pain prevention – in neonates and infants.

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PART 6

Appendices

Als ik had gewild dat je het zou begrijpen,

dan had ik het wel beter uitgelegd

Johan Cruyff

CHAPTER 6.1

Summary/ Samenvatting

Summary

Children benefits of adequate pain treatment. Nevertheless, evidence-based treatment guidelines are largely lacking. In this thesis we aimed to provide insight in the assessment of pain by evaluating adherence to a postoperative pain treatment protocol, describing side effects of regularly used drugs on the ICU, and evaluating whether surgical techniques as minimal access techniques are less painful. Finally we provide evidence of the morphine-sparing potential of intravenous paracetamol in young infants and neonates after major non-cardiac surgery.

In order to adequately treat and study pain in children, validated assessment of pain is of utmost importance. In **Chapter 1.2** we describe different methods for the assessment of pain in non-verbal children. In **Chapter 1.3**, we discuss endpoints that can be used in pain studies. These do not only include pain assessment, but also the need for analgesics and their disposition.

Optimal treatment consists of several steps; (re-)assessment with appropriate assessment tools, (non-) pharmacological treatment with preferably evidence based dosages and follow up. Challenging tasks in assessment include 1. finding a pain assessment tool that is effective and appropriate for the specific subpopulation; and 2. implementing pain treatment protocols in daily practice. Implementation is a process that requires ongoing education, commitment of nurses or physicians to check compliance, and face-to-face contact with practitioners to promote enthusiasm. In **Chapter 2.1** we evaluated the compliance to our postoperative pain algorithm. This is a treatment decision-tree based on scores obtained with the validated pain assessment tools COMFORT- behaviour scale and numeric rating scale-11 (COMFORT-B and NRS-11). We evaluated all scores obtained over a one-year period that signaled pain (either high NRS and low COMFORT-B or high NRS and high COMFORT-B) or distress (high COMFORT-B and low NRS). We then established whether the indicated action was undertaken. The first step is non-pharmacological action, followed when needed by pharmacological treatment and always followed by reassessment. Morphine is administered in case of pain; midazolam in case of distress. We evaluated records of 200 children with a median age at surgery of 98 days (IQR 6-320). A mean of 11 assessments per patients in the first 72 hours postoperative had been recorded (SD 6; total 2103). Pain scores suggested comfort in 1675 assessments (79.7%), not requiring any action. Drug treatment was provided by protocol in 27.8% of the remaining 428 assessments.

No more than 39.7% of protocol-dictated reassessments had been performed, with a significant better compliance during the evening shift (45.2%) compared to the day (22.3%) and night shifts (33.7%) (Chi-square test p=0.01). More than half of the non-ventilated children (58.3%) never received protocol-dictated medication versus 37.0% of the ventilated children (p=0.024). Overall, in almost 85% of all episodes of pain, the postoperative pain protocol was violated, indicating poor compliance. The patient's sex, age, and mechanical ventilation had no significant influence on compliance. Although compliance was marginal in case of pain or distress, the postoperative pain protocol applied in our ICU appears to be effective as scores indicated that most patients (79.7%) were comfortable during the postoperative period.

To date, morphine is the preferred primary analgesic in major surgery. Its use is associated, however, with significant adverse drug reactions such as respiratory depression, extreme sedation, nausea and vomiting. Therefore, drug regimens reducing morphine doses while reaching adequate analgesia might result in safer therapy. In **Chapter 3.1** we evaluate the morphine sparing effect of paracetamol in children under the age of 1 year undergoing non-cardiac thoracic or abdominal surgery. Patients were randomized to receive intravenous paracetamol or morphine as primary analgesic, with morphine as rescue medication. We enrolled 74 patients, of which 33 received paracetamol and 38 morphine; three patients were excluded. The most frequent procedures were closure of congenital diaphragmatic hernia, intestinal atresia and esophageal atresia repair, with no significant differences between both groups in patient characteristics.

Intravenous paracetamol was significantly morphine sparing. In the paracetamol group, the cumulative morphine dose was 66% lower than that in the morphine group [121 (IQR 99-264) mcg/kg vs. 357 (IQR 220-605) mcg/kg, p< 0.001). Results were similar when two age groups were considered separately (reduction in cumulative morphine dose of 49% for the neonates 0-10 days (p=0.002) vs. 73% for infants > 10 days (p< 0.001). The total number of patients receiving rescue morphine medication did not differ between the morphine and the paracetamol group (23 vs. 22 patients, p=0.59). Neither the total dose of rescue morphine, nor the number of rescue morphine interventions (bolus or infusion start/increase) differed significantly between the two treatment groups. Again, the results were similar when both age groups were considered.

Adverse drug reactions did not differ significantly between both study groups, although naloxone was given three times in the morphine group and not at all in the paracetamol group (p=0.10), while all patients received a morphine loading dose during surgery. The median numbers of NRS-11 and COMFORT-B scores did not differ between the paracetamol and the morphine groups.

In **Chapter 3.2** we studied if minimal access pediatric surgery (MAS) in neonates undergoing surgery for the repair of esophageal atresia (EA) or congenital diaphragmatic hernias (CDH) would be less painful postoperatively than open surgery. In a cohort study with controls, we evaluated the cumulative amount of postoperative opioids as a measure for postoperative pain. Mean cumulative opioids doses were compared at 12, 24, 48 hours and 7 days postoperatively. Twenty-four surgery patients (14 EA; 10 CDH) were matched to forty-eight control patients (28 EA; 20 CDH). Patient characteristics, except for duration of MAS (being significantly longer than that of open surgery, p=0.002 for EA and p= 0.017 for CDH) did not differ significantly between groups. Median cumulative opioid doses did not significantly differ between patients (EA and CHD) who underwent MAS and the controls at any postoperative time point. In conclusion, our data do not support a reduction of postoperative pain as reflected by postoperative opioid consumption by the use of MAS instead of open surgery, at least in newborns.

Rational drug therapy does not only constitute effective, but also safe therapy. This topic is addressed in Chapter 4. **Chapter 4.1** describes morphine induced muscle rigidity and laryngeal spasm in a 2-day-old term neonate. This resulted in acute respiratory failure on two separate occasions after morphine administration following surgery for anorectal malformation. Administration of the opioid antagonist naloxone immediately resulted in a patent airway and spontaneous breathing. An objective causality assessment using the Naranjo Probability Scale revealed that the adverse drug reaction was highly likely to definitely due to the administration of morphine. Cases of muscle rigidity following fentanyl have been described in the literature but morphine related cases have not been reported up to now.

In **Chapter 4.2** we determined the likelihood that recommended doses of paracetamol are associated with acute liver failure (ALF) in patients with myopathies. Initial causality analysis using the Roussel Uclaf Causality Assessment Method (RUCAM) for drug-induced liver injury (DILI) and in combination with a literature review, pointed towards two other anesthetic drugs as possibly related to

the ALF. The RUCAM has a high reproducibility and validity for drug-induced liver injuries. To strengthen the causality for paracetamol, paracetamol protein adduct levels were determined.

Both patients (Patient A: 12-year-old, 40-kilogram girl with spinal muscular atrophy (SMA) type II and patient B: 17-year-old, 55-kilogram girl with congenital muscular dystrophy, carnitine deficiency) developed ALF in the presence of therapeutic doses of paracetamol and the absence of toxic levels. Paracetamol adduct formation correlates with toxicity in experimental models of paracetamol toxicity and in paracetamol overdose patients, even in the absence of toxic paracetamol blood concentrations. The serum paracetamol protein adduct levels (patient A 260-150 nmol/ml, patient B 110 nmol/ml) were consistent with the values previously reported in children with ALF following paracetamol overdoses. Causality assessment of our cases was repeated with these results, again using the RUCAM scale. This confirmed a probable relationship between paracetamol and ALF for both patients (RUCAM +6 and +8 for patient A and B, respectively).

A literature search revealed two relevant papers, containing reports on three patients, two adults and one 12-year-old child with myopathies who developed ALF after recommended doses. Another patient was found by personal communication; a 12-year-old boy with SMA type II who developed ALF, necessitating liver transplantation. The underlying mechanism in the development of APAP toxicity in patients with myopathies is unknown. Gluthatione depletion due to relative malnutrition, inflammation and/or mitochondrial dysfunction could be contributing factors.

As most drugs used in the pediatric intensive care unit (ICU) are prescribed off-label, often on the guidance of limited information from commonly used drug formularies, prescribing the right dose, is often a challenge for the pediatric intensivist. This may reduce the risk of therapy failure and drug toxicity. The aim of the study in **Chapter 4.3** was to evaluate availability and reliability of pediatric drug dosing guidelines for intensive care patients in selected formularies. Availability of dosing information was evaluated for drugs prescribed during a one year period on a pediatric ICU. Dosing guidelines were compared among four formularies frequently used in the ICU (Micromedex®, LexiComp®, Drug Formulary for Children, Drug Doses). Reliability of dosing guidelines was assessed by evaluating labeling status and literature data for the three most (midazolam, acetaminophen and amoxicillin/clavulanic acid) and the three least (bosentan, ketanserin and iloprost) prescribed

drugs. The selected formularies covered only 68-86% of all 257 prescribed drugs. Guidelines differed widely on daily doses per kilogram, dose description, dosing regimen and age range for drugs prescribed in the ICU. Physicians should be aware of the limitations of these formularies for daily practice use.

Chapter 5 contains a general discussion and options for future pain management and research in infants and children. These recommendations for optimal pain assessment consist of gaining more evidence through research on effectiveness of guidelines. In the absence of a 'golden standard' with regard to objective assessment several measurement tools are reviewed. Suggestions on future pharmacological research is proposed- from optimizing the use of known analgesics in neonates and children to new techniques such as the loco- regional techniques, this in addition to our study proving intravenous paracetamol can be used as primary postoperative analgesic.

To further elucidate the occurrence of ADRs we propose that in case of any suspected ADR bloodsamples are obtained to determine biomarkers. The same held true for blood samples for the determination of DNA in the light of pharmacogenetics, to improve future pain treatment in neonates and infants.

Samenvatting

Hoewel kinderen profiteren van een adequate pijnbestrijding, ontbreken de 'evidence based' richtlijnen. In dit proefschrift wordt getracht inzicht te verschaffen in de mate van compliance van een postoperatief pijnprotocol, worden bijwerkingen beschreven van enkele veelgebruikte medicamenten op de intensive care (IC) en wordt de pijnlijkheid van een nieuwe operatieve methode geëvalueerd. Tenslotte wordt het morfine sparende effect van intraveneuze paracetamol in pasgeborenen en kinderen onder het jaar, na operatieve ingrepen aan de thorax of het abdomen beschreven.

Voor de effectieve behandeling en evaluatie van pijn in kinderen zijn gevalideerde pijnscores van essentieel belang. In **Hoofdstuk 1.2** beschrijven we verschillende methoden voor het scoren van pijn in preverbale kinderen. In **Hoofdstuk 1.3** worden eindpunten die gebruikt kunnen worden in pijnstudies besproken. Deze eindpunten bestaan uit methoden voor het meten van de pijn, de analgetica en hun werkingsmechanismen.

De optimale behandeling van pijn bestaat uit meerdere stappen. Ten eerste de (her-)score van pijn met de juiste, op de patiënt afgestemde methode, en de daarop volgende farmacologische behandeling met doseringen die gebaseerd zijn op leeftijd en gewicht. Ten tweede de follow-up van de behandeling. De uitdagingen die betrekking hebben op de pijnscores zijn het vinden van de pijnscore die specifiek is voor de subpopulaties zoals die op de IC opgenomen zijn en de implementatie van de pijnscores in een pijnprotocol welke ook de behandelstappen benoemd. Deze implementatie is een moeilijk proces wat continue aandacht behoeft door educatie van alle betrokkenen en het vervolgen van de compliance. In **Hoofdstuk 2.1** evalueren we deze compliance van ons postoperatieve pijnprotocol. Dit protocol bestaat uit gevalideerde pijnscores; de COMFORT- behaviour scale en de numeric rating scale-11 (COMFORT-B en NRS-11). Alle scores gedurende een jaar welke op pijn (hoge NRS en lage COMFORT-B of een hoge NRS en een hoge COMFORT-B) of onrust duiden (hoge COMFORT-B en lage NRS) zijn verzameld. Geëvalueerd werd of de scores gevolgd werden door de juiste stappen volgens het postoperatieve pijnprotocol; een (niet) farmacologische actie en herevaluatie van de pijn door een herhaalde score. In geval van pijn wordt morfine toegediend, in geval van onrust midazolam. De 2103 scores van 200 patiënten werden geëvalueerd, waarbij er in de studieperiode van 72 uur postoperatief 11 scores (SD 6) per patiënt werden

verricht. In een ruime meerderheid van de scores (1675; 79,7%) was er geen sprake van pijn. Wanneer er sprake was van hoge scores (428; 20,3%) die op pijn of onrust wezen werd het protocol slechts in 66 scores (15,4%) gevolgd. De leeftijd van de patiënten, het geslacht en of patiënten beademd werden was niet van invloed op de mate van compliance. Ondanks dat de compliance niet optimaal was lijkt het postoperatieve pijnprotcol in de praktijk wel degelijk te werken, met bijna 80% van de scores die op de afwezigheid van pijn duiden.

Op dit moment is morfine het analgeticum van eerste keuze na een grote operatie. Het gebruik van morfine is geassocieerd met ernstige bijwerkingen zoals ademhalingsdepressie, oversedatie, misselijkheid en braken. Daarom wordt er gezocht naar medicatie die het morfine gebruik verminderd of geheel overbodig maakt. In **Hoofdstuk 3.1** wordt het morfine sparende potentieel van intraveneuze paracetamol bij kinderen onder het jaar onderzocht na een grote abdominale of thorax operatie. Patiënten werden gerandomiseerd voor oftewel intraveneuze paracetamol of morfine postoperatief. In beide groepen werd morfine als rescue medicatie toegediend, indien de pijnscores hiervoor aanleiding gaven. 74 patiënten werden geïncludeerd, waarvan 33 voor intraveneuze paracetamol en 38 voor morfine, 3 patiënten werden geëxludeerd. De meest voorkomende operatieve ingrepen waren correctie van een congenitale hernia diafragmatica, intestinale atresieën en herstel van een oesofagus atresie. Patiënt karakteristieken in beide groepen waren niet significant verschillend.

In de intraveneuze paracetamol groep was er sprake van een significante reductie van 66% in de totale morfine behoefte, in vergelijking met de morfine groep [121 (IQR 99-264) mcg/kg vs. 357 (IQR 220-605) mcg/kg, $p< 0.001$]. De resultaten waren vergelijkbaar wanneer de twee leeftijdscategorieën (jonger en ouder dan 10 dagen) in beschouwing werden genomen. Een reductie van 49% ($p=0.002$) in de 0-10 dagen groep vs. 73% reductie in de groep ouder dan 10 dagen ($p< 0.001$).

Het aantal patiënten dat rescue morfine nodig had verschilde niet significant tussen beide groepen (23 vs. 22 patiënten, $p=0.59$). De totale hoeveelheid rescue morfine of de hoeveelheid extra handelingen verschilden eveneens niet significant. Ook verschilden de resultaten niet significant wanneer beide leeftijdscategorieën werden vergeleken.

Het aantal bijwerkingen in beide groepen verschilden niet significant. Drie patiënten in de morfine groep hadden naloxone nodig in verband met een adem-

halingsdepressie. Er traden geen verschillen op in de mediaan van de pijnscores, te weten de NRS-11 en de COMFORT-B scores.

In **Hoofdstuk 3.2** wordt een cohort studie met controle patiënten beschreven. Hierin wordt onderzocht of minimal access surgery (MAS) in neonaten die geopereerd worden voor de correctie van een oesofagus atresie (EA) of een congenitale hernia diafragmatica (CDH) minder pijnlijk is in vergelijking met de conventionele technieken. Geëvalueerd werd de cumulatieve hoeveelheid opiaten die patiënten 12 uur, 24 uur en 7 dagen postoperatief nodig hadden. Vierentwintig MAS patiënten (14 EA; 10 CDH) werden gekoppeld aan 48 controle patiënten die middels conventionele technieken waren geopereerd. De patiënt karakteristieken verschilden niet, behoudens de duur van de operatie, welke significant langer bleek te zijn in de MAS patiënten (p=0.002 voor de EA en p= 0.017 voor de CDH patiënten). De gepresenteerde data toont niet aan dat MAS minder pijnlijk zou zijn dan de conventionele operatieve technieken, gemeten aan het totale postoperatieve opiaten verbruik.

In **Hoofdstuk 4.1** wordt een twee dagen oude neonaat beschreven die een morfine geïnduceerde spierrigiditeit met larynx spasme ontwikkelde. Op twee separate momenten na morfine toediening ontwikkelde de patiënt een respiratoire depressie. Toediening van naloxone resulteerde in onmiddellijk herstel van de ademhaling. De Naranjo Probability Scale liet een duidelijk verband zien tussen de ademhalingsdepressie en het morfine gebruik. In de literatuur waren al eerder patiënten met spierrigiditeit na fentanyl gebruik beschreven maar na morfine was dit fenomeen niet eerder beschreven.

In **Hoofdstuk 4.2** wordt de mogelijkheid dat paracetamol in therapeutische doseringen kan leiden tot acuut leverfalen in myopathie patiënten onderzocht. Voor deze analyse werd de Roussel Uclaf Causality Assessment Method (RUCAM) for drug-induced liver injury (DILI), in combinatie met een literatuur review uitgevoerd. De RUCAM liet een mogelijk verband zien, wat verder geanalyseerd werd door bepaling van de paracetamol protein adduct spiegels.

Beide patiënten die worden beschreven ontwikkelen een acuut leverfalen na therapeutische paracetamol doseringen, in afwezigheid van toxische spiegels. Patiënt A is een 12 jarig, 40 kilogram wegend meisje, bekend met een SMA type II en patiënt B is een 17 jarige, 55 kilogram wegend meisje met een congenitale musculaire dystrofie en een carnitine deficiëntie.

De vorming van paracetamol adduct is gecorreleerd aan toxiciteit, zelfs in de afwezigheid van toxische paracetamol spiegels. In de beschreven patiënten waren de serum paracetamol protein adduct spiegels consistent met eerder beschreven toxische concentraties- patiënt A 260-150 nmol/ml, patiënt B 110 nmol/ml. Evaluatie met behulp van de RUCAM schaal bracht een mogelijk verband tussen het optreden van acuut leverfalen en het paracetamol gebruik aan het licht.

In de literatuur werden eerder drie patiënten met myopathieën beschreven die acuut leverfalen ontwikkelden na therapeutische doseringen van paracetamol, en een vierde patiënt werd persoonlijk medegedeeld. Het onderliggende mechanisme waarop de patiënten met een myopathie acuut leverfalen ontwikkelen na therapeutische doseringen paracetamol is onbekend, er wordt gespeculeerd dat een gluthathion depletie, relatieve malnutritie, inflammatie of een mitochondriële dysfunctie aan de basis kunnen liggen.

De meeste medicatie op de pediatrische intensive care worden off-label voorgeschreven. Door de marginale beschikbare informatie in veel gebruikte formularia is het juist doseren van medicatie een uitdaging. In **Hoofdstuk 4.3** wordt een studie beschreven die als doel heeft om de beschikbaarheid en betrouwbaarheid van de doseringsadviezen van enkele veel gebruikte formularia te evalueren, te weten Micromedex®, LexiComp®, Drug Formulary for Children en Drug Doses. De betrouwbaarheid van de doseringsadviezen werden onderzocht door literatuurevaluatie voor de drie meest (midazolam, paracetamol en amoxicilline clavulaanzuur) en de drie minst (bosentan, ketanserin and iloprost) voorgeschreven medicamenten. In de onderzochte formularia was er voor de 257 voorgeschreven medicamenten in 68-86% een beschikbaar doseringsadvies. De doseringsadviezen verschilden in de hoeveelheid doseringen, wijze van voorschrijven, dosering en leeftijden. Artsen moeten zich realiseren dat er grote verschillen tussen de verschillende formularia bestaan.

In **Hoofdstuk 5**, de discussie, worden aanbevelingen voor pijnbestrijding bij kinderen en toekomstig onderzoek gedaan. De aanbevelingen zijn onderverdeeld in het meten en de behandeling van pijn, veiligheid in medicatie gebruik en de genetica met betrekking tot pijn en farmacogenetica, met als doel de pijnbestrijding bij kinderen in de toekomst verder te optimaliseren.

Dankwoord

Eindelijk… hij is af! Een proefschrift schrijf je niet alleen, en ik heb de hulp van velen gehad. Tijdens deze 'weg' heb ik veel bijzondere momenten meegemaakt- genoeg om nog een boek te laten drukken! Ook jij bent vast één van die mensen zonder wie ik deze weg niet had kunnen afleggen: ik kan je daarvoor niet genoeg bedanken.

HARTELIJK DANK!

Curriculum Vitae

The author of this thesis was born on August 25th, 1977 in Rolde, the Netherlands. In 1996 she completed high school education on Atheneum level on the CS Vincent van Gogh, Assen, and started her medical study at the Free University Amsterdam (VUmc), the Netherlands. During this period she worked within the student teaching team. During her clinical rotation she worked for 6 months in the Diakonessen Hospital, Paramaribo, Surinam. She received her medical degree, cum laude, in July 2003.

After working for a year as a pediatric resident in the Gemini Hospital, Den Helder, the Netherlands, she started as resident on the Intensive Care Unit of the Erasmus M- Sophia Children's Hospital, Rotterdam in January 2005. During her work here she became more aware of the lack of evidence on pediatric pain and in June 2006 she started her PhD degree work under the supervision of Professor D. Tibboel, Dr S.N. de Wildt and Dr M. van Dijk. She worked within the department of Pediatric Surgery on a project entitled 'Pain; postoperative analgesics in infants and neonates'. From February 2010 until January 2011 she combined her research with a pediatric residency at the Wilhelmina Children's Hospital - UMC in Utrecht, the Netherlands. As from November 2011 she will start her residency Anesthesiology in Leiden at the Leiden University Medical Center (head; prof. dr. L.P.H.J. Aarts)

PhD Portfolio

Name PhD student	Ilse Ceelie
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PhD period	July 2006- September 2011
Promotor	Prof. dr. D. Tibboel
Supervisors	Dr. S. N. de Wildt and Dr. M. van Dijk

	Year	Workload (hours)
Courses		
Good Clinical Practice Consultatiecentrum Patiëntgebonden Onderzoek (CPO), Rotterdam	2009	40
Genetic Analysis in Clinical Research NIHES Wintercourse, Rotterdam	2009	60
Engels presenteren en discussiëren Erasmus MC opleidingsinstituut, Rotterdam	2008	80
Pediatric drug research NIHES Wintercourse, Rotterdam	2008	50
Cursus Farmacokinetiek LACDR, Oss 24- 26 januari	2007	80
Introduction to data analysis NIHES Summercourse	2007	25
Introduction for beginning PhD students Erasmus MC- het Congresbureau, Rotterdam	2006	8
Mini cursus methodologie van patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen Erasmus MC – het Congresbureau, Rotterdam	2006	8
Seminars and workshops		
Pharmacological research meetings, Pediatric Intensive Care ErasmusMC Sophia Children's Hospital, Rotterdam	2008-2010	50
Pain in children, ErasmusMC Pain knowledge centre, Rotterdam	2009	3
ESDP Education day, ErasmusMC, Rotterdam	2008	6

Pharmacogenetic research meetings, Department Clinical Chemistry ErasmusMC, Rotterdam	2007-2008	40
Conferences and presentations		
ESDP, Chamonix *"Acute liver failure following paracetamol use in three patients with myopathies" (oral)*	2009	40
ESDP, Chamonix *"Opioid consumption in thoracoscopic and open repair of esophageal atresia and congenital diaphragmatic hernia; does it make a difference?" (oral)*	2009	40
Pijn Kennis Centrum, Rotterdam *"Endoscopic surgery; Does it hurt less?" (oral)*	2009	30
ESDP, Rotterdam *"Can existing drug formularies help the prescribing physician in the pediatric intensive care?" (poster)*	2008	30
ASCPT, Anaheim *"Prescription errors at the PICU: blame the doctor or the formulary?" (poster)*	2007	30
Teaching activities		
Several presentations on pharmacological aspects of pain treatment for nursing staff of the ICU	2007-2008	10
Supervising medical student during research activities	2007-2009	40