From the Department of Physiology and Pharmacology
Section of Anesthesiology and Intensive Care
Karolinska Institutet, Stockholm, Sweden

Pharmacokinetic and pharmacodynamic aspects on opioid administration, morphine and ketobemidone, in the pediatric population

Stefan Lundeberg

Karolinska Institutet

Stockholm 2012

All previously published papers were reproduced with permission from the publisher.

Published by Karolinska Institutet. Printed by AJ E-print AB.

© Stefan Lundeberg, 2012
ISBN 978-91-7457-840-9

Velocius cobra !

Abstract

Opioids are the mainstay of the treatment of severe nociceptive pain in both children and adults. The studies in this thesis have focused on different aspects of opioid treatment in the pediatric population with special interest in morphine and ketobemidone. Ketobemidone has been in use for a long period of time but there has been very limited published data about the pharmacokinetics and pharmacodynamics of this drug. The aim has been to increase the knowledge of both pharmacokinetic and pharmacodynamic effects of morphine and ketobemidone.

In the sequence of studies the first one dealt with the pharmacokinetics of rectally administered morphine. Two different formulations of morphine were used and compared. Secondly the child's acceptance of the two formulations was examined from a pain perspective.
Further on, the potency of ketobemidone in children was compared to morphine in a postoperative setting using PCA as a drug delivery system.
Pharmacokinetic studies in children have been scarce despite the long time use of ketobemidone. In two studies the pharmacokinetics were explored in neonates, infants and children.

From the results the following conclusions were drawn:

- A morphine gel adapted for rectal use, with a higher pH than the regular saline solution, did not show any significant higher bioavailability but a tendency for an improved uptake. Bioavailability of rectally administered morphine is relatively low (about 30 %) and shows a large inter-individual variability in children.
- A morphine gel developed for rectal administration induces less pain in children aged 1-6 years. Most children tolerate rectal administration of morphine well when used for premedication.
- The opioid ketobemidone is equipotent to morphine when used for postoperative pain treatment. The frequency of adverse effects of ketobemidone and morphine are comparable when PCA is used for postoperative pain relief in children.
- The pharmacokinetic characteristics of ketobemidone administered in children older than 1 month appear to be similar to those in adults.
- The elimination of ketobemidone appeared to be slower in full-term neonates compared to children older than one year of age.

The analgesic effect of opioids can differ between individuals in the pediatric population to a large extent. Dose recommendations can therefore not be based solely on pharmacokinetic knowledge. The best analgesic for the patient is the one that will effectively decrease pain to a minimum or acceptable pain levels, with as little side effect as possible and without patient disagreement upon administration.

List of publications

This thesis is based on the following paper, referred to by Roman numerals I-V.

I. **Lundeberg S**, Beck O, Olsson GL, Boreus LO.
Rectal administration of morphine in children. Pharmacokinetic evaluation after a single-dose. Acta Anaesthesiol Scand. 1996; **40**: 445-51.

II. Jylli L, **Lundeberg S**, Langius-Eklöf A, Olsson GL.
Comparison of the analgesic efficacy of ketobemidone and morphine for management of postoperative pain in children: a randomized, controlled study.
Acta Anaesthesiol Scand. 2004; **48**: 1256-9.

III. **Lundeberg S**, Hatava P, Lagerkranser M, Olsson GL.
Perception of pain following rectal administration of morphine in children: a comparison of a gel and a solution.
Paediatr Anaesth. 2006; **16**: 164-9.

IV. **Lundeberg S**, Stephanson N, Lafolie P, Olsson GL, Stiller CO, Eksborg S.
Pharmacokinetics after an intravenous single dose of the opioid ketobemidone in children.
Acta Anaesthesiol Scand. 2010; **54**: 435-41.

V. **Lundeberg S**, Stephanson N, Stiller CO, Eksborg S.
Pharmacokinetics after a single intravenous dose of the opioid ketobemidone in neonates.
Acta Anaesthesiol Scand. 2012; **56**: 1026-31.

Contents

List of abbreviations

ALPS	Astrid Lindgren Children's Hospital Pain Scale
ASA	American Society of Anesthesiologists classification of health condition
AUC	Area Under the Curve
BSA	Body Surface Area
CAS	Colored Analogue Scale
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale
CNS	Central Nervous System
FAS	Faces Affective pain Scale
FPS	Faces Pain Scale
FPS-R	Faces Pain Scale – Revised
FLACC	Face, Legs, Activity, Cry, Consolability scale
GABA	Gaba Amino Butyric Acid
HPLC	High Performance Liquid Chromatography
IASP	International Association of the Study of Pain
Iv	Intravenous
LC-MS	Liquid Chromatography – Mass Spectrometry
M3G	Morphine-3-Glucuronide
M6G	Morphine-6-Glucuronide
MOR	Mu Opioid Receptor
NMDA	Non-Methyl-D-Aspartate
NRS	Numeric Rating Scale
PCA	Patient Controlled Analgesia
TCA	Tricyclic Anti-depressants
VAS	Visual Analogue Scale
UV	Ultra Violet

1 Introduction

Pain is a vital physiological sign of injury or tissue damage and is essential for human survival. The International Association of the Study of Pain defines pain as *An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such.* Pain is subjective and it is only the individual who can describe the pain or the anticipation of pain. The non verbal population such as newborns, infants and some disabled individuals cannot describe their pain perception and are not capable of self-reporting pain. It is well established that infants from the gestational age of about 20 weeks have a functional pain system, even if immature, which can perceive and respond to tissue injury. Therefore it was suggested by Anand and Craig to widen the definition of pain to include behavioral reactions caused by pain comparable to self report. It is also suggested that the perception of pain does not require an earlier unpleasant incident.

Routine assessment is essential in detecting pain as well as the management of pain. Self-reporting pain assessment tools are used when possible. In the non verbal population observation of behaviors that suggest pain, physiological and biological markers are used.[1, 30, 33]

Prolonged or repetitive nociceptive input and stress is harmful to the nervous system especially in the neonatal period of life. The nervous system show a high degree of plasticity and untreated pain can lead to long-term undesired changes. [2, 14, 28] Preventing or treating pain is a primary goal in infants and children. Reducing the number of painful procedures as well as anticipating and treating post operative pain following surgery is of major concern in children. Although there is a dramatic increase in the knowledge concerning pain inadequate treatment is still quite common.

Pain management includes analgesics as well as non-pharmacological approaches. A multimodal strategy is often used. [19, 41, 54, 56, 72, 81, 87] Analgesic combinations are more effective than using single drugs in high doses. A combination of analgesics also reduces the risk of toxicity and undesirable side effects. Opioids are one of the most frequently given analgesic agents in children with severe acute pain. There are several different opioids available today but the information of the pharmacokinetics in children has been sparse except for morphine. [20, 38, 39,

[53, 69, 76] Morphine is still the most commonly used opioid for children but there is need for assessing alternative opioids due to the side effects created by morphine and its metabolites.

Administration of analgesics should be well accepted by the child. Intramuscular injections are painful and seldom used today. Intravenous access is preferred for fast onset and the possibility of titrating the amount of drug needed. In the absence of intravenous access several routes are possible such as oral, rectal, transdermal and intranasal.[32, 42, 52, 55, 57, 68, 79, 80] Drug formulations should be prepared to create as little discomfort as possible to the child and provide suitable pharmacokinetic properties.

2 Background

2.1 DEVELOPMENTAL NOCICEPTIVE AND PAIN NEUROBIOLOGY

The management of pain in children was neglected for in medical practice until recently. In the 1980s, a number of studies demonstrated very little use of analgesics in children even after major surgery. The following 20 years have witnessed a vast increase in this interest in the pediatric pain field. Developments in the knowledge in pain physiology, pain assessment, monitoring and analgesic techniques have led to enhanced pain management. Improvements and further development are still necessary especially in neonates and infants.

It is shown that a neonate has functional nociceptive system from about 20 gestational weeks. The pain system matures rapidly during the first years of life but does not reach full maturity until adolescence. The descending inhibitory system is not developed by birth and matures slower than the ascending pathways. The nociceptive input in a child is more intense and goes on for a longer period after a trauma compared to in adults.[28] This implies a higher risk for nerve cell death or alterations in the nervous system due to the known plasticity occurring during intense or prolonged stimulation in the pain pathways. It is therefore of major importance to reduce pain stimulation and treat pain in children when needed.

Another challenge, in the newborn child and infants, is the susceptibility to various analgesics and sedatives. Inhalation anesthetics, barbiturates, benzodiazepines and NMDA antagonists have been demonstrated to be neurotoxic to the developing brain.[22, 63, 83, 88] In summary pain itself can create as much cell destruction as commonly used analgesics. The problem is probably best solved by minimizing pain, using as little analgesics as possible and minimal acceptance of observed pain. In verbal patients acceptable levels of pain on an individual basis should be aimed at. During these circumstances pain assessment is necessary to accomplish a satisfactory pain management.

2.2 PAIN ASSESSMENT AND PAIN MEASUREMENT

Pain assessment includes the individuals' experiences of pain in a global perspective including biological, personal and social contexts. Pain measurement on the other hand is the application of some quantitative or qualitative aspect of pain and is the basis for evaluation from a management and scientific aspect. Developmental factors are important as well as the ability to understand and describe pain changes with increasing age.

Table 1 *CHEOPS*

Item	Behaviour	Score
Cry		
	No cry	1
	Moaning	2
	Scream	3
Facial		
	Composed	1
	Grimace	2
	Smiling	0
Child verbal		
	None	1
	Pain complaints	2
	Positive	0
Torso		
	Neutral	1
	Tense	2
	Restrained	2
	Shifting	2
	Shivering	2
Touching wound or painful area		
	Not touching	1
	Reach	2
	Touch	2
	Grab	2
Legs		
	Neutral	1
	Squirming	2
	Drawn up/tensed	2
	Restrained	2

In the pre-verbal child self reporting scales are not applicable. Instead behavioral, physiological and biological parameters are used to measure what we believe is pain or stress, although, pain or stress can be hard to distinguish from each other. Pain can be stressful but stress does not have to be associated with a pain experience. The situation has to be taken into consideration when evaluating the patient reaction. Several pain scales have been developed using a summation of behavioral measurement with or without physiological markers.[60, 79]

Specific types of distress behaviors associated with pain are vocalization, facial expression and body movement, and they are often part of established pain scales. The CHEOPS is one of the first developed scales and is validated for short, sharp pain like procedural and postoperative pain. The CHEOPS is presented in its entirety in table1. Other commonly used scales, in Sweden, for pre verbal children are for instance FLACC, and ALPS I & II.

In younger aged verbal children different scales such as Poker Chip Tool, Colored analogue scale (CAS), faces affective scale (FAS), Wong Baker faces scale, Smiley faces scale, faces pain scale (FPS) and commonly faces pain scale-revised (FPS-R).[18, 60, 61, 62, 77] The FPS-R consists of 6 different faces and has been validated to other pain scales as well as the visual analogue scale (VAS). The FAS consists of 9 different faces and measure the affective part of pain to a larger extent than the FPS. In the Perrott study a good correlation was demonstrated between the FAS, CAS and FPS with regards to pain measurement.[75] When using self-reporting scales in this age group it is important to introduce the scale in advance and make sure the patient understand the used scale. The self-reporting scales mentioned above can be used in ages between 3 and 7 years, although there are no strict age limits.

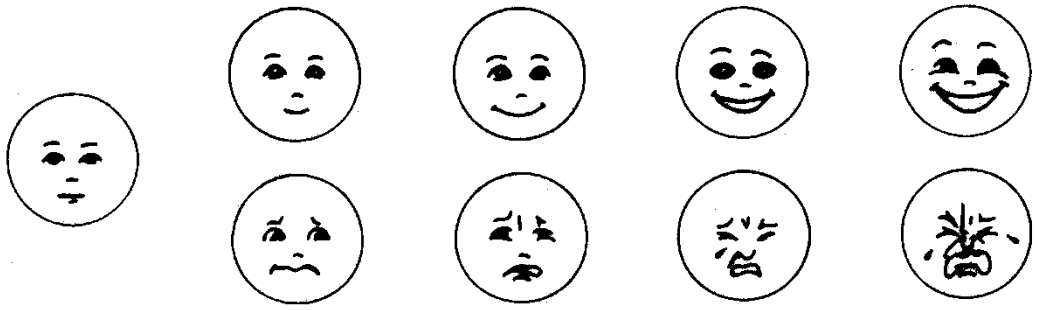

Figure 1 Faces affective scale FAS by McGrath, front

In children over 7 years of age the VAS or the numeric rating scale (NRS) is most often used. The VAS is usually a 10 cm long line with a sliding marker put where the person indicates the pain intensity. The far left is no pain and the far right is worst possible (imaginable) pain.

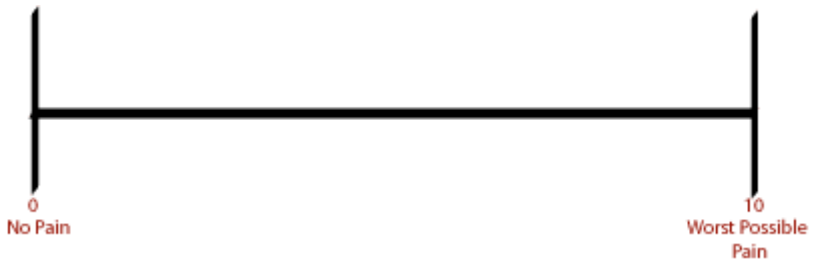

Figure 2 Visual analogue scale VAS

2.3 TREATMENT STRATEGIES

A good knowledge of the basic pharmacology of analgesic drugs, including indications, contraindications, dosage and routes of administration, is necessary for the optimum use of these drugs in children.[34, 35] A multimodal analgesic approach in combination with non-pharmacological complimentary methods (distraction, guided imagery, relaxing, cryo therapy) can often generate an acceptable pain level without

major side effects. [6, 19, 41, 54, 56, 72, 80, 87] Usually drugs should be administered on a regular basis and in a more severe pain situation a drug combination like opioids, local anesthetics and alfa-2 adreno agonist could be used as a continuous infusion.

Patient controlled analgesia (PCA) is a method which gained a lot of interest when introduced.[7, 29, 48, 59, 66, 89] The advantages of PCA include a high degree of patient contentment owing the benefits of self control. The technique allows for ample variability in individual requirements and circumvents delays in analgesic administration. PCA normally refers to a technique of intravenous administration in which the patient controls infusion equipment which delivers a bolus of analgesic drug on demand. A lock out time is used to limit the risk of over dosage and a background infusion can be added. During night hours a strict PCA bolus dose regime has some disadvantage because it might interfere with an optimal sleep pattern. PCA is often used as the golden standard of drug delivery in scientific research, when comparing drugs or methods, because it is the patient who decides on the dose needed. PCA as a method can be used from the age of 5-7 years. From a clinical point of view PCA is more seldom used at our hospital today during the first postoperative night.

Drug administration should be without discomfort and create as little pain as possible to the child. Topical anesthetics (EMLA®, Rapydan®) have clearly advanced the treatment of pediatric procedural pain, with many dosage forms available, including gels, sprays, creams, ointments, and patches. Intramuscular injections are abandoned due to the high degree of pain they generated.

2.4 PHARMACOLOGY – KINETICS AND DYNAMICS

Pharmacokinetics describes the different phases of uptake and elimination of a certain drug.[79] Several mathematical models have been constructed to describe the movement of a drug in the human body. A procedure is to follow concentration of the drug in plasma during a time period and from levels measured a model is used for the best fit. Today there are several computer programs used for calculation of the different pharmacokinetic values. Commonly used models are one or even up to four compartment models depending on the route of administration used. Parameters describing the kinetics are often time to maximum concentration, maximum concentration, distribution time, elimination time, volume of

distribution, clearance of a drug, area under the curve (measure of available amount of drug in time) and bioavailability.

Distribution is the fast phase with a rapid decreased of the levels of the drug in plasma. Distribution is to a large extent depending on the lipid solubility of the drug. High lipid solubility leads to a large volume of distribution and in combination with a high cardiac output the distribution is fast. Pediatric patients normally have a higher cardiac output per kg bodyweight as compared to adults.

Elimination of most drugs is liver dependable due to metabolism in the liver cells. Different enzyme and metabolic systems are engaged in the metabolism. The cytochrome P450 enzymes metabolize potentially toxic compounds including drugs principally in the liver. The liver in newborns is often immature in function and matures quite rapidly during the first 6 months of life. [8, 11, 16, 49, 64] The effect will usually be a lower metabolic rate in small children. During the next phase around 1-3 years of age an increased metabolism compared to adults are often the case. The liver metabolism of a drug produces metabolites which generally are more hydrophilic and therefore more prone to be excreted through the kidneys. The metabolites are sometimes active and contribute to the effect of the mother drug.

Excretion of a drug does not always depend on liver metabolism. The drug could also be excreted unchanged via the kidneys mainly and through the gastrointestinal tract. The total clearance is a sum of metabolism and excretion.

Bioavailability describes how much of a drug is absorbed when given via an alternative route to intravenous administration. The fraction of the absorbed drug (the area under the curve) is divided by the area under the curve for the same dose given intravenously. The ratio in percent describes the bioavailability and the maximum value is 100 %.

Pharmacodynamics describes the effect of the drug. The target organ for most analgesics is within the central nervous system (CNS) and the effect does not to have to correspond to the levels of concentration in plasma. Passage speed over the blood brain barrier is an important factor and amount of drug which passes over to the CNS. The free fraction of the drug is most often responsible for the dynamic effect and the degree of free fraction varies to a large extent between different analgesics.
Pharmacodynamics and kinetics differences are of importance mainly in the neonatal and infant period.

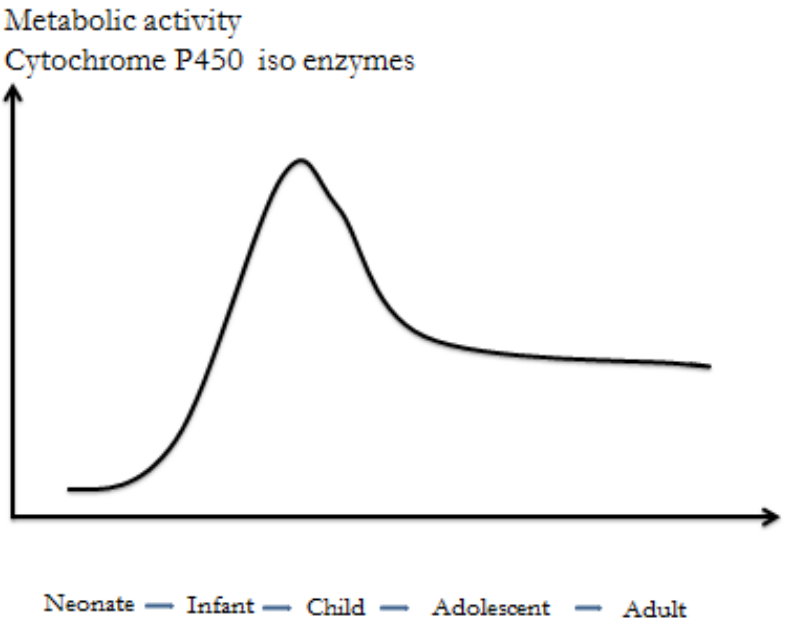

Figure 3 Traditional view of cytochrome P450 development. Modified from Leeder & Kearns. Pharmacogenetics in pediatrics.[47]

2.5 ANALGESICS

The use of drugs such as paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs, alfa-2 adreno agonists, local anesthetics and opioids has become the cornerstone of pediatric analgesia. They all play a part in a multimodal analgesic strategy for nociceptive pain (such as trauma and post-operative pain). Neuropathic pain, which is not as common as nociceptive pain in children, is usually treated with other types of analgesics such as gabapentine (anti-epileptic), NMDA blockers and TCAs (tricyclic anti-depressants). Nociceptive pain often responds to analgesic treatment where neuropathic pain which is rather unaffected by analgesics.

2.6 OPIOIDS

Opium is the dried latex from opium poppy. The cultivation of opium poppies for food, anesthetics and for religious rituals dates back to the Stone Age. The useful psychological and physiologic effects of opium have been known for centuries by physicians and the general public. Opioids have been classified according to their origins, composition and actions. One classification is based on their relative efficacy at various opioid receptors (agonist, partial agonist or antagonist).[79]

Over the years a large number of opioid receptors and subtypes have been identified including mu, delta and kappa receptors (table 2). The mu receptor is believed to have several subtypes. The mu-1 receptor mediates analgesia and the mu-2 receptor respiratory depression. Mu receptors are also associated with sedation, euphoria, nausea and vomiting. Morphine and to some extent fentanyl commonly causes pruritus. Opioid induced itching is histamine release dependent or induced by central mu receptor activity.

Opioid has also shown to modulate the immune system and can give immune suppressive effects. This knowledge is quite novel and cannot be ignored from a clinical perspective.[13, 36, 91]

Opioid tolerance and physical dependence is common to all opioid agonists after prolonged use and cross tolerance develops between all opioids. Several mechanisms contribute to opioid tolerance. Physical dependence develops at all ages. Withdrawal symptoms develop if the opioid medication is discontinued abruptly and can be observed as early as 24 hours after drug termination. Short term use of opioids, 24-48 hours, can in neonates be plentiful to create withdrawal symptoms. In older patients withdrawal signs can be noted from 4 – 5 days of opioid treatment.

There seems to be differences between individuals and opioid response to the different opioids. Opioid rotation, changing opioids, could be used if the patient responds with pronounced side effects or insufficient analgesic effects. The understanding to opioid rotation is limited but the clinical effect is repeatedly quite striking.[27, 97]

Receptor	Subtypes	Function
mu (μ)	μ_1, μ_2, μ_3	μ_1: • analgesia • physical dependence μ_2: • respiratory depression • miosis • euphoria • reduced GI motility • physical dependence μ_3: • unknown
kappa (κ)	κ_1, κ_2, κ_3	• analgesia • sedation • miosis • inhibition of ADH release • dysphoria
delta (δ)	δ_1, δ_2	• analgesia • antidepressant effects • physical dependence
nociceptin receptor	ORL_1	• anxiety • depression • appetite • development of tolerance to μ agonists
toll-like receptor*	TLR_4	• pro-nociceptive

*Table 2. Opioid receptors subtypes and function. *Receptor mediating the opioid modulating effects on the immune system.*

Opioids are still underutilized in children for many reasons. Misconceptions, insufficient training and lack of understanding are some of the reasons. Opioids commonly used in pediatric pain management

include morphine, meperedine, ketobemidone, oxycodone, codeine, methadone and fentanyl.[79] The opioids clinically used differ to a large extent in their lipid and water solubility and pharmacodynamic profile. All opioids are metabolized in the liver with the one exception of the short-acting agent remifentanil. Morphine and ketobemidone is in focus in this thesis and will be discussed in more detail below.

The sensitivity to opioids and risk of respiratory depression is most prominent in the first 3 months of life. Pharmacokinetic and pharmacodynamic differences in neonates and young infants may cause the increased sensitivity.

2.6.1 MORPHINE

Morphine (from the Greek god of sleep, Morpheus) is a natural existing opioid derived from the opium plant. Morphine is still considered the gold standard which other opioids are compared to in clinical studies of pharmacokinetics and pharmacodynamics.

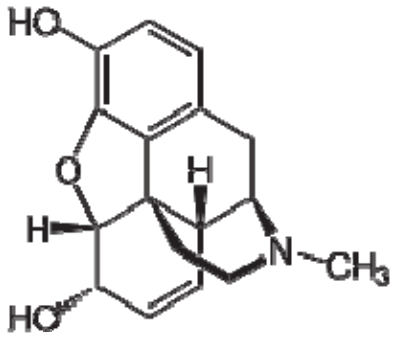

Figure 4 Structure of morphine

Morphine is a specific mu receptor agonist and the most hydrophilic opioid in clinical use. The hydrophilic quality results in slower passage across membranes like intestinal mucosa and the blood brain barrier. The analgesic response is slow even if given intravenously. The bioavailability is greatly reduced when administered orally or rectally and with a significant inter individual difference.

Morphine is metabolized in the liver by conjugation to morphine-3- and morphine-6-glucuronide.[15, 16, 85] The metabolites are

excreted via the kidneys. M6G is an active agonist at the mu receptor.[31, 70, 71, 73, 90] M3G on the other hand is not active as an opioid agonist but does have some convulsive action which is mediated through GABA/glycinergic receptors.This can lead to clinical problems especially in younger infants and after prolonged use. In neonates the metabolic pathway is mainly via formation of M3G. There are limited human studies concerning the effects of M3G. On the other hand we have experienced a clinical effect of excitation in infants on morphine infusions as described by Smith.[82] The elimination half-life in prematures and younger infants is considerably longer compared to older children and adults. The use of fixed infusions rates produce a wide range of plasma concentrations and studies show a low correlation of plasma levels and analgesic effect. It is always important with all opioids to titrate dosing carefully to achieve the desired clinical effect.

Excessive plasma concentrations of morphine might create central nervous depression, gastrointestinal immotility, urinary retention and occasionally seizures.

2.6.2 KETOBEMIDONE

Ketobemidone, a phenylpiperidine structurally related to meperidine, is an agonist at the mu opioid-receptor (MOR). The affinity of ketobemidone for the delta and kappa opioid receptors is twenty and hundred fold lower, respectively, than for MOR.[17, 43] In addition, ketobemidone has been shown to inhibit the excitatory effect of NMDA receptor agonists to a considerable extent, an effect that might also contribute to analgesia in certain pain conditions. [3, 24]

Ketobemidone has predominantly been used in the Scandinavian countries in both adults and children for over 50 years.[4, 9, 10, 86, 95] The dosage of ketobemidone in children and infants is largely based on clinical experience, since data on its pharmacokinetic properties in children have been lacking until recently.

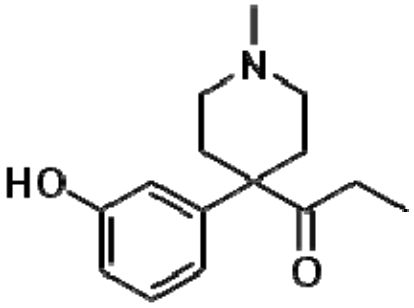

Figure 5 Structure of ketobemidone

Ketobemidone has a somewhat higher lipophilicity than morphine. Pharmacokinetic effects of intravenous, oral and rectal administrations of ketobemidone have been studied in adults.[9, 10] Ketobemidone is metabolized in the liver and is a substrate for cytochrome P450 enzymes (CYP), CYP2C9 and CYP3A4.[46, 96] Furthermore, the liver cytochrome P 450 exists in a fetal form (CYP3A7) and shifts into CYP3A4 during the neonatal period.[37] Ketobemidone is generally considered to lack pharmacologically active metabolites, an advantage in patients with renal insufficiency or immature renal function. Norketobemidone, the major metabolite in adults, is considered to be inactive.

3 Aims

Opioids play an important role in the management of nociceptive pain in the pediatric population. Rectal morphine is an alternative to other routes of administration. Ketobemidone has been used as an opioid agonist for some time in children but there has been a lack of pharmacokinetic studies in children. The overall aims of this thesis were to further explore the knowledge of morphine and ketobemidone and its use in the pediatric population.

Against this background the more specific aims were;

1. To compare pharmacokinetic parameters in children after rectal administration of either a parenteral solution or a gel formulation of morphine. (Study I)

2. To determine the analgesic potency of ketobemidone in comparison to morphine in children in a postoperative setting using patient controlled analgesia. (Study II)

3. To evaluate children's acceptance of administration of rectal morphine, using a solution and a gel. (Study III)

4. To investigate the pharmacokinetic profile of intravenous ketobemidone in children. (Study IV)

5. To investigate the pharmacokinetic profile of intravenous ketobemidone in neonates. (Study V)

4 Ethics

The studies were performed in accordance with the declaration of Helsinki. All studies were approved by the Regional Ethical Review Board of Stockholm, Sweden. Individual or parental consent were obtained in all cases. The investigations were performed at Astrid Lindgren Children's Hospital and in ***Study III*** in cooperation with the Ear Nose and Throat department at Karolinska University Hospital.

5 Material and Methods

5.1 PATIENTS POPULATION AND DEMOGRAPHICS

Study I: A total of 26 children were included. 20 children received rectal morphine (10 a morphine solution and 10 a morphine gel). 6 children received intravenous morphine.

Study II: 60 children aged 6-16 years, ASA class I or II, were enrolled in his randomized controlled study. Four children in the ketobemidone group and two in the morphine group were withdrawn from evaluation.

Study III: 120 patients in two centers were enrolled. Children were randomized to receive a morphine solution or a morphine gel. The patients were in three age groups (1-2, 3-6 and 7-10 years), 40 children in each.

Study IV: This pharmacokinetic study was based on 30 children, in newborns up 10 years of age divided in three age groups. 6 children were excluded from analysis because of incomplete blood sampling. Ketobemidone hydrochloride was administered as a single intravenous bolus dose

Study V: 15 full-term neonates scheduled for surgery, more than 37 gestational weeks at birth, were included in the pharmacokinetic study of ketobemidone. Ketobemidone hydrochloride was administered as a single intravenous bolus dose.

No significant differences with regard to demographic data were detected between compared groups in ***Study I-III***.

5.2 ANESTHETIC AND PCA PROTOCOL

In ***Study I*** atropine was given as premedication and anesthesia induced with thiopentone and fentanyl. Actracurium was given prior to intubation. Anesthesia was maintained by inhalation of isoflurane in oxygen and

nitrous oxide. Before surgery all children were administered morphine hydrochloride 0.2 mg/kg.

In ***Study II*** midazolam and atropine was given as premedication and anesthesia induced with thiopentone and fentanyl. Actracurium was given prior to intubation. Anesthesia was maintained by inhalation of sevoflurane in oxygen and nitrous oxide. Fentanyl 1-2 microg/kg was administered per operatively when additional analgesia was required. The study drug, ketobemidone or morphine, was given postoperatively as a loading dose to achieve pain relief followed by PCA. The PCA setting was a bolus dose of 20 microg/kg, a lockout time of 5 minutes and no background infusion.

Anesthesia in ***Study IV*** and ***V*** was induced according to usual clinical routines. Induction was with intravenous barbiturates in most cases. Inhalation with sevoflurane was used in 10 patients in ***Study IV*****.** In ***Study IV*** and ***V*** one patient each received propofol for induction and in ***Study V*** two patients did not receive any induction because they were on ventilator treatment before surgery. Anesthesia was maintained with sevoflurane and intermittent doses of fentanyl. A single dose of the study drug, ketobemidone, was administered intravenously prior to surgery in ***Study IV*** and ***V***.

5.3 BLOOD SAMPLING AND PLASMA CONCENTRATION MEASUREMENTS

Blood sampling was performed in ***Study I, IV*** and ***V***. Samples were taken up to 6 hours in S***tudy I***, 8 hours in ***Study IV*** and 10 hours in ***Study V*** after administration of the test drug. The heparinized samples were cooled and centrifuged within 1 hour. Plasma was separated and kept frozen until analyzed.

In ***Study I*** levels of morphine and the metabolites M3G and M6G were determined with HPLC using UV and electrochemical detection. In ***Study IV*** ketobemidone and norketobemidone were determined and in ***Study V*** ketobemidone but not the metabolite norketobemidone. In ***Study IV*** a detailed description of the LC-MS method used in ***Study IV*** and ***V*** is available in publication IV.

Blood sampling volume never exceeded 3 % of the patient's blood volume.

5.4 PHARMACOKINETIC EVALUATION

Pharmacokinetic parameters were calculated by means of computer programs using standard compartmental methods. In the morphine study a PC version of SIPHAR/Base version 4 (Societé Simed, Cretiel, France) was used. In the ketobemidone studies GraphPad Prism version 5.02 (Graph Pad software Inc, CA) (***Study IV***) and WinNonlin program Standard Edition version 1.5 (Pharsight Corporation, Mountain View, CA, USA) (***Study V***).

5.5 PAIN ASSESSMENT AND SEDATION SCORE.

Pain assessments were carried out in ***Study II*** and ***III*** using validated age appropriate tools. In ***Study II*** the VAS and in ***Study III*** CHEOPS (group 1-2 years), FAS (group 3-6 years) and VAS (group 7-10 years).
In ***Study II*** pain and sedation was assessed every 3 hours. Assessments were not made during sleep. In ***Study III*** the pain was assessed before test drug administration and 3 minutes after.

5.6 STATISTICAL ANALYSIS

The statistical methods used are described for each study. *P* values < 0.05 were considered significant.

Study I: Differences in age and weight were analyzed using Kruskal-Wallis one-way test of variance. The Mann-Whitney U-test was used for evaluation of differences between individual groups. Linear regression was applied for correlation analysis.

Study II: Non-parametric methods were used. Group differences between opioids used were analyzed by means of the Mann-Whitney U-test, chi-square test and Fisher's exact test.

Study III: The Student's *t*-test was used to analyze parametric data and chi-square test for differences in gender. The Mann-Whitney U-test with

Bonferroni correction for multiple comparisons was applied to analyze the non-parametric data of the observed or self-reported pain score (difference in pain scores before and after administration of the study drug).

Study IV: The Mann-Whitney U-test was used for comparison of the elimination half-lives in the present pediatric population with individual data from adult patients. The Spearman Rank Correlation test was performed to evaluate the relation between age of the patients and the dose normalized AUC (area under the plasma concentration time curve) -values (AUC/mg/kg and AUC/mg/m^2, respectively).

Study V: The Mann-Whitney U-test was used for comparison of the derived pharmacokinetic parameters in the present neonatal population with previously published data from children aged > 1 year and for the comparison of derived pharmacokinetic parameters after venous and arterial sampling. The Spearman Rank Correlation test was used to evaluate the degree of correlation between age of the patients and the derived pharmacokinetic parameters.

6 Results

6.1 RECTAL ADMINISTRATION OF MORPHINE IN CHILDREN *(STUDY I)*

Time to maximum peak concentration of morphine tended to be longer in the rectal gel group. Peak concentrations of morphine did not differ between the two different rectal groups but there was a tendency towards higher concentration in the gel group. Inter-individual variation of maximum concentration was high in both rectal groups. Bioavailability of morphine and the metabolites were calculated by using the mean value of the intravenously administered morphine as reference. No significant difference could be demonstrated with regards to morphine bioavailability. There was significant higher value ($p < 0.02$) of the sum of AUC of the metabolites M3G and M6G in the rectal gel group compared to the solution group. Pharmacokinetic results are shown in table 3.

	Morphine				**M3G**		**M6G**	
	Elimination half-life	Bioavailability	Tmax	Cmax	Tmax	Cmax	Tmax	Cmax
Formulation	(hours)	(%)	(hours)	(nmol/l)	(hours)	(nmol/l)	(hours)	(nmol/l)
Intravenous	1.2 (0.7-2.3)	100		2196 (1773-2527)	2.8 (1-6)	466 (351-627)	1.3 (1-2)	71 (51-86)
Rectal gel	1.5 (0.9-2.4)	35 (18-59)	0.73 (0.3-2)	76 (25-129)	2.6 (1-4)	307 (175-548)	3.0 (2-4)	46 (27-62)
Rectal solution	2.9 (1.4-10)	27 (6-93)	0.48 (0.2-0.7)	59 (15-140)	3.0 (0.7-5)	194 (65-315)	3.0 (1-5)	34 (5-47)

Table 3. Pharmacokinetic data after morphine administration. Bioavailability based on AUC $_{0\text{-}6\ hours,}$ time to maximum concentration (Tmax), maximum concentration (Cmax). Values in mean and (range).

Taking into account the variability of the individuals in the group receiving morphine intravenously the bioavailability of the two rectal groups was recalculated. The results are shown in figure 6. Heart rate and saturation levels were stable all through the study phase.

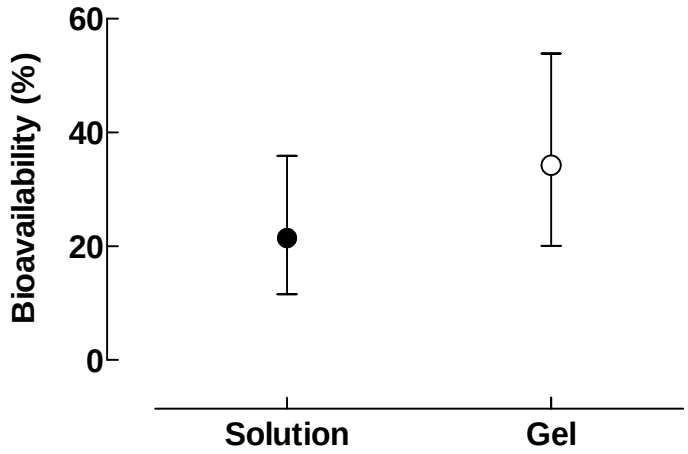

Figure 6 Median and 95% confidence interval of the two rectal groups receiving the morphine solution or the morphine gel. Calculations were based on Wilcoxon's signed rank test according to Tukey. [21, 84]

6.2 ANALGESIC EFFICACY OF KETOBEMIDONE AND MORPHINE IN POSTOPERATIVE PAIN IN CHILDREN *(STUDY II)*

The results showed a non significant difference in total opioid consumption between the ketobemidone and the morphine group. The mean dose ratio of ketobemidone/morphine was 0.80 and corresponding median value 0.94.

The number of children decreased each day as a result of decreased post operative pain. There was no difference regarding rescue doses needed.

Four patients in the morphine group and one in the ketobemidone group had adverse effect leading to discontinuation of the PCA treatment. The adverse effects are shown in table 4.

Type of adverse effect	Ketobemidone %	Morphine %
Nausea	63	67
Vomiting	67	47
Itching	56	47
Over sedation	15	20
Respiratory depression	7	7

Table 4. Percentage of patients experiencing adverse effect during treatment.

6.3 PERCEPTION OF PAIN FOLLOWING RECTAL ADMINISTRATION OF MORPHINE IN CHILDREN (*STUDY III*)

The overall pain scores in all groups were low. Children aged 1-2 years (group A) and 3 to 6 years (group B) had significantly lower pain scores when morphine gel was compared to the morphine solution, $p < 0.001$ and $p < 0.05$ respectively. Individual changes in pain scores are shown in figure 7.

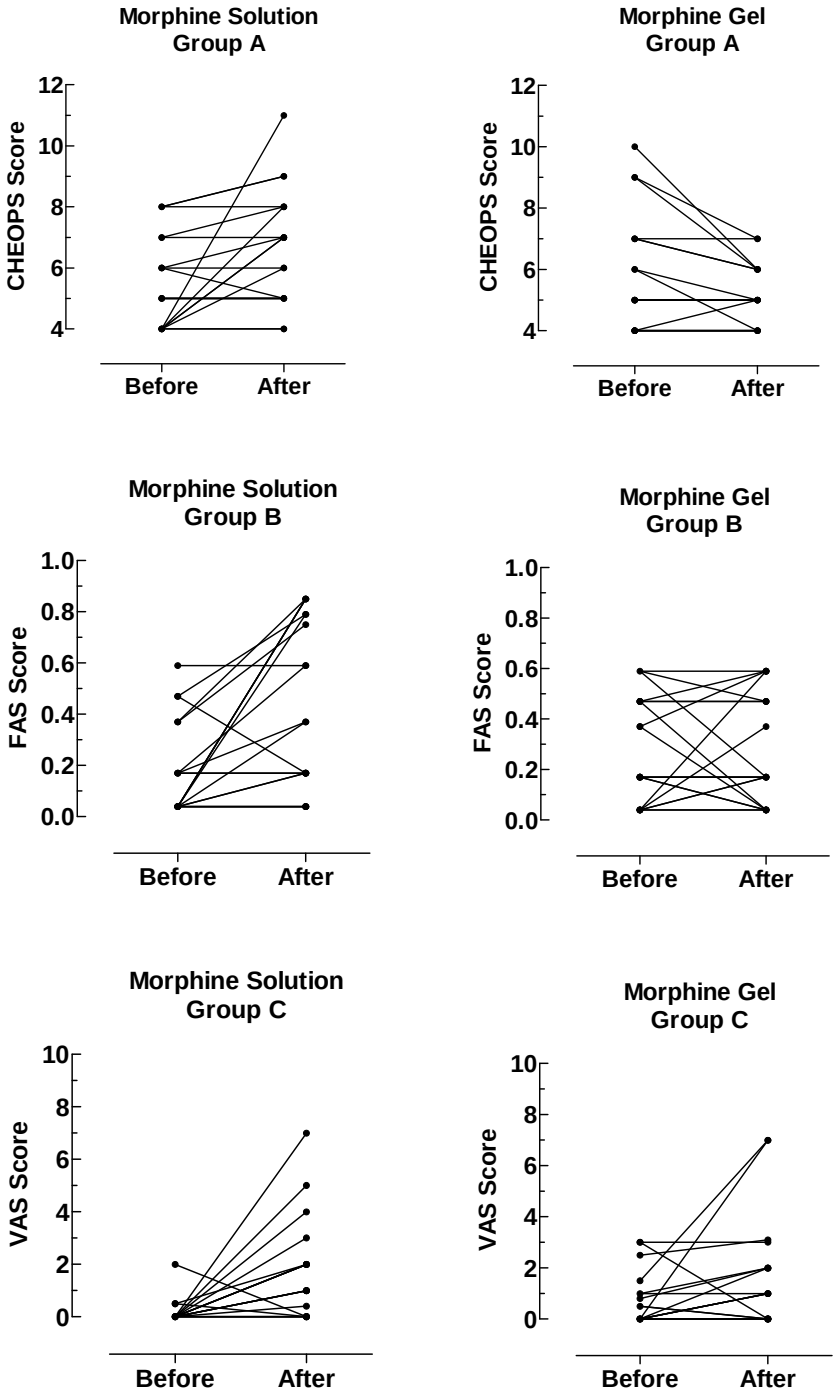

Figure 7 Individual scores before and after administration of the test drug. Aged appropriate pain assessment tools were used.

6.4 PHARMACOKINETICS AFTER INTRAVENOUS KETOBEMIDONE IN CHILDREN (*STUDY IV*)

The individual plasma levels-time curves of ketobemidone after intravenous administration are presented in figure 8.

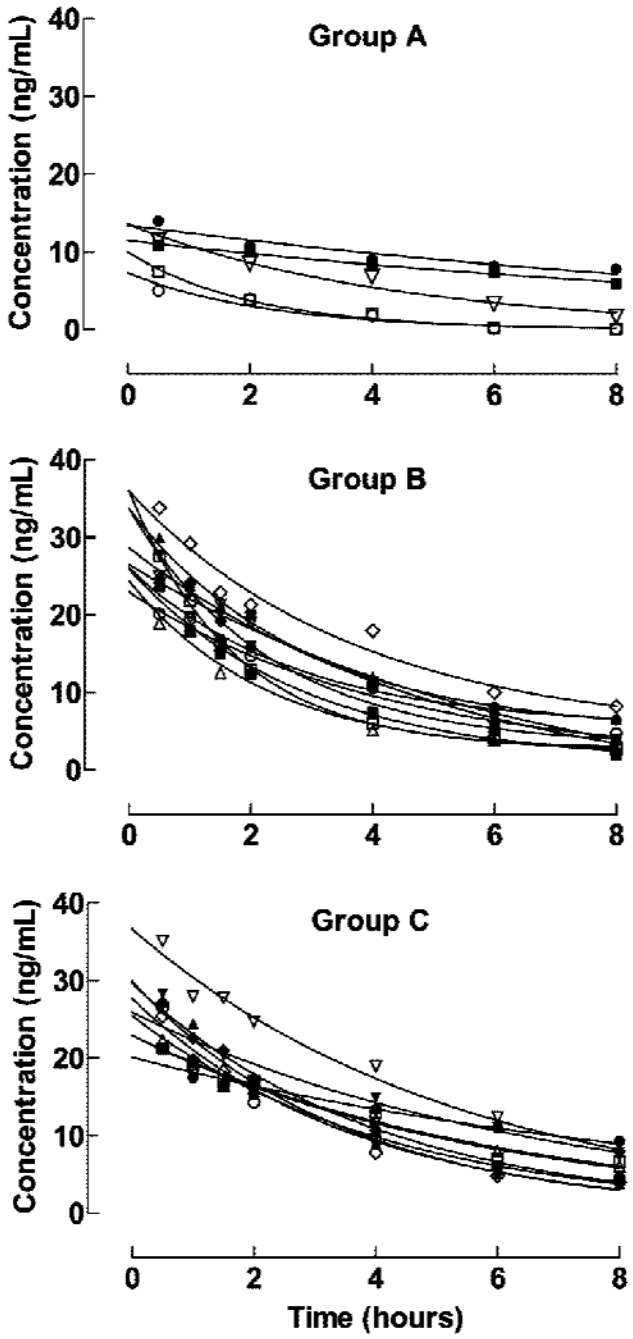

Figure 8 The concentration of ketobemidone during the first 8 hours after i.v. injection of a single bolus dose. Group A represents (0-90 days), Group B (1-2.5 years) and Group C (7-10 years), respectively. Individual concentration-time measurement is shown. The lines illustrate fitted curves when using pharmacokinetic modeling for each individual.

The elimination half-lives of ketobemidone in children over one month of age did not differ from the data obtained from adults. A complete list of pharmacokinetic data is shown in table 5.

Parameter	Group A 0-90 days *(n=5)*	Group B 1-2.5 years *(n=10)*	Group C 7-10 years *(n=9)*
$t_{½}$ (hours)	3.0	2.0	3.7
Range	1.4 - 8.9	1.2 - 4.7	2.4 - 6.9
Cl (L/hour/kg)	0.84	0.89	0.74
Range	0.29 - 3.0	0.55 - 1.35	0.5 - 0.99
AUC (mg/m^2)	79.3	57.0	47.9
Range	19.8 - 243.4	37.7 - 85.5	39.6 - 78.1
AUC (mg/kg)	1191	1125	1344
Range	333 - 3422	741 - 1813	1008 - 1987
V_z (L/kg)	4.4	2.6	3.9
Range	3.7 - 6.9	2.0 - 5.6	2.7 - 5.0

Values are expressed as median and interval. **$t_{½}$ =** elimination half-life ;
Cl = clearance; **AUC** (expressed in ng·hour/mL) = area under the plasma concentration time; **V_z** = apparent volume of distribution

Table 5. Pharmacokinetics of plasma ketobemidone after an intravenous dose in the three study groups

6.5 PHARMACOKINETICS AFTER INTRAVENOUS KETOBEMIDONE IN *NEONATES (STUDY V)*

Matched to our previous study in children over one year of age, the elimination of ketobemidone showed to be slower in full-term neonates.

There was no correlation between age and any of the pharmacokinetic parameters assessed.

Median values of clearance were 0.46 l/hour/kg, apparent volume of distribution 4.64 l/kg, volume of the central compartment 1.71 l/kg, distribution half-life 0.047 hours and elimination half-life 7.26 hours, respectively. Plasma clearance (Cl) ranged from 0.23 to 0.84 l/hour/kg taking all patients into consideration. The apparent volume of distribution (Vz) ranged from 3.50 to 7.31 l/kg. The first elimination phase (distribution) half-life and elimination half-life ranged from 1.04 to 10.78 min and 3.52 to 11.27 hours, respectively.

Individual measurements and calculations of elimination half-life, volume of distribution is shown in figures 9 and 10.

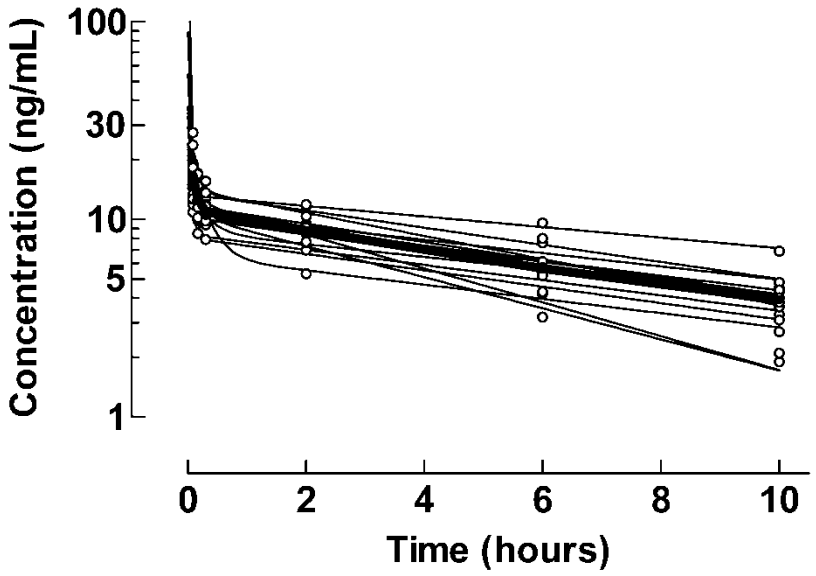

Figure 9 The concentration of ketobemidone during the first 10 hours after i.v. injection of a single bolus dose. Each individual concentration-time measurement is indicated. The lines illustrate fitted curves in the pharmacokinetic modeling for each individual. Mean is indicated as a thick line.

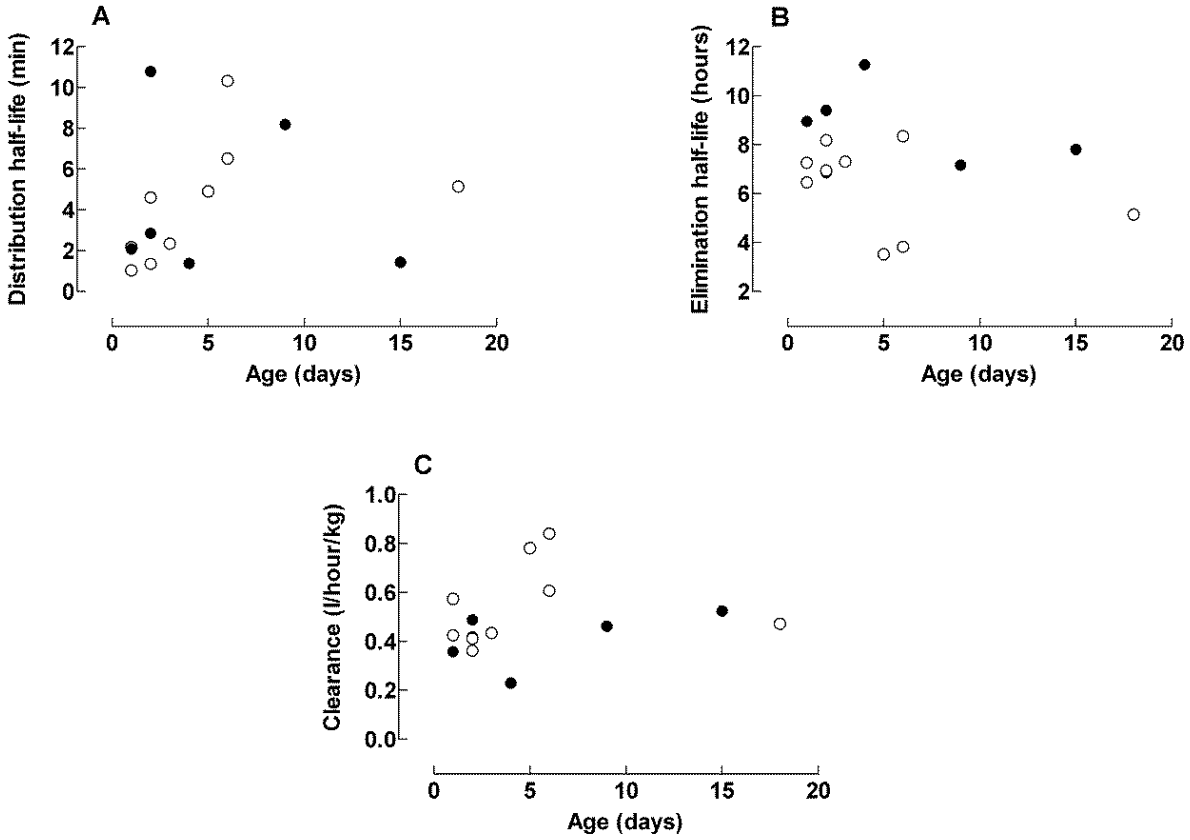

Figure 10 Distribution half-life (A), elimination half-life (B) and ketobemidone clearance (C) related to age in 15 full-term neonates after an intravenous dose of 0.05 mg/kg of ketobemidone. Open circles represent venous sampling and filled circles arterial sampling.

6.6 EXCLUDED PATIENTS

In ***Study I*** one patient was excluded in the morphine solution group because of substantial rectal leakage

Four children in the ketobemidone and two in the morphine group were excluded in ***Study II***. Reasons included cancelled surgery (3), no need of PCA (2) and respiratory depression in patient receiving morphine.

6 children were excluded in ***Study IV*** because of incomplete blood sampling whereof 5 were in the youngest age group (0-90 days).

7 Discussion

NOCICEPTION AND PAIN IN CHILDHOOD

Over the past 4 decades, the practice of pediatric pain management has advanced from a phase of anecdotal statement to a research supported standard of care. Declarations, such as the one delivered by Swafford and Allan in a textbook of Pediatrics from 1968, are now considered obviously false: *"Pediatric patients seldom need medication for the relief of pain. They tolerate discomfort well. The child will say he does not feel well, or that he is uncomfortable or that he wants his parents but often will not relate this unhappiness to pain "*. However, challenges in pediatric pain assessment, cognitive and behavioral changes in a developing patient population, and limitations of controlled and randomized investigations in helpless children still influence the field. Luckily, health care providers no longer assume that "neurological immaturity "limits an infant or child's appreciation and experience of pain.

Anatomical, neurochemical, and neuroimaging studies describe a functional nociceptive system present during the fetal period and maturing all through childhood.[2, 28] Neuromodulatory systems present predominantly after birth and still demonstrate robust neuroplasticity into late adolescence. Research, to a large extent carried out in animals, has demonstrated that newborn and young offsprings are even more vulnerable to pain stimulation than adults. Pain stimulation with regards to nociceptive afferents show a lower nociceptor thresholds, a longer activation, higher amplitude, a higher number of active receptors, larger receptor fields and less active inhibition of nociceptive signaling than in a fully developed system.

From a clinical point of view, nociceptive pain is the most common cause of pain in pediatric patients. Post operative pain is an example of nociceptive pain and is directly related to the surgical procedures.[23, 58] Pain develops as a result of tissue damage and the ensuing inflammatory process. Within minutes after the surgical damage, secondary hyperalgesia develops and pain is amplified via segmental reflexes within the spinal cord.

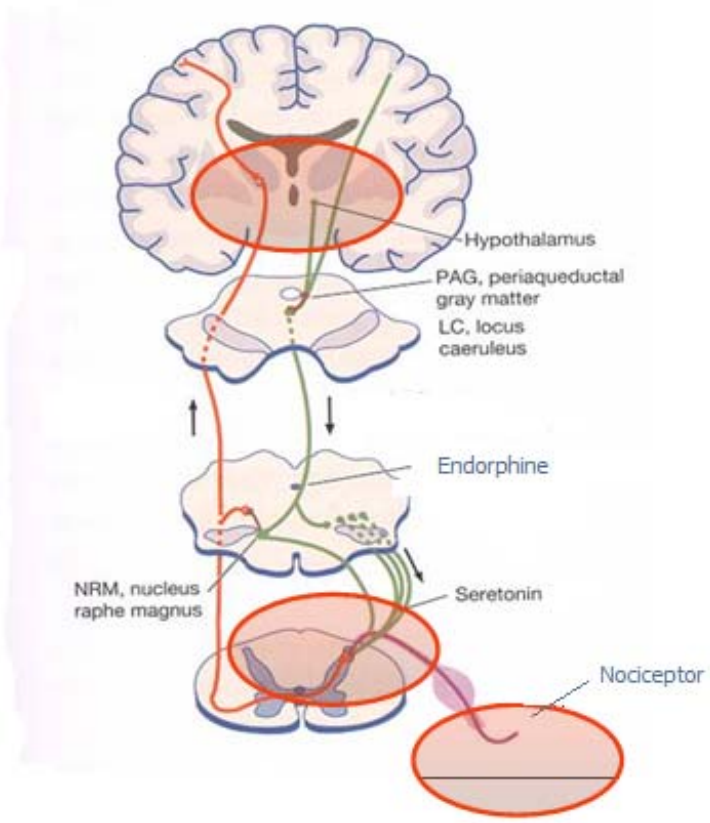

Figure 11 Schematic drawing of the nociceptive system with both afferent and efferent pathways. Anxiety, fear and limit self control increases the pain experience. Modulated from the original drawing, with permission from the Swedish Research council and Annika Röhl. Pain is a subjective experience where cortical and limbic systems are involved

Nociceptive and inflammatory pain may result in cell damage and cell death (excitotoxicity) including long-standing neuroplastic changes. Another challenge to consider is the neurotoxicity of analgesics and anesthetics which has to be considered in the treatment of pain especially in a maturing system. With this knowledge it is crucial to treat pain as effectively as possible and limit the negative effects of analgesic drugs.

ANALGESICS AND TREATMENT STRATEGY

Most of the analgesic drugs used in children are not tested or approved of in this age group. There is to a large extent a lack of studies of

pharmacokinetics and pharmacodynamics. Morphine, paracetamol and local anesthetics have for a long time been the main analgesics used in the pediatric patient. Opioids are commonly associated with side effects including nausea, itching, constipation and also with respiratory depression.

Furthermore the administration of the analgesic itself can be painful as intramuscular injections or induce pain by using concentrated solutions. A low pH of an injectable solution may also generate pain when administered. It is not uncommon that a child in pain avoids communication if the treatment with the analgesics itself induces pain.

A modern pain treatment strategy is to combine drugs with different targets combination with non-pharmacological therapies. [19, 41, 54, 56, 72, 80, 87] From a clinical point of view several combinations of analgesics can be used to achieve a good pain relief with limited side effects.

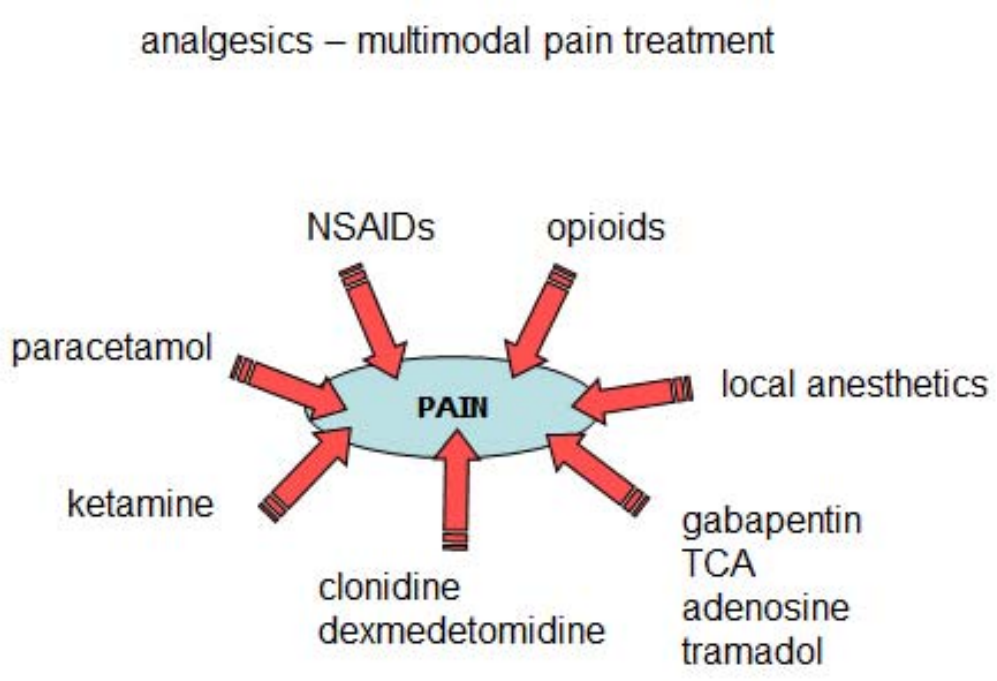

Figure 12 Different analgesics possible to be used in a multimodal pain treatment strategy.

OPIOIDS

Opioids act via different opioid receptors and there seems to be individual subtypes as well. Opioid rotation is the clinical term for the change of opioids to achieve less undesired side effects or to achieve a better result. In complex pain conditions a combination of opioids can be used to accomplish improved pain control.

drug	receptor/mechanism of action
morphine	μ
ketobemidone	μ, NMDA
methadone	μ, δ, NMDA, serotonin
oxycodone	μ, κ
buprenorphine	μ, κ

Table 6. Commonly used opioids and opioid receptor binding and non opioid receptor mechanism.

DOSE STRATEGIES IN REFERENCE TO BODY AREA OR BODY WEIGHT

Dose strategies for pediatric patients have been discussed widely for decades. Many reference textbooks propose calculation of drug dosages for children according to BSA.[12, 45] This method has commonly been adopted for dosing anti neoplastic drugs, but only rarely for other types of drugs.[25, 26] Mosteller presented a simplified formula for evaluation of BSA from routine clinical measurements of height and body weight.[67] It should be noted that BSA can be estimated from the body weight alone when values of height are lacking.

ETHICAL CONSIDERATIONS

Ethical considerations are special in children.[40] Formal consent from the child is often not possible and is dependent on the caregivers. In studies when blood sampling is part of the study it is important to limit the blood volume samples, the rate of sampling and the procedural trauma inflicted. As pediatric studies cannot be ethically carried out in healthy volunteers, blood samples can only be obtained in children planned for medical procedures with indwelling catheters inserted at the time of procedure. Our pharmacokinetic studies (***Study I***, ***IV*** and ***V***) have been carried out in surgical procedures. Results from plasma analysis may therefore be influenced by confounding factors such as interactions with other drugs administered during the course of anesthesia, perioperative cardiac output, distribution of blood and blood loss.

THESIS AND SPECIFIC DISCUSSION *STUDIES I-V*

The studies in this thesis have focused on different aspects of opioid treatment in the pediatric population with special interest in morphine and ketobemidone. The aim has been to increase the knowledge of both pharmacokinetic and pharmacodynamic effects of these two opioids.

RECTAL MORPHINE – PHARMACOKINETICS AND ACCEPTANCE OF RECTAL ADMINISTRATION *(STUDY I & III)*

Opioids like morphine are a first-line analgesic in patients with severe nociceptive pain. A lack of intravenous access calls for other routes and rectal administration is one possibility which is regularly used in children. Local and nationwide customs and attitudes undoubtedly affect the choice in route of administration. In general today rectal administration has a declining interest in favor of nasal and buccal administration. There are still conditions where rectal administration of opioids has its place in pain management. Drug formulations manufactured for intravenous delivery is

often administered via other routes disregarding their suitability from a pharmacokinetic or pharmacodynamic perspective.

The purpose in ***Study I*** and ***III*** was to explore if a rectal gel tailored for rectal use had advantages compared to a regular solution with a lower pH.[65] The tailored gel formulation had a higher pH (pH 5) than the morphine standard solution (pH 3-4). The rationale was to achieve a better uptake and to induce less distress and pain upon rectal administration. In our clinical practice we had previously noticed that solutions such as midazolam and to some degree morphine evoked pain when given rectally to children.

The results from the pharmacokinetic (***Study I***) did not reveal any significant bioavailability difference between the two rectal groups. Mean plasma levels, after a dose of 0.2 mg/kg, were in the range of concentrations shown to achieve adequate analgesia in children. A problem with rectal administration of drugs is the erratic uptake. This was also demonstrated in the present study. There was a large inter-individual variation in both groups regarding maximum plasma concentration and bioavailability. The same findings have been shown in several other studies.[4, 32, 50, 51, 92-94] From a clinical point of view this creates a dose problem especially in combination with a big variation in plasma levels related to an analgesic response. When rectal morphine is used repeatedly it is of clinical importance to evaluate individual response.

In ***Study III*** we used two different preparations of morphine for premedication. Age appropriate validated pain scales were used to compare children's acceptance of rectal administration.

Interestingly enough the general pain scores were low in all age groups receiving either of the two test drugs. In infants and younger children there was significantly less pain from administration of the morphine gel compared to the morphine solution which not could be demonstrated in children 7-10 years. Even if a non-statistical significant difference was found in older children the figure 7 shows a tendency of lower pain scores for the morphine gel.

As stated earlier, pain is an unpleasant and personal emotional experience. In children less than 10 years of age pain is not so distinguishable from other types of discomfort. It could be argued that the results are more of discomfort than a clear pain measurement. Some children might have been responding to the handling of rectal administration itself but this probability cannot explain the differences between groups that were shown in the study.

The rectal method of drug administration can be considered as a feasible alternative when an intravenous access in not available. In general rectal administration has gained less popularity during the last decades for reasons of both parental and health care personnel's opinions. Nasal administration on the other hand has been more popular at our hospital and especially as part of the treatment of procedural pain. Patient satisfaction is especially important when treating children. Disregarding the mode of delivery the aim should be to use or develop drug formulations that are acceptable by the patient and have favorable pharmacokinetic properties.

KETOBEMIDONE – EQUIPOTENCY AND SIDE EFFECTS WHEN COMPARED TO MORPHINE *(STUDY II)*

Previous studies in adults have shown a variation in analgesic potency when ketobemidone and morphine were compared. [74, 86, 95, 98] In one study using PCA for postoperative pain treatment the relationship between ketobemidone and morphine was almost equivalent.[98]

This study is the first published study in children looking at the analgesic effect of ketobemidone in comparison with morphine in a postoperative setting. The use of PCA has shown to be a reliable method for carrying out comparative treatment studies. The PCA settings were a true patient controlled technique with a bolus dose of 20 microg/kg, no background infusion and with a frequently used lockout time of 5 minutes. A difference in total consumption of less than 25 % was considered a non significant clinical difference. The limit of 25 % was based on a consensus of pain treatment staff, doctors and nurses, and a pharmacologist.

The results showed an equipotent relationship between ketobemidone and morphine which was all in line with our clinical experience. The median ratio of ketobemidone and morphine consumption was 0.94 for the total consumption and in the same range for the first two postoperative days. During the following two days an increase in opioid consumption was observed in the patients receiving morphine as compared to ketobemidone. Differences for example in receptor profile and metabolite formation could explain this finding. The number of patients was declining during the last two days of the study period, thereby interpretation of the increase in morphine consumption should be careful.

Adverse effects of morphine such as nausea, vomiting and itching are common in the pediatric population.[44, 79] In our study adverse effects of both opioids used were quite prominent and lead to discontinuation of PCA in 4 children in the morphine group despite the distressing pain situation. During this study period multimodal treatment strategy was not developed to a large extent which might explain the high number of opioid related side effects. Opioid rotation is more frequently used today.

PCA as a method gained a lot of interest when introduced into pediatric pain management. The advantage is that the patient was in control of his or her own treatment. Today the use of PCA at our hospital has decreased substantially. The PCA as a method does not provide optimal pain control especially during the first postoperative night. There is no PCA device today that can be programmed for an automatic shift from PCA daytime to a continuous infusion during night hours which would be preferred as based on clinical experience.

PHARMACOKINETICS OF KETOBEMIDONE IN NEONATES AND OLDER CHILDREN (*STUDY IV & V*)

Ketobemidone has been in use in children in Scandinavia for several decades. Surprisingly, these two studies in children and neonates are the first ones describing its pharmacokinetics. The results from the two studies have been compared with previous published studies in adults.[4 ,5 ,9, 10] Our results in children aged over one month show similar pharmacokinetic values as in adults. In the patient group aged one to two and a half years we could observe a trend towards a shorter elimination half-life of ketobemidone. This finding is probably caused by an increased metabolic rate which has been demonstrated for several drugs.

In ***Study IV*** two of the youngest patients (neonates) showed a decreased metabolic rate but no conclusions could be drawn from the findings because of the limited numbers of children involved. It was therefore decided to further explore the pharmacokinetics in the neonatal population (***Study V***). The protocol was somewhat modified and blood samples were also taken in the early phase which allowed for calculation of the fast distribution phase as well as the slower elimination phase (elimination half-life). Our results show that children during the first

month of life have a considerably longer elimination half-life time compared to the older children in our previous study. This is most likely accounted for in their reduced metabolic rate. An increased variability in the pharmacokinetic profile has in a similar way been observed for morphine and oxycodone. The decreased metabolism of drugs carries the risk of high concentrations of the particular drug with repetitive administration which should be taken into account in the clinical situation.

The opioid ketobemidone is a substrate for cytochrome P450 enzymes (CYP), CYP2C9 and CYP3A4. The cytochrome systems are often immature at birth. Furthermore, the liver cytochrome 450 is exists in a fetal form (CYP3A7) and shifts into CYP3A4 during the neonatal period. A lower metabolic rate for ketobemidone in the neonates in our study could to some extent be explained by a decreased expression of CYP3A4 enzymes.

The main metabolite of ketobemidone is norketobemidone, with a high affinity for the mu-receptor, and has been detected in urine in adults but not in plasma.[10] Norketobemidone could not be detected in children in ***Study IV*** and the metabolite was not examined in ***Study V***. The lack of active metabolites is generally considered to be an advantage in patients with renal insufficiency or immature renal function. Morphine metabolism is also affected by age and neonates predominantly produce a higher degree of the excitatory metabolite M3G. This might cause a problem in neonates when morphine is used for a prolonged period, a problem which we have noted clinically. In the neonatal population it is therefore suggested that ketobemidone might be a suitable opioid to use.

The results from ***Study IV*** show that AUC normalized for mg per body weight increasing with increasing age. Therefore, the systemic drug exposure (AUC) to ketobemidone will decrease with decreasing age when dosage is based on body weight. In contrast, dosage based on BSA is likely to provide a more predictable systemic drug exposure. The pharmacokinetic results in neonates (***Study V***) indicates on the other hand, that dosing of ketobemidone based on body weight will give as low inter-individual variability in systemic drug exposure as dosing based on BSA in infants aged 1-18 days.

CLOSING REMARKS

Knowledge of a drug's pharmacokinetics is important to clinicians. Unfortunately pharmacokinetic studies have been a neglected area in the pediatric population. The analgesic effect can however differ between individuals to a large extent. Dose recommendations can therefore not be based solely on pharmacokinetic knowledge but need to take individual variability into account. The individual variability to opioid treatment can be affected by several background mechanisms (table 7).

The best analgesic for the patient is the one that will effectively decrease pain to a minimum or acceptable pain levels, with as little side effect as possible and without patient disagreement during administration.

Table 7 Opioid effect variability - plausible mechanisms

Genetic polymorphism	**two or more clearly different phenotypes exist in the same population (for example UGT2B7, CYP3A4 and CYP2D6 in codeine breakdown) which will affect metabolism, receptor function**
Receptor subtypes	**leading to differences in analgesic response between individuals (see Table 2)**
Age dependent receptor distribution	**higher density of opioid receptors in prematures**
Immature nociceptive system	**more diffuse response in small children, underdeveloped descending inhibition**
Immune system activation	**interaction with gliacell activity, for example in sepsis or infections, leading to increased pain signaling**
Age dependent metabolic rate	**immature metabolic pathways, in neonates and small infants**
Erratic uptake	**following enteral administration as compared to intravenous administration**
Drug interactions	**in metabolistic pathways (between ketobemidone and propofol) at receptor site (antagonist/agonist action of naloxone, buprenorphine and ketobemidone))**
Type of surgical trauma and/or stress	**more intense ascending nociceptive signaling, following larger incision/wound area and following longer duration of surgery**
Repeated surgical interventions	**peripheral and central sensitization (including wind up), memory of surgical pain and/or fear**
Psychological status	**personality trait, memory of pain and fear (including parental interaction), allostatic load**

8 Conclusion

From the studies in this thesis the following conclusions are drawn.

- Study I

A morphine gel adapted for rectal use did not show any significant higher bioavailability but had a tendency for a better uptake.
Bioavailability of rectally administered morphine is relatively low and shows a large inter-individual variability in children.

- Study II

The opioid ketobemidone is equipotent to morphine when used for postoperative pain treatment.
The frequency of adverse effects of ketobemidone and morphine are comparable when PCA is used for postoperative pain relief in children

- Study III

A morphine gel developed for rectal administration generates less pain in children aged 1-6 years when a tailored morphine gel was compared to a regular morphine solution.
Most children tolerate rectal administration of morphine when used as premedication.

- Study IV

The pharmacokinetic parameters of the opioid ketobemidone in children over 1 month of age appear to be similar to those in adults. Due to the small number of neonates included further studies are necessary to be able to draw accurate conclusions.

- Study V

The elimination of ketobemidone appeared to be slower in full-term neonates compared to our previous study in children older than one year of age. It is recommended to individualize the dose of ketobemidone based on observations of analgesic efficacy.

9 Acknowledgements

To all of you making this thesis come true putting an end to a never ending story. Without your help, cheerfulness, positive questions and remarks it might have been another ending.

All patients and parents for their participation and support in the studies.

Associate professor ***Gunnar L Olsson,*** main supervisor, for introducing me to the scientific field of pediatric pain. Always positive and supportive. It took a long time to finish all the work and I think I broke your record. Major benefactor for the development of the Pediatric Pain Treatment Service.

Professor ***Staffan Eksborg***, co-supervisor, who joined my force during the last years of work. Energy like a Duracell rabbit. Always supporting, most skilled in statistics and pharmacokinetics. A pleasure to get acquainted to.

Associate professor ***Carl Olav Stiller***, co-author with lots of skills which has been helpful. A valuable man in regards of getting blood samples analyzed.

The pain treatment staff ***Anders Lindberg, Marianne Segerberg & Lisa Skogström***, Skilled as few doctors in the field of pediatric pain. Always helpful in my scientific work. Pleased that the thesis is finished so we can go ahead.

Leena Jylli, co-author, co-worker. Escorting me to Boston Children's Hospital to get the right background for starting our Pain Treatment Service – not a co-incidence. Good times when you still were at Astrid Lindgren Children's Hospital North Site. Aiming for evidence grade A for best treatment.

My ***colleagues, doctors and nurses***, at the department of Pediatric Anesthesia and Intensive Care for the support in all different possible ways in my thesis work. Day time as well as night time.

The ***secretary staff***, ***Paula Toumie and Rita Bexar*** for supplying me with the right papers, paying bills, Finnish liquorices, exotic Finnish dishes and entertaining mails. Always grade A fun.

Fellow pain doctors abroad for valuable comments throughout the years and memorable meetings.

The department of Pediatric Anesthesia and Intensive Care for giving financial support through departmental research funding.

Neighbors & friends looking forward to the end of the never ending story –for various reasons.

At last and most importantly the support during the whole journey from ***my parents***, ***brothers and their families*** and my own family & fw ***Viktor, Mikaela & Tina***.

अंत

10 References

1. Abu-Saad H. Assessing children's responses to pain. Pain 1984; 2: 163-71.

2. Anand K, Stevens B, McGrath PJ. Pain in Neonates and Infants: Pain Research and Clinical Management Series. Elseiver 2007.

3. Andersen S, Dickenson AH, Kohn M, Reeve A, Rahman W, Ebert B. The opioid ketobemidone has a NMDA blocking effect. Pain 1996; 67: 369-74.

4. Anderson P, Arnér S, Bondesson U, Boréus LO, Hartvig P. Clinical pharmacokinetics of ketobemidone. Its bioavailability after rectal administration. Eur J Clin Pharmacol 1981; 19: 217-23.

5. Anderson P, Arnér S, Bondesson U, Boréus LO, Hartvig P. Single-dose kinetics and bioavailability of ketobemidone. Acta Anaesthesiol Scand Suppl 1982; 74: 59-62.

6. Astuto M, Disma N, Rizzo G, Messeri A. Developments in the treatment of postoperative pain in paediatrics. Minerva Anestesiol. 2002; 68: 428-32.

7. Berde CB, Kehn BM, Yee JD, Sethna NF, Russo D. Patient controlled analgesia in children and adolescents: a randomized prospective comparison with intramuscular administration of morphine for postoperative analgesia. J Pediatr 1991; 118 (3): 460-6.

8. Blake MJ, Gaedigk A, Pearce RE, Bomgaars LR, Christensen ML, Stowe C, James LP, Wilson JT, Kearns GL, Leeder JS. Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. Clin Pharmacol Ther. 2007; 81: 510-6.

9. Bondesson U, Arnér S, Anderson P, Boréus LO, Hartvig P. Clinical pharmacokinetics and oral bioavailability of ketobemidone. Eur J Clin Pharmacol 1980; 17: 45-50.

10. Bondesson U, Hartvig P, Danielsson B. Quantitative determination of the urinary excretion of ketobemidone and four of its metabolites after intravenous and oral administration in man. Drug Metab Dispos 1981; 9: 376-80.

11. Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. Br J Anaesth 2004; 92; 208-17.

12. Boyd E. The Growth of the surface area of the human body. The University of Minnesota Press 1935.

13. Brack A, Rittner HL, Stein C. Immunosuppressive effects of opioids--clinical relevance. J Neuroimmune Pharmacol. 2011; 6: 490-502.

14. Bhutta AT, Anand KJ. Vulnerability of the developing brain. Neuronal mechanisms. Clin Perinatol. 2002; 29: 357-72.

15. Choonara IA, McKay P, Hain R, Rane A. Morphine metabolism in children. Br] Clin Pharmacol 1989: 28: 599-604.

16. Choonara I, Lawrence A, Michalkiewicz A, Bowhay A, Ratcliffe J. Morphine metabolism in neonates and infants. Br J Clin Pharmacol 1992: 34: 434-437.

17. Christensen CB. The opioid receptor binding profiles of ketobemidone and morphine. Pharmacol Toxicol 1993; 73: 344-5.

18. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimeters? Pain 1997; 72: 95-7.

19. Crews J.C. Multimodal pain management strategies for office-based and ambulatory procedures. JAMA, 288 (2002), pp. 629-632.

20. Dahlstrom B, Bolme P, Feychting H, Noack G, Paalzow L. Morphine kinetics in children. CIiri Pharrnacol Ther 1979: 26:354-365.

21. Daniel WW: Applied Nonparametric Statistics. Boston, Houghton Mifflin. 1978, pp 40-43.

22. Davidson AJ. Neurotoxicity and the need for anesthesia in the newborn: does the emperor have no clothes? Anesthesiology. 2012; 116: 507-9.

23. Demyttenaere S, Finley A, Johnston C et al. Pain treatment thresholds in children after major surgery. Clin J Pain 2001; 17: 173–177.

24. Ebert B, Andersen S, Krogsgaard-Larsen P. Ketobemidone, methadone and pethidine are non-competitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. Neurosci Lett 1995; 187: 165-8.

25. Eksborg S, Söderäll S, Frostvik-Stolt M, Lindberg A Liliemark E. Plasma pharmacokinetics of etoposide (VP- 16) after i.v. administration to children. Anticancer Drugs 2000; 11: 237-41.

26. Eksborg S, Pal N, Kalin M, Palm C, Söderhäll S. Pharmacokinetics of acyclovir in immunocompromized children with leukopenia and mucositis after chemotherap: can intravenous acyclovir be substituted by oral valacyclovir? Med Pediatr Oncol 2002; 38: 240-6.

27. Fine PG, Portenoy RK; Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation. Establishing "best practices" for opioid rotation: conclusions of an expert panel. J Pain Symptom Manage. 2009; 38: 418-25.

28. Fitzgerald M, Beggs S. The neurobiology of pain: developmental aspects. Neuroscientist. 2001; 7: 246-57.

29. Franson HE.Postoperative patient-controlled analgesia in the pediatric population: a literature review. AANA J. 2010; 78: 374-8.

30. Gauthier JC, Finley A, McGrath PJ. Children's self-report of postoperative intensity and treatment threshold: determining the adequacy of medication. Clin J Pain 1998; 14: 116-120.

31. Gong QL, Hedner J, Björkman R, Hedner T. Morphine-3-glucuronide may functionally antagonise morphine-6-glucuronide induced antinociception and ventilatory depression in the rat. Pain 1992: 48: 249-255.

32. Hamunen K, Maunuksela EL, Seppala T et al. Pharmacokinetics of i.v. and rectal pethidine in children undergoing ophthalmic surgery. Br J Anaesth 1993; 71: 823-826.

33. Howard R, Carter B, Curry J, Morton N, Rivett K, Rose M, Tyrrell J, Walker S, Williams G; Pain assessment. Association of Paediatric Anaesthetists of Great Britain and Ireland. Paediatr Anaesth. 2008; 18 Suppl 1: 14-8.

34. Howard R, Carter B, Curry J, Morton N, Rivett K, Rose M, Tyrrell J, Walker S, Williams G; Association of Paediatric Anaesthetists of Great Britain and Ireland. Postoperative pain. Paediatr Anaesth. 2008; 18 Suppl 1: 36-63.

35. Huntink-Sloot MT, Faber-Nijholt R, Zwierstra RP et al. Better postoperative pain management in children by introduction of guidelines; a prospective study. Ned Tijdschr Geneeskd 1997; 141: 998-1002 (in Dutch).

36. Hutchinson MR, Shavit Y, Grace PM, Rice KC, Maier SF, Watkins LR. Exploring the neuroimmunopharmacology of opioids: an integrative review of mechanisms of central immune signaling and their implications for opioid analgesia. Pharmacol Rev. 2011; 63: 772-810.

37. Johnson TN, Tucker GT, Rostami-Hodjegan A. Development of CYP2D6 and CYP3A4 in the first year of life. Clin Pharmacol Ther. 2008; 83: 670-1.

38. Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 1-Pharmacokinetics. Paediatr Anaesth 1997; 7: 5-11.

39. Kart T, Christrup LL, Rasmussen M. Review article. Recommended use of morphine in neonates, infants and childrenbased on a literature review: Part 2- Clinical use. Paediatr Anaesth 1997; 7: 93-101.

40. Kauffman RE, Kearns GL. Pharmacokinetic studies in paediatric patients. Clinical and ethical considerations. Clin Pharmacokinet 1992; 23:10-29.

41. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth 1997, 78, 606-617.

42. Kendall JM, Latter VS. Intranasal diamorphine as an alternative to intramuscular morphine: pharmacokinetic and pharmacodynamic aspects. Clin Pharmacokinet. 2003; 42: 501-13.

43. Kristensen K, Christensen CB, Christrup LL, Nielsen LC. The mu1 and mu2 opioid receptor binding of ketobemidone, norketobemidone and 3-dimethylamino-1,1-diphenylbutene. Pharmacol Toxicol 1996; 79: 103-4.

44. Kokinsky E, Thornberg E, Nilsson K, Larsson LE. Postoperative nausea and vomiting in children using patient-controlled analgesia: the effect of prophylactic intravenous dixyrazine. Acta Anaesthesiol Scand 1999; 43: 191-5.

45. Lack JA, Stuart-Taylor ME. Calculation of drug dosage and body surface area of children. Br J Anaesth 1997; 78: 601-5. 21.

46. Lacroix D, Sonnier M, Moncion A, Cheron G, Cresteil T. Expression of CYP3A in the human liver – evidence that the shift between CYP3A7 and CYP3A4 occurs immediately after birth. Eur J Biochem 1997; 247: 625-34.

47. Leeder JS, Kearns GL. Pharmacogenetics in pediatrics. Implications for practice. Pediatr Clin North Am 1997; 44: 55-77.

48. Lehmann KA. Recent developments in patient-controlled analgesia. J Pain Symptom Manage. 2005; 29: S72-89.

49. Leeder & Kearns Pharmacogenetics in pediatrics. Implications for practice. Pediatr Clin North Am. 1997

50. Leow K, Cramond T, Smith M. Pharmacokinetics and pharmacodynamics of oxycodone when given intravenously and rectally to adult patients with cancer pain. Anesth Analg 1995; 80: 296-302.

51. Leow K, Smith M, Watt J, Williams B, Cramond T. Comparative oxycodone pharmacokinetics in humans after intravenous, oral, and rectal administration. Ther Drug Monit 1992; 14: 479-84.

52. Ljung B, Andréasson S. Comparison of midazolam nasal spray to nasal drops for the sedation of children. J Nucl Med Technol 1996; 24: 32-34.

53. Lugo RA, Kern SE. The pharmacokinetics of oxycodone. J Pain Palliat Care Pharmacother. 2004; 1 8: 17-30.

54. Lundeberg S, Lönnqvist PA. Update on systemic postoperative analgesia in children. Paediatr Anaesth. 2004; 14: 394-7.

55. Lundeberg S, Roelofse JA. Aspects of pharmacokinetics and pharmacodynamics of sufentanil in pediatric practice. Paediatr Anaesth. 2011; 21: 274-9.

56. Lönnqvist PA, Morton NS. Postoperative analgesia in infants and children. Br J Anaesth. 2005; 95: 59-68.

57. Lönnqvist PA, Bergendahl HT, Eksborg S. Pharmacokinetics of clonidine after rectal administration in children. Anesthesiology. 1994; 81: 1097-101.

58. Mather L, Mackie J. The incidence of postoperative pain in children. Pain 1983: 15: 271-282.

59. McDonald AJ, Cooper MG. Patient-controlled analgesia: an appropriate method of pain control in children. Paediatr Drugs. 2001; 3: 273-84.

60. McGrath PA. Pain in Children: Nature, Assessment and Treatment. Guildford Publications, New York, NY, 1990.

61. McGrath PA, Seifert CE, Speechley KN et al. A new analogue scale for assessing children's pain: an initial validation study. Pain 1996; 64: 435-443.

62. McGrath PJ, Johnson G, Goodman JT. The CHEOPS: a behavioral scale to measure postoperative pain in children. In Fields HL, Dubner R, Cervero F, eds. Advances in Pain Research and Therapy. New York: Raven Press, 1985: 395-402.

63. Mellon RD, Simone AF, Rappaport BA. Use of anesthetic agents in neonates and young children. Anesth Analg. 2007; 104: 509-20.

64. Mikkelsen S, Feilberg VL, Christensen CB, Lundstrøm KE Morphine pharmacokinetics in premature and mature newborn infants. Acta Paediatr 1994; 83: 1025-8. 16.

65. Moolenar F, Yska JP, Visser PH, Meijer DKF. Drastic improvement in the rectal absorption profile of morphine in man. Eur] CIin Pharmacol 1985: 29: 119-121.

66. Morton NS, O'Brien K. Analgesic efficacy of paracetamol and diclofenac in children receiving PCA morphine. Br J Anaesth 1999; 82: 715-7.

67. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987; 31: 1098.

68. Mudd S. Intranasal fentanyl for pain management in children: a systematic review of the literature. J Pediatr Health Care. 2011; 25: 316-22.

69. Olkkola KT, Maunuksela EL, Korpela R, Rosenberg PH. Kinetics and dynamics of postoperative intravenous morphine in children. CIin Pharnacol Ther 1988: 44: 128-136.

70. Osborne R, Joel S, Trew D, Slevin M. Analgesic activity of morphine-6-glucuronide Lancet 1988: 331:828.

71. Osborne R, Thompson P, Joel S, et al. The analgesic activity of morphine-6-glucuronide. Br J CIin Pharmacol 1992: 34: 130-138.

72. Pasero C. Multimodal balanced analgesia in the PACU. J Perianesth Nurs. 2003; 18: 265-8.

73. Pasternak GW, Bodnar RJ, Clark JA, Inturrisi C.E. Morphine- 6-glucuronide, a potent mu agonist. Life Science 1987: 41:2845-2849.

74. Peltola P, Soisala P. The analgesic properties and addictionliability of ketobemidone and morphine. AMA Arch IntenMed 1958; 101: 741-6.

75. Perrott D, Goodenough B, Champion D. Children's ratings of the intensity and unpleasantness of post-operative pain using facial expression scales. Eur J Pain 2004; 8: 119-127.

76. Pokela ML, Anttila E, Seppälä T, Olkkola KT. Marked variation in oxycodone pharmacokinetics in infants. Paediatr Anaesth 2005; 15: 560-5.

77. Pothmann R. Comparison of the Visual Analog Scale (VAS) and a Smiley Analog Scale (SAS) for the evaluation of pain in children. In: Tyler D, Krane E, eds. Advances in Pain Research Therapy Vol 15. New York: Raven Press, Ltd, 1990: 95-99.

78. Schneider AJ. Assessment of risk factors and surgical outcome. Surg Clin North Am 1983; 63: 1113-1126.

79. Schechter N, Berde S, Yaster M. Pain in Infants, Children, and Adolescents. Lippincott Williams & Wilkins 2002.

80. Seth N, Llewellyn NE, Howard RF. Parental opinions regarding the route of administration of analgesic medication in children. Paediatr Anaesth 2000; 10: 537–544.168 S.

81. Shannon M, Berde C. Pharmacologic management of pain in children and adolescents. Pain 1989: 36: 855-871.

82. Smith MT, Watt JA, Cramond T. Morphine-3-glucuronide – a potent antagonist of morphine analgesia. Life Sciences 1990: 47:579-585.

83. Soriano SG, Anand KJ. Anesthetics and brain toxicity. Curr Opin Anaesthesiol. 2005; 18: 293-7.

84. Steinijans VW, Diletti E. Generalization of distribution--free confidence intervals for bioavailability ratios. Eur J Clin Pharmacol. 1985; 28: 85-8.

85. Svensson JO, Rane A, Sawe J, Sjoqvist F. Determination of morphine, morphine-3-glucuronide and (tentatively) morphine- 6-glucuronide in plasma and urine using ion-pair high performance liquid chromatography. J Chrornatography 1982: 230: 427-432.

86. Tamsen A, Bondesson U, Dahlström B, Hartvig P. Patient-controlled analgesic therapy, Part III: pharmacokinetics and analgesic plasma concentrations of ketobemidone. Clin Pharmacokinet 1982; 7: 252-65.

87. Tobias JD. Postoperative pain management. Pediatr Ann. 1997; 26: 490-500.

88. Tung A, Herrera S, Fornal CA, Jacobs BL.The effect of prolonged anesthesia with isoflurane, propofol, dexmedetomidine, or ketamine on neural cell proliferation in the adult rat. Anesth Analg. 2008; 106: 1772-7.

89. Tyler C, Pomietto M, Womack W. Variations in opioid use during PCA in adolescents. Paediatr Anaesth 1996; 6: 33-8.

90. Van Dorp EL, Morariu A, Dahan A. Morphine-6-glucuronide: potency and safety compared with morphine. Expert Opin Pharmacother 2008; 9: 1955-61.

91. Wang X, Loram LC, Ramos K, de Jesus AJ, Thomas J, Cheng K, Reddy A, Somogyi AA, Hutchinson MR, Watkins LR, Yin H. Morphine activates neuroinflammation in a manner parallel to endotoxin.Proc Natl Acad Sci U S A. 2012; 109: 6325-30.

92. Westerling D, Lindahl S, Andersson K-E, Andersson A. Absorption and bioavailability of rectally administered morphine in women. Eur J Clin Pharmacol 1982: 23: 59-64.

93. Westerling D, Anderson KE. Rectal administration of morphine hydrogel: absorption and bioavailability in women. Acta Anaesthesiol Scand 1984: 28: 540-543.

94. Westerling D. Rectally administered morphine: Plasma concentration in children premedicated with morphine in hydrogel and in solution. Acta Anaesthesiol Scand 1985: 29: 653-656.

95. Wolff T, Leward S, Hagman A, Andersson M, Larsson L Elgen K. Analgesic treatment in acute myocardial infarction. A double-blind comparison of ketobemidone + the spasmolytic A29 (Ketogan) and morphine. Acta Med Scand 1988; 223: 423-30.

96. Yasar U, Annas A, Svensson JO, Lazorova L, Artursson P, Al-Shurbaji A. Ketobemidone is a substrate for cytochrome P4502C9 and 3A4, but not for P-glycoprotein. Xenobiotica 2005; 35: 785-96.

97. Zernikow B, Michel E, Craig F, Anderson BJ. Pediatric palliative care: use of opioids for the management of pain. Paediatr Drugs. 2009; 11: 129-51.

98. Öhqvist G, Hallin R, Gelinder S, Lang H, Samuelson S. A comparison between morphine, meperidine and ketobemidonein continuous intravenous infusion for postoperative relief. Acta Anaesthesiol Scand 1991; 35: 44-8.