

KUOPION YLIOPISTON JULKAISUJA D. LÄÄKETIEDE 269
KUOPIO UNIVERSITY PUBLICATIONS D. MEDICAL SCIENCES 269

HENRI TUOMILEHTO

**Pain Management and Outcome in
Children After Adenoidectomy**
A Special Reference to Different
Administration Routes of Ketoprofen

Doctoral dissertation

To be presented by permission of the Faculty of Medicine of the
University of Kuopio for public examination in
Auditorium, Kuopio University Hospital,
on Friday 8th March 2002, at 12 noon

Department of Otorhinolaryngology
Department of Anaesthesia and Intensive Care
Faculty of Medicine
University of Kuopio
Kuopio University Hospital



KUOPION YLIOPISTO

KUOPIO 2002

- Distributor:** Kuopio University Library
P.O.Box 1627
FIN-70211 Kuopio
FINLAND
Tel.+358 17 163 430
Fax+358 17 163 410
- Serial editors:** Professor Esko Alhava, M.D., Ph.D.
Department of Surgery

Professor Martti Hakumäki, M.D., Ph.D.
Department of Physiology
- Authors Address:** Department of Otorhinolaryngology
Kuopio University Hospital
P.O.Box 1777
FIN-70211 Kuopio
FINLAND
Tel.+358 17 173 311
Fax+358 17 172 509
- Supervisors:** Professor Juhani Nuutinen, M.D.
Department of Otorhinolaryngology
University of Kuopio

Docent Hannu Kokki, M.D.
Department of Anaesthesiology and Intensive Care
University of Kuopio
- Reviewers:** Docent Heikki Löppönen, M.D.
Department of Otorhinolaryngology
University of Oulu

Docent Päivi Annila, M.D.
Department of Anaesthesiology and Intensive Care
University of Tampere
- Opponent:** Professor Markus Rautiainen, M.D.
Department of Otorhinolaryngology
University of Tampere

ISBN 951-781-869-6
ISSN 1235-0303

Savon kopiokeskus Oy
Kuopio 2002
Finland

Tuomilehto, Henri. Pain management and outcome in children after adenoidectomy: a special reference to different administration routes of ketoprofen. Kuopio University Publications D. Medical Sciences 269. 2002. 84 p.
ISBN 951-781-869-6
ISSN 1235-0303

ABSTRACT

The purpose of this study was to evaluate: 1) perioperative and postoperative pain in children, aged 1-10 years, following a day-case adenoidectomy with a special reference to different administration routes of ketoprofen, 2) the pharmacokinetics of ketoprofen in young children, aged 1-5 years, after a single oral and intramuscular administration, and 3) postoperative behavioural changes in children at one and three weeks after day surgery when proactive pain treatment was used.

A total of 363 children were included in five different studies. In studies I-III postoperative pain and pain treatment of 343 children with oral, rectal, intramuscular and intravenous administration routes of ketoprofen was assessed during a day-case adenoidectomy. In these studies the study design was prospective, randomised, double-blind, double dummy with a placebo control. In study IV, the pharmacokinetics of ketoprofen was evaluated in 20 patients who underwent surgery below the umbilicus under spinal anaesthesia. The study design was a prospective, longitudinal, open clinical trial. In study V, the recovery of the first consecutive 300 children out of 343 during a three-week period after discharge was reported. Specially trained nurses performed the follow-up of the children in hospital, and the questionnaires after discharge, were completed by the children's guardians.

Ketoprofen provided significantly better analgesic effect than placebo, but there was no difference in the requirement or in the proportion of children needing rescue analgesics between different administration routes of ketoprofen. The rate and extent of absorption, and the elimination of ketoprofen were comparable after intramuscular and oral administration in young children. Therefore, there is no justification to administer ketoprofen by intramuscular injection in children with an i.v.-line in place or who can swallow.

The present study shows that pain after adenoidectomy in children is common, 9 out of 10 children needing analgesics with a mean number of 6 doses. Significant pain lasts around three days after discharge with the first postoperative day being the worst. The incidence of significant behavioural problems when proactive pain treatment is used is rare. Furthermore, when behavioural changes are noted, they are as often positive, as well as negative.

National Library of Medicine Classification: WV 430, WS 200, WO 184

Medical Subject Headings: adenoidectomy; ambulatory surgical procedures; pain; postoperative; child; pain/psychology; ketoprofen; ketoprofen/pharmacokinetics; drug administration routes; prospective studies; controlled clinical trials

ACKNOWLEDGEMENTS

This study was carried out at the Department of Otorhinolaryngology and the Department of Anaesthesiology and Intensive Care of Kuopio University Hospital during the years 1998-2002.

I wish to express my thanks to my supervisor, Professor Juhani Nuutinen, for his guidance and help during this work. He made it possible for me to continue and finish my studies smoothly alongside my clinical work.

I owe my deepest gratitude to my other supervisor, Docent Hannu Kokki, for his everlasting enthusiasm and encouragement. He had always time and patience for me and for my, often even silly questions. I also want to thank him for the friendship that we have gained during these years.

I want to thank my former Professor Eero Vartiainen who encouraged and advised me in the initiation of my thesis.

I am grateful to my official reviewers, Docent Päivi Annila and Docent Heikki Löppönen, for their expert advise and constructive criticism of the manuscript.

I owe my warm thanks to Professor Riitta Ahonen who has helped and advised me a great deal during my work.

I am deeply grateful to my co-authors Kati Tuovinen, MSc, and Marko Karvinen, MD, for their help during these studies.

I wish to express my warmest thanks to personnel of Polyclinic of the Department of Otorhinolaryngology and Day Surgery Center, especially to Ulla and Marja, who have made an enormous effort to help me with these studies.

I want to thank Paula Räsänen, for her great work in information processing and with the Figures and Pirjo Halonen, MSc, for her help in the statistical analysis for the original manuscript V.

I wish to express my gratitude to all my colleagues in the Department of Otorhinolaryngology for a great atmosphere at work and, especially at freetime for the entertaining evenings and our never-ending competition in golf (watch out for next summer, the thesis is now completed).

I am grateful to Docent Malcolm Richardson, for revision of the English language in most original papers and the final manuscripts.

I want warmly to thank my close friends in Helsinki and Tampere; Hannu, Tommi, Petri and Heikki, for their friendship during many years. You guys have showed me that life is much more than just medicine. I wish also to thank warmly my close friends in Kuopio; Jussi, Janne, Ari, Jarmo, Marko and Grigori, for making my living here in Kuopio very enjoyable.

I wish all the best for little brothers Petteri, Tuomas and Kristian in their future lives. May they be happy and successful.

Finally, loving thanks to my parents Kaija-Maria and Jaakko, for their support over the years. You are the greatest.

Financial support by EVO funding of Kuopio University Hospital, Orion Pharma and the Finnish Otolaryngology Association are acknowledged with gratitude.

Kuopio March 2002

Henri Tuomilehto

ABBREVIATIONS

ASA	The American Society of Anesthesiologist's Physical Status Grading
Asa	acetyl salicylic acid
CAS	coloured analogue scale
CNS	central nervous system
COX	cyclo-oxygenase
EEG	electroencephalograph
ENT	ear-, nose-, and throat
i.m.	intramuscular
i.v.	intravenous
NSAID	non-steroidal anti-inflammatory drug
PACU	post-anaesthesia care unit
SD	standard deviation
VAS	visual analogue scale
VRS	verbal rating scale

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals.

I. Tuomilehto H, Kokki H, Tuovinen K. Comparison of intravenous and oral ketoprofen for postoperative pain after adenoidectomy in children. *Br J Anaesth* 2000; 85: 224-227.

II. Kokki H, Tuomilehto H, Tuovinen K. Pain management after adenoidectomy with ketoprofen: comparison of rectal and intravenous routes. *Br J Anaesth* 2000; 85: 836-840.

III. Tuomilehto H, Kokki H. Parenteral ketoprofen for pain management after adenoidectomy: comparison of intravenous and intramuscular routes of administration. Accepted in *Acta Anaesth Scand*

IV. Kokki H, Tuomilehto H, Karvinen M. Pharmacokinetics of ketoprofen following oral and intramuscular administration in young children. *Eur J Clin Pharmacol* 2001; 57: 643-647.

V. Tuomilehto H, Kokki H, Ahonen R, Nuutinen J. Postoperative behavioural changes in children after adenoidectomy. Submitted

The original papers in this thesis have been reproduced with the permission of the publishers.

CONTENTS

1. INTRODUCTION	15
2. REVIEW OF THE LITERATURE	17
2.1. Day surgery	17
2.2. Adenoidectomy	18
2.3. Anaesthesia in day surgery in children	20
2.3.1. Preoperative assessment	20
2.3.2. Fasting	20
2.3.3. Premedication	21
2.3.4. Induction and maintenance	22
2.3.4.1. Intravenous anaesthetics	22
2.3.4.2. Inhalation agents	23
2.3.4.3. Neuromuscular blocking agents	23
2.4. Pain and pain assessment in children	24
2.4.1. Physiology of acute pain	24
2.4.2. Background of pain assessment	25
2.4.3. Observed pain scales	26
2.4.3.1. Maunuksela pain scale	26
2.4.3.2. Other observed pain scales	26
2.4.4. Expressed pain scales	27
2.5. Treatment of postoperative pain in children	28
2.5.1. General	28
2.5.2. NSAIDs	29
2.5.2.1. Different routes of administration of NSAIDs	31
2.5.3. Paracetamol	32
2.5.4. Opioids	33
2.5.5. Postoperative pain treatment	34
2.5.6. Treatment of postoperative pain at home	35

2.6. Ketoprofen	36
2.6.1. General	36
2.6.2. Pharmacokinetics	36
2.6.2.1. Absorption	36
2.6.2.2. Metabolism and excretion	37
2.6.3. Pharmacodynamics	38
2.6.4. Toxicology	39
2.6.5. Clinical usage	39
2.6.6. Adverse events	40
2.6.6.1. Gastrointestinal adverse events	40
2.6.6.2. Renal adverse events	40
2.6.6.3. Effect on platelet function and bleeding time	41
2.6.6.4. Other adverse events	41
2.7. Postoperative behavioural changes in children	42
3. PURPOSE OF THE PRESENT STUDY	44
4. PATIENTS AND METHODS	45
4.1. Patients	45
4.2. Surgical technique of adenoidectomy	47
4.3. Anaesthesia technique	47
4.4. Assessment of postoperative pain	48
4.4.1. In hospital	48
4.4.2. After discharge	48
4.5. The treatment of pain (studies I-III)	49
4.6. The pharmacokinetics of ketoprofen (study IV)	50
4.7. Postoperative behavioural changes (study V)	50
4.8. Intraoperative bleeding and adverse events	51
4.9. Discharge criteria	51
4.10. Statistical methods	51
4.11. Ethical aspect	52

5. RESULTS	53
5.1. Comparison of different administration routes of ketoprofen	53
5.1.1 Patients characteristics	53
5.1.2. Occurrence of pain in PACU	54
5.1.3. Intraoperative bleeding	55
5.1.4. Need for rescue analgesic	56
5.1.5. Adverse events in PACU	58
5.1.6. Pain after discharge	59
5.1.7. Adverse events after discharge	60
5.2. Pharmacokinetics of oral and intramuscular ketoprofen	62
5.3. Postoperative behavioural changes	63
6. DISCUSSION	65
6.1. Pain treatment with different administration routes of ketoprofen	65
6.1.1. Analgesic effect of ketoprofen	65
6.1.2. Adverse events in hospital	67
6.1.3. Adverse events after discharge	68
6.2. Pharmacokinetics of ketoprofen	68
6.3. Postoperative behavioural changes after proactive pain treatment	69
6.4. Limitations of the present study	70
6.5. Recommendations for effective and safe pain management after day-case adenoidectomy	72
7. CONCLUSIONS	73
8. REFERENCES	74
9. APPENDIX	
Questionnaires completed at home one and three weeks after adenoidectomy	
Original articles I - V	

1. INTRODUCTION

In recent years there has been a tendency towards performing minor surgery on a day basis, adenoidectomy being one of the most common operations in children. The justification for the increased use of day surgery is that it increases efficiency by reducing costs per case while maintaining the quality of care. Successful surgical management provides a major challenge for the providers of health care, requiring a multidisciplinary approach for evaluation of the quality of the day service. The criteria are a minimal postoperative morbidity, low inpatient admission rates and a high parental and child satisfaction (Brennan 1999).

Unfortunately, also minor surgery is associated with morbidity. Some reports show that more than 50% of children undergoing a day surgery experience clinically significant pain after discharge (Kokki and Ahonen 1997, Wolf 1999). Furthermore, the pain experienced by the child in hospital after adenoidectomy predicts the behavioural problems and pain at home after discharge (Kotiniemi et al. 1997).

On the other hand, the underlying disease itself may cause behaviour changes (Rosenfeld et al. 2000). Overall, there are very few studies comparing pre- and postoperative parameters in behaviour profiles in children.

Non-opioid analgesics have been shown to be effective in the treatment of mild and moderate pain in children (Maunuksela et al. 1992a, Nikanne et al. 1997, Brennan 1999, Morton 1999). Non-steroidal anti-inflammatory drugs (NSAID) not only produce a good analgesia but also reduce the consumption of opioids and the incidence and severity of adverse events, such as nausea and vomiting (Kokki et al. 1999a, Brennan 1999). Ketoprofen is a propionic acid derivative and a commonly used NSAID among adults in many countries. The efficacy and safety of ketoprofen are recognised also in paediatric patients (Maunuksela 1993, Kokki et al. 1998). Ketoprofen can be administered by both enteral and parenteral routes. However, different administration routes of ketoprofen, as well as, other NSAID have not been properly compared in pain treatment after surgery (Tramèr et al. 1998).

The aims of the present study were firstly, to evaluate the perioperative and postoperative pain in children after adenoidectomy with special reference to different administration routes of ketoprofen: oral mixture, rectal suppository, intramuscular (i.m.) injection, and intravenous (i.v.) injection; secondly, to determine the pharmacokinetics of ketoprofen after a single oral and intramuscular administration; and thirdly, to assess postoperative behavioural changes in young children after the surgery and to determine the effect of proactive pain treatment on behavioural changes in children during the postoperative period.

2. REVIEW OF THE LITERATURE

2.1. Day surgery

Day surgery is defined as a treatment when admission, procedure and discharge are planned to be performed during the same day with time frame up to 8 hours excluding an overnight stay (Royal College of Surgeons of England 1992, Roberts and Worden 1998). Over the years, many different terms have been used, such as in-and-out-, come-and-go-, downtown-, outpatient-, day-, day-case, same day-, day stay-, day care-, ambulatory anaesthesia and surgery (Roberts and Worden 1998). In this text the terms day or day-case surgery are primarily used.

In recent years there has been a trend towards performing increasing amounts of surgery on children on a day basis. Children make excellent candidates for day surgery as they are usually healthy, free of systemic disease and typically require straightforward, minor or intermediate surgical procedures (Brennan 1999). For example, in the UK, the Royal College of Surgeons of England (1992) and the National Health Service Executive (1993) have estimated that over 50% of all elective surgery, particularly in children, may be performed as day surgery (Royal College of Surgeons of England 1992, National Health Service Executive 1993). In USA, approximately 80% of paediatric surgery is performed on an ambulatory basis (Coté 1999). Furthermore, during early childhood ear-nose-throat (ENT) procedures are the most common surgical operations, accounting, for example in France, for up to two-thirds of operations in children under 4 years old (Clerque et al. 1999). In many countries adenoidectomy is the most common day-case ENT-procedure (Kokki and Ahonen 1997).

The main reason for the change from inpatient care to day surgery undoubtedly is the economics. The health care systems all over the world struggle to meet the increasing demands for health care without an increase in health budgets. Major savings and a reduction in surgery caseload can result by changing common children's procedures from inpatient care to a day basis (Leighton et al. 1993, Pestian et al. 1998, Brennan 1999, Castells

et al. 2001). This also releases inpatient resources for those requiring more complex surgical procedures.

Apart from economic benefits, day surgery confers major advantages for the child and family. It has been known for a long time that hospitalisation causes common behavioural problems in children such as eating problems, sleep disturbances, enuresis, regression to earlier levels of psychological and social functioning and increased anxiety (Vernon et al. 1966).

From the psychological perspective, evidence which has been collected to date points to the benefits of day care for minor paediatric surgery for the majority of children and families (Scaife and Johnstone 1990).

Consistent provision of high-quality day surgery is challenging and needs continuous evaluation. The criteria for judging the quality of the day service are minimal postoperative morbidity, low inpatient admission rates and high parental and child satisfaction (Grenier et al. 1998, Brennan 1999).

2.2. Adenoidectomy

Adenoidectomy is one of the most common surgical procedures during childhood. Children being usually healthy, they make excellent candidates for day surgery. In many countries adenoidectomy is performed as day surgery, with increasing reports testifying to its safety, making adenoidectomy even more approved as a day procedure (Mahmoud 1995, Mitchell et al. 1997, Brennan 1999). In the Kuopio University Hospital area of Finland, representing a population of 250000, around 500 adenoidectomies are carried out annually in the age group of 0-7 years.

The main indications for adenoidectomy are: 1) recurrent or chronic otitis media with effusion (Linder et al. 1997); 2) adenoid hypertrophy obstructing respiration (Deutsch 1996); 3) chronic or recurrent sinusitis (Vanderberg and Heatley 1997). Relative indications

for adenoidectomy include: 1) recurrent sore throat; 2) recurrent otalgia; 3) recurrent or chronic rhinitis; 4) recurrent upper respiratory infections; 5) snoring or mouth breathing; (however, obstructive symptoms may continue after adenoidectomy alone, therefore adenotonsillectomy may be needed) (Nieminen et al. 2000); 6) failure to thrive; 7) cervical lymphadenopathy; 8) tuberculosis adenitis; 9) systemic disease secondary to beta-haemolytic streptococcal infection (Kornblut and Kornblut 1991). Contraindications to adenoidectomy are mainly relative and they include: 1) blood dyscrasia; 2) uncontrolled systemic disease; 3) cleft palate; 4) acute infections (Kornblut and Kornblut 1991).

Adenoidectomy is commonly performed by curettage under indirect vision with a mirror under general anaesthesia. Adenoid tissue should be curetted in its entirety and special attention should be paid when selecting the size of the curettage, and when removing the tissue around the orifices of the Eustachian tube. Too small a curettage does not remove the tissue properly and on the other hand too large a curettage can cause damage to the openings of the Eustachian tubes (Kornblut and Kornblut 1991). If needed, remnants of the lymphoid tissue can be removed with forceps or scissors (Cowan and Hibbert 1997). Other less commonly used techniques for adenoidectomy are for example; powered instrumentation with an endoscopic shaver system, and adenoidectomy with a laser or suction cautery (Koltai et al. 1997). Haemostasis is controlled with nasopharyngeal packs, and electrocautery as needed. If bleeding still continues topical adrenaline can be applied with a swab or in severe cases, a postnasal pack can be inserted for 24 hours (Cowan and Hibbert 1997).

Although adenoidectomy is considered as a minor procedure, complications can be significant and may result in a severely compromised patient (Kornblut and Kornblut 1991). In addition to anaesthetic complications, there can exist some typical complications following adenoidectomy, such as, pain, excessive haemorrhage, local infections of the pharyngeal wall, surgical trauma of the soft palate or Eustachian tubes, and velopalatal incompetence. Speech may be affected, resulting a hypernasal speech. Scarring of the nasopharynx may also result as a complication (Kornblut and Kornblut 1991, Deutsch 1996, Cowan and Hibbert 1997).

2.3. Anaesthesia in day surgery in children

2.3.1. Preoperative assessment

Although paediatric anaesthesia carries a relatively low morbidity and mortality, the problem of postoperative pain, nausea and vomiting remains significant, and for example emetic complaints may have been increased by the greater use of opioid analgesic drugs (Hatch 1999). Therefore, anaesthetic methods play a significant role in the success of day surgery in children.

Careful preoperative assessment is the basis of safe anaesthetic practice as it allows for optimum planning of the child's anaesthetic and perioperative care. Children between the ages of 2 to 5 years are particularly prone to unreasonable fears because they do not have the intellectual ability to rationalise these (Kotiniemi et al. 1997).

2.3.2. Fasting

The purpose of fasting is to ensure emptiness of the stomach to prevent vomiting and aspiration of the gastric contents with the subsequent risk of aspiration pneumonitis. Recently fasting guidelines has been liberalised (Coté 2000).

Fasting guidelines for paediatric patients in Kuopio University Hospital are given here (Kokki 1998).

FASTING TIME (h)

AGE (months)	MILK AND SOLID FOOD (h)	CLEAR FLUIDS (h)
< 12 mo	3	2
12-24 mo	4	2
> 24 mo	6	2

2.3.3. Premedication

The aims of premedication in children are to facilitate a smooth parting from the parents and to ease the induction of anaesthesia. In general, almost every premedication regimen is successful in 80% and fails in 20% of paediatric patients. However, some children are bound to be anxious before and during induction whether or not any premedication is given (Coté 1999). Moreover, the use of premedication may delay the early recovery, while not improving the quality of the recovery in young children (Viitanen et al. 1999a, Viitanen et al. 1999b).

Benzodiazepines are commonly used premedicants in children, the most popular benzodiazepines used are diazepam and midazolam. Diazepam is a benzodiazepine with anticonvulsant, anxiolytic, sedative, muscle relaxant and amnesic properties, along with a lack of significant emetic activity. Diazepam acts promptly on the brain, and its initial effects decrease rapidly as it is distributed into fat depots and tissues (Coté 1999).

Midazolam is also a benzodiazepine, producing similar effects to diazepam but with a shorter duration. The main disadvantages of oral midazolam being its bitter taste and cytochrome P450 3A4 inhibition (Martindale 1996). Other drugs, such as ketamine are used also as premedicants. Ketamine is a dissociative anaesthetic. It is rapidly acting and is often accompanied by atropine to reduce the potential of ketamine for causing laryngospasm caused by secretions (Coté 1999). A combination of midazolam and ketamine is increasingly being used drug combination for premedication (Funk et al. 2000).

Anticholinergic agents are used to prevent parasympathetically mediated reflex bradycardia following the manipulation of the airway, and bradycardia as a result of hypoxia (Bailey and Valley 1991). However, Annala and co-workers (1998) showed that routine pretreatment with anticholinergics is unnecessary in children undergoing adenoidectomy during halothane anaesthesia from the cardiac arrhythmias point of view. In contrast, the antisalivary effect of anticholinergics is particularly beneficial in ENT-operations, and in managing the airways in unintubated children (Bailey and Valley 1991).

Atropine is the most widely used anticholinergic medication. Its most reliable effect is achieved when it is administered intravenously immediately before induction (Bailey and Valley 1991). Another commonly used anticholinergic medication is glycopyrrolate. However, the oral bioavailability of glycopyrrolate is negligible and therefore intravenous glycopyrrolate should be used as a paediatric premedication (Rautakorpi et al. 1998).

2.3.4 Induction and maintenance

Induction via the i.v. or inhalation route is suitable for paediatric day cases (Brennan 1999). Volatile anaesthetics remain the commonest agents for maintenance of anaesthesia, but since the introduction of sodium thiopental, intravenous agents have been used also for induction (Fox and Rowbotham 1999).

For the maintenance of anaesthesia, spontaneous breathing and intermittent positive pressure ventilation may be used. Studies indicate that the use of intermittent positive pressure ventilation offers more haemodynamic stability than spontaneous breathing (Stow and White 1987, Khan and Memon 2001).

2.3.4.1. Intravenous anaesthetics

Since the main goal in induction of anaesthesia is to undertake atraumatic, safe, smooth and rapid events, the availability of topical anaesthetic products for example, an eutectic mixture of lidocaine and prilocaine and tetracaine gel has improved the acceptance of intravenous induction in children (Maunuksela and Korpela 1986, Manner et al. 1987).

Thiopental is a barbiturate used as a short-acting anaesthetic agent. It does not produce excitation, and it is commonly combined with muscle relaxant and analgesic agents before intubation (Annala et al. 1995, Annala et al. 1999). Another commonly used intravenous anaesthetic agent for induction of anaesthesia is propofol. It induces anaesthesia smoothly and rapidly, and also recovery is fast. The disadvantage of propofol is pain on injection, which occurs in approximately 20-50% of children (Valtonen et al. 1989, Morton 1990).

2.3.4.2. Inhalation agents

Inhalation induction is particularly suitable for the needlephobic patient or those children with difficult venous access. Halothane has been the gold standard inhalation induction agent for years, but since it was introduced sevoflurane is rapidly becoming the first-choice volatile agent for this purpose. Sevoflurane is a non-flammable volatile halogenated anaesthetic and has a pleasant smell, non-irritant to airways, and a rapid onset of action (Martindale 1996, Brennan 1999). In maintenance of anaesthesia, the low blood: gas solubility of sevoflurane allows easier control of anaesthetic depth and more rapid return of consciousness and airway reflexes (Hatch 1999). However, a three-fold greater incidence of emergency agitation have been detected with sevoflurane compared to halothane (Lerman et al. 1996). Also the pain scores are significantly higher in the early recovery period with sevoflurane (Hatch 1999). Davis and co-workers (1999) have shown that intraoperatively administered NSAID reduced emergency agitation and enabled children to feel more comfortable in the immediate postoperative period. Nonetheless, the discharge times have been similar when sevoflurane was compared to halothane (Lerman et al. 1996, Viitanen et al. 2000).

2.3.4.3. Neuromuscular blocking agents

Neuromuscular blocking agents are used commonly in paediatric anaesthesia, both to facilitate tracheal intubation, and during surgery. Because of maturational changes, dosing requirements may differ markedly with age. In general, onset is more rapid and duration is longer in younger patients than in adolescents and adults (Brandom et al. 1998, Taivainen et al. 2000).

Cis-atracurium, a cis-form of atracurium besylate, is a competitive, non-depolarising skeletal muscle relaxant (Coté 2000, Taivainen et al. 2000). With intravenous cis-atracurium dose muscle relaxation begins in about 2 to 3 minutes and lasts 15 to 35 minutes (Martindale 1996). Other non-depolarising neuromuscular blocking agents include for example, mivacurium and rocuronium. Succinylcholine, a depolarising

neuromuscular blocking agent, has been used in children during adenoidectomy, because of it is fast-acting (Annala et al. 1999, Fisher 1999).

2.4. Pain and pain assessment in children

2.4.1. Physiology of acute pain

Pain is an unpleasant sensation induced by noxious stimuli and generally received by specialised nerve endings. Moreover, acute pain is a constellation of unpleasant sensory, emotional, and mental experiences and certain autonomic responses and psychological and behavioural reactions provoked by tissue damage (Bonica 1990).

Surgery induced trauma constitutes a noxious stimulus to peripheral nerves endings for pain (nociceptors) and causes cellular breakdown with liberation of different types of intracellular biochemical substances. Some substances activate nociceptive afferent fibers and produce pain by local application (including bradykinin, acetylcholine and potassium). Other substances facilitate the pain evoked by chemicals and physical stimuli by sensitisation of nociceptors but are ineffective in evoking pain themselves (the prostaglandins). Other substances produce extravasation, such as substance P. In combination with local edema this results in inflammation and sensitization of nociceptors.

In brief, nociceptors transduce the stimuli into nociceptive impulses that are transmitted to the dorsal horn of the spinal cord. After being subjected to these modulating influences in the dorsal horn, segmental nocifensive reflex responses are provoked. Also, suprasegmental reflex responses are provoked in the brainstem and brain resulting in a powerful motivational drive and unpleasant affect and other psychological reactions, which activate motor systems that determine behaviour (Bonica 1990).

2.4.2 Background of pain assessment

The severity and duration of pain in patients is assessed by different scales, questionnaires, and other test methods. Pain assessment is a cornerstone of adequate pain treatment. Pain is difficult to measure precisely and reliably in young children and this has led to the proliferation of a multiplicity of pain measurement tools and scores for children of different ages. Moreover, pain assessment is a broader concept than pain measurement and should take into account the many dimensions of pain experience. Factors affecting pain assessment are cognitive, physiological, sensory, behavioural, affective, sociocultural and environmental (Maunuksela et al. 1987, Morton 1990).

All this assumes that the hospital staff taking care of children are adequately trained and sensitive to the manifestations of acute pain in various age groups and are experienced in intervening safely, effectively and appropriately to control the pain (McQuay et al. 1997, Sepponen et al. 1999, Morton 1999).

Pain assessment must be carried out regularly and management adjusted to maintain an acceptable level of pain control (McQuay et al. 1997, Morton 1999, Joshi 1999). During the immediate recovery period continuous re-evaluation of analgesic efficacy, adverse events, such as sedation, respiratory depression, cardiovascular changes and emesis should be a routine (Morton 1990). Pain assessment is most accurate when the patients can tell staff about the pain that they are experiencing. However, there is a large group of young patients who are not capable of assessing and informing subjectively the staff about their pain, especially during the immediate postoperative period when they are under the effect of anaesthetic agents (Maunuksela et al. 1987, McQuay et al. 1997, Morton 1999). Therefore, both expressed and observed pain scales are used in children. It is possible for children over three years of age to self-report the severity and location of pain using developmentally appropriate terms. Younger children cannot do so readily (Maunuksela et al. 1987, Morton 1999).

2.4.3. Observed pain scales

2.4.3.1. Maunuksela pain scale

The Maunuksela pain scale is a behavioural pain assessment scale for children in the age range of 1-17 years, introduced in Finland in 1987. The scale is based on mimic, vocalisation, movements of limbs and body, response to handling and irritability together with the measured cardiorespiratory parameters. A specially trained nurse scores the pain observed on the scale 0-9; 0 = no pain, 1-3 = slight pain, 4-5 = moderate pain, 6-8 = severe pain and 9 = worst possible pain. This pain scale has later been modified by Nikanne and co-workers (1997), and the pain scores are estimated as 0 = no pain, 1-3 = slight pain, 4-6 = moderate pain, 7-9 = severe pain, 10 = worst pain. Features characteristics of increasing pain are: 1) distortion of face such as lowering of the brow, broadening of the nasal root, an angular and squarish mouth, tightly closed eyes, and tightening of the jaw; 2) vocalisation changing from sobbing or groaning to crying; 3) colour, temperature, and moisture of the skin changing from pink to pale, warm to cool, dry to sweating; 4) increasing rigidity of the body and limbs and resisting movements and handling; 5) respiratory pattern changing from regular, deep, and relaxed to irregular, superficial, and jerky; 6) blood pressure and heart rate changing from normal according to age with large pulse pressure or in some cases low blood pressure or bradycardia (Maunuksela et al. 1987).

The Maunuksela pain scale has been compared with others and a significant correlation was detected between self-reporting scales and behavioural assessment of pain intensity without dependency on age or gender (Maunuksela et al. 1987, Kokki et al. 1999a, Kokki et al. 1999b).

2.4.3.2. Other observed pain scales

Other commonly used observational pain scales include the Objective Pain Scale (OPS) (Broadman et al. 1988), the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)

(McGrath et al. 1985), the Toddler-Preschooler Postoperative Pain Scale (TPPPS) (Tarbell et al. 1992), and the COMFORT Scale (Ambuel et al. 1992). They are all based on different categories of behavioural and physiological signs. Objective Pain Scale is documented to be easy in use, whereas some other observational pain scales mentioned above are more complex in clinical use. Moreover, these scales cannot be used in intubated or paralysed patients (Morton 1997).

2.4.4. Expressed pain scales

Many children over the age of three to four years can differentiate the presence or absence of pain and can self-report pain intensity with words or visual aids provided the number of choices is limited (Morton 1997).

Different face scales have been developed for younger children. The basis of these scales is that the child identifies the level of pain intensity using one of the numerous pictures presenting faces of children (Maunuksela and Korpela 1986).

The Coloured Analogue Scale (CAS) is widely used in children over five years of age. The coloured area reflects the pain intensity. The colour changes to more intensive and the coloured area grows wider when moving from "no pain" to "most pain". The Coloured Analogue Scale has been found a practical tool for clinical use in children (McGrath et al. 1996).

The classical horizontal 100 mm Visual Analogue Scale (VAS), 0 mm point indicating "no pain" and 100 mm point indicating "worst possible pain" (Huskisson 1974), can be operated by children from around the age of seven years but younger children seem to understand better if VAS is presented vertically (Beyer and Aradine 1987). However, during the immediate postoperative period VAS is not suitable to use because its small size (Maunuksela et al. 1987, Tigerstedt and Tammisto 1988). Therefore, special attention should be paid when assessing pain during that period.

Nonetheless, Maunuksela (1987) proved in children a significant correlation between Verbal Rating Scale (VRS), VAS and Maunuksela pain scale. If children are able to express the pain with self-reporting scales, the assessment can be trusted on the condition that the child has comprehended the use of the scales during the preoperative visit.

2.5. Treatment of postoperative pain in children

2.5.1. General

The aim of postoperative pain treatment is to minimise pain throughout the recovery period, not only at rest but also during mobilisation and appropriate activity. Pain management is a dynamic process, which includes frequent patient assessments and adjustments of analgesic regimen, and knowledgeable treatment of the adverse events (Joshi 1999).

Uncontrolled pain is associated with increased incidence of nausea, anxiety and delirium, prolonged postanesthesia care unit (PACU) stay, delayed discharge from the ambulatory facility, unanticipated hospital admissions and delayed resumption of normal activities (Joshi 1999).

Previously, it has been a common belief that children do not feel pain as severely as adults and that the magnitude and duration of its impact may be less than in adults (Anand and Carr 1989). Moreover, several studies have indicated that children in hospital receive less medication following the same type of procedure compared to adults (McGrath and Johnson 1988, Lloyd-Thomas 1995).

The development of pain pathways and stress responses in the fetus, neonate, infant and child compared to adults has been elucidated recently and has led to widespread acceptance that for moral, ethical, humanitarian and psychological reasons, pain should be anticipated, and safely and effectively prevented and controlled in all age groups (Morton 1999).

Sufficient postoperative analgesia without severe adverse events is necessary to facilitate discharge after day surgery. Pain in PACU should be treated quickly and effectively (Joshi 1999). Proactive approach of pain treatment is advocated and thus, breakthrough of pain may be avoided (Wolf 1999). Postoperative pain is common also after minor surgeries and it has been shown that more than 50% of children experience pain after discharge and therefore need analgesic at home, emphasising the importance of proper pain management also at home (Kokki and Ahonen 1997).

2.5.2. NSAIDs

Acetyl salicylic acid (Asa, aspirin) was synthesised in 1899 (Björkman 1995). Although these agents were widely used in clinical medicine, it was not until 1971 that Asa was shown to act as an inhibitor of the enzyme cyclo-oxygenase (COX) which transforms arachidonic acid into prostaglandins and related compounds (Vane 1971).

All the NSAIDs have anti-inflammatory, antipyretic and analgesic properties which have been attributed to inhibition of distinct steps in the arachidonic acid cascade, particularly the cyclo-oxygenase pathway, resulting in a reduced synthesis of eicosanoids, such as, prostaglandins, prostacyclin and thromboxane (Björkman 1995, Fitzgerald and Patrono 2001).

During last decade two different COX-isomeres are recognised, coded by different genes. COX-1 is constitutively expressed in most mammalian tissues. COX-1 performs a "housekeeping" function to synthesise prostaglandins which regulate normal cell activity, such as, platelet function, gastric cytoprotection, renal function and vascular homeostasis. The prostaglandins produced are, thus, protective to the organism. Therefore, the inhibition of COX-1 by NSAIDs is primarily responsible for adverse events of these drugs. However, the protective effect of aspirin in heart attacks and strokes is also due to inhibition of COX-1 in platelets (Vane and Botting 1996, Fitzgerald and Patrono 2001).

COX-2 is the inducible isomere of COX and there can be found only small amount of COX-2 in resting cells of mammalian tissues. However, COX-2 expression is increased significantly after exposure of fibroblasts, vascular smooth muscle or endothelial cells to growth factors, phorbol esters or cytokines. Thus, inhibition of COX-2 reduces inflammation by preventing the production of prostaglandins, which contribute to the inflammatory process, thus, having a therapeutic effect (Vane and Botting 1996).

Most currently available NSAIDs are more potent inhibitors of COX-2 than COX-1. Warner and co-workers (1999) noted that on the premise of their recent study inhibition of COX-1 underlies the gastrointestinal toxicity of NSAIDs. The higher COX-2/ COX-1 ratio (concentrations which reduce prostaglandin biosynthesis by 50%) of drug, the higher the potency against COX-1 compared with COX-2. NSAIDs that preferentially inhibit COX-2 reduce inflammation with less inhibition of the production of physiologically active eicosanoids so potentially reducing the risk of adverse events (Vane and Botting 1996, Fitzgerald and Patrono 2001). The COX-2/COX-1 ratio for ketoprofen is relatively low (1-4.6), compared with several other NSAIDs, e.g. for aspirin the ratio is 166, for piroxicam 250, for ibuprofen 15, for naproxen 0.6 and for diclofenac 0.7 (Vane and Botting 1996, Warner et al. 1999).

COX-3 has been proposed to exist, but not yet characterised. It could represent the brain enzyme, explaining, for example, the therapeutic effect of paracetamol (Vane 1994, Willoughby et al. 2000).

Other mechanisms than cyclo-oxygenase whereby NSAIDs interfere with the arachidonic acid cascade, involves the inhibition of lipo-oxygenase and therefore reduction of leukotrienes formation. Leukotrienes are important mediators of asthma and this mechanism could thus play a part in the pathophysiology of "aspirin asthma" (Malmsten 1986).

Besides the peripheral analgesic effect of NSAIDs, related to reduced formation of algogenic prostanoids as mentioned above, accumulating evidence indicates that NSAIDs,

such as ketoprofen elicit some their analgesic actions within the central nervous system (CNS) (Björkman 1995, Ossipov et al. 2000).

In healthy volunteers, Willer and co-workers (1989) tested the hypothesis of a central analgesic effect of ketoprofen and noted that the spinal noniceptive reflex was inhibited after intravenous ketoprofen while, in contrast, it remained without any significant effect in paraplegic patients with a total spinal injury

NSAIDs are now used primarily in the treatment of chronic arthritic conditions and certain soft tissue disorders associated with pain and inflammation. NSAIDs are also used widely in the treatment of mild to moderate acute pain. In the treatment of postoperative pain NSAIDs have several advantages making them suitable for day surgery use, including opioid sparing effects, minimal sedation and lack of respiratory depression and emetic adverse events (Brennan 1999, Joshi 1999).

NSAIDs are also finding a notable place as adjuncts to local and regional anaesthesia by minimising the breakthrough pain, because of their prolonged duration of analgesia and properties mentioned above (Morton 1999). NSAIDs should be avoided in patients with renal impairment (plasma creatine above normal), hyperkalaemia, hypovolaemia, systemic inflammatory response syndrome, circulatory failure, severe liver dysfunction, during renal transplantation, and aspirin-sensitive asthma (Royal College of Anaesthetists 1998).

2.5.2.1. Different routes of administration of NSAIDs

There are different ways administrating a drug to a site in a patient from where the drug is absorbed into blood and delivered to the target tissue. Different administration routes of NSAIDs have not been adequately compared in pain treatment after surgery. If there exist no differences in analgesic efficacy or onset of pain-relief of alternative routes of the same drug, oral medication, when possible to use, would be a reasonable choice of administration (McQuay et al. 1997, Tramèr et al. 1998).

NSAIDs are available in intravenous, intramuscular, oral, rectal and topical formulations. There are some limiting factors to all different routes of administration. The intravenous route is accurate and practical during the perioperative period as long as the patient has an intravenous line in place (Nikanne et al. 1997). Intramuscular administration is effective, but because of the injection pain, it should be avoided in awake children (Royal College of Anaesthetists 1998). The oral route is cheap, pleasant and effective and the medications can be administered as small tablets or as a mixture. However, the oral route cannot be used when the patient is unable to swallow, is unconscious, nauseated, or is not co-operative (McQuay et al. 1997, Tramèr et al. 1998, Kokki et al. 2000a, Kokki et al. 2000b).

Drug absorption after rectal administration may be delayed and erratic (Montgomery 1995, Morton and O'Brien 1999). The rectal route is disliked by children. Moreover, if administered in the conscious child, consent of the child is appropriate and should be obtained (Royal College of Anaesthetists 1998, Sepponen et al. 1999).

2.5.3. Paracetamol

The derivative of paracetamol was first introduced into clinical medicine in 1893 (Clissold 1986, Björkman 1995). The mechanism of action is still not fully understood. It is thought that the clinical effects of paracetamol are elicited in the CNS rather than in peripheral tissue. Although paracetamol possesses potent analgesic and antipyretic properties, it lacks anti-inflammatory effects. Paracetamol does not inhibit prostaglandin synthesis in other tissues and therefore does not interfere with platelet function and does not prolong the bleeding time. It is mostly used by subjects who have hypersensitivity to the NSAIDs, but overdose can cause fatal hepatic damage (Clissold 1986, Björkman 1995). Paracetamol is widely used, convenient, safe and effective in children for mild and moderate pain (Morton 1999, Brennan 1999). Because of a different mechanism of action, paracetamol may be combined with NSAIDs (Willoughby et al. 2000). Adverse events of paracetamol are rare and are usually mild, such as rashes. However, blood disorders have occasionally been reported (Martindale 1996). Unfortunately, the therapeutic index of paracetamol is narrow.

2.5.4. Opioids

Opioids are primary drugs used in the management of moderate and severe postoperative pain. Opioid analgesics include the opium alkaloids morphine, codeine and their derivatives as well as synthetic substances with agonist, partial agonist, or mixed agonist-antagonist activity at opioid receptors (Martindale 1996). Morphine is a prototype of opioid analgesic and can be taken as a standard with which others are compared. The most adverse events of morphine are common to all opioids. These include nausea, vomiting, constipation, drowsiness, confusion, depression of ventilation and cough reflex, and with long term use psychological and physical dependence, and tolerance. Morphine may also cause difficulties in micturition, ureteric or biliaric spasms, antidiuretic effect, itching, sweating and drying of the mouth (Martindale 1996). Morphine is conjugated into metabolites; the main ones being morphine-3-glucourinide and morphine-6-glucuronide. The latter is considered to produce the analgesic effect of morphine, however, morphine-3-glucourinide appears to be devoid of significant activity (Penson et al. 2000). In children, morphine metabolism follows the course seen in adults from the age of 6 months (Martindale 1996).

Oxycodone is a semisynthetic opioid commonly used for postoperative pain in some countries. In adults oxycodone has been considered about as potent as morphine (Silvasti et al. 1998). However, less oxycodone was needed than morphine, when both drugs were given intravenously for postoperative analgesia to adults (Kalso et al. 1991). In children oxycodone and morphine seem to be quite similar, however, oxycodone does not release histamine and may be less nauseating than morphine (Pöyhiä et al. 1993). Oxycodone is expected to cause greater ventilatory depression than comparable analgesic doses of other opioids (Olkola et al. 1994).

Fentanyl citrate is a synthetic opioid analgesic related to pethidine with similar properties to morphine. It is short-acting after single doses, but has a relatively long elimination half-life because of the rapid redistribution in the body. Therefore with high or repeated doses, fentanyl becomes a relatively long-acting drug. Unlike morphine, fentanyl is reported not

to cause significant histamine release (Martindale 1996). Fentanyl can be administered intravenously as an injection or infusion, intramuscularly, transdermally, oral transmucosally, intranasally, and epidurally (Martindale 1996). Pain in PACU should be treated quickly and effectively with small doses of potent, rapidly acting opioid analgesics (Joshi 1999). Therefore, fentanyl is usually given intravenously in the treatment of postoperative pain. In children, doses of 0.5 to 2 $\mu\text{g kg}^{-1}$ should be used (Brennan 1999). Furthermore, during anaesthesia the use of fentanyl has been shown to reduce significantly the requirement of sevoflurane (Kato et al. 2000).

2.5.5. Postoperative pain treatment

Pain following surgery is best managed by providing medication on a regular basis preventing the pain from recurring. The concept of proactive pain management with the nonopioid medication is best achieved when the drug is administered as early as possible, before the pain has broken through and should be continued after that on regular basis for as long as the pain is expected to last (Wolf 1999). Using this approach of pain management the amount of pain medication is not attempted to be reduced. However, the postoperative pain is better controlled when given on a regular basis and therefore unwanted break-through of pain and unnecessary suffering is avoided.

The theory of pre-emptive analgesia is based on preventing a prolonged change in the central nervous system function by blocking of afferent input before the surgical stimulation may eliminate central sensitisation and prevent amplification and prolongation of postoperative pain (Dahl and Kehlet 1993).

Preoperative administration of opioid or nonopioid analgesics (NSAIDs and local anaesthetics) may reduce the degree of pain and the need for analgesics in the postoperative period (Woolf and Chong 1993, McQuay 1995, Royal College of Anaesthetists 1998). However, studies so far have failed to confirm this theory (Dahl and Kehlet 1993, McQuay 1995, Nikanne et al. 1999, Salonen et al. 2001).

Multimodal analgesia consists of a combination of analgesic regimens. Combination of modalities provides more effective analgesia with a reduced incidence of adverse events (Kehlet and Dahl 1993). Combining opioids with NSAIDs/paracetamol, to produce local and regional anaesthesia has been found particularly useful in paediatrics and have been assumed increasing importance in the management of postoperative pain (Kokki and Ahonen 1997, McQuay et al. 1997, Morton 1999, Joshi 1999). Also, the emotional component of pain must be addressed by using instinctive comforting measures, provision of child-friendly surroundings and distraction techniques (Morton 1999).

2.5.6. Treatment of postoperative pain at home

More than half of children need pain medication after a day-case adenoidectomy (Kokki and Ahonen 1997, Viitanen and Annala 2001). Moreover, more than one out of five children experience severe pain at home after surgery (Nikanne et al. 1999). However, several studies indicate that children are often treated inadequately for pain (Finley et al. 1996, Rømsing et al. 1996).

The reasons for inadequate delivery of analgesia at home may be caused because parents underestimate children's pain after day surgery. Moreover, parents may have problems in administering the analgesic to their children or they may assume that medication causes adverse events or addiction (Finley et al. 1996). A recent study indicated that training of medical staff and parents improves pain management after adenoidectomy (Sepponen et al. 1999).

To provide and improve high-quality analgesia at home after day surgery, emphasis in the future should be on developing techniques to optimise the dosing schedules of systemic analgesia and administering analgesia more effectively. Also, an effort should be made to educate parents to assess pain better and to maintain the access for parents to contact the hospital if needed (Wolf 1999).

Pain following surgery is best managed by providing medication on a regular basis preventing the pain from recurring. The non-opioid medication should be administered as early as possible and proactively before the pain has broken through. In addition to regular and pre-emptive dosing, there should be emphasis on a multimodal technique, combining NSAIDs and paracetamol in the pain management of children at home (Wolf 1999). For example, propionic acid derivatives, such as ibuprofen and ketoprofen have proved to be an effective and safe analgesic also in children (Maunuksela et al. 1992a, Kokki et al. 1994, Alam and Takrouri 1999).

2.6. Ketoprofen

2.6.1. General

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID), synthesised in 1967 (Kantor 1986). It belongs to the group of 2-phenylpropionic acids and has anti-inflammatory, antipyretic and analgesic properties. The structural formula of ketoprofen is 2-(3-benzophenyl)-propionic acid and its molecular weight is 254.29 (Kantor 1986). The appearance of intravenous ketoprofen is a clear, colourless solution, thus enabling easily the blinding with placebo (0.9% saline). Although ketoprofen possesses a chiral centre, only the S-enantiomer possesses the beneficial pharmacological activity such as prostaglandin inhibition, while R-enantiomer has no such effect (Jamali and Brocks 1990). The pharmacokinetics of ketoprofen appear to exhibit little stereoselectivity (Martindale 1996).

2.6.2. Pharmacokinetics

2.6.2.1. Absorption

In adults, when administered by mouth, ketoprofen is rapidly absorbed through the gastrointestinal tract. The bioavailability of ketoprofen is higher than 90% after oral administration. Peak plasma levels are reached approximately 1-2 hours after ingestion

(Kantor 1986). In children absorption of ketoprofen mixture is more rapid. Otherwise, the pharmacokinetics of ketoprofen in children are very similar to that reported in adults and is not affected by age between 6 months and 7 years (Kokki et al. 2000a).

In adults ketoprofen is also absorbed well following administration by the intramuscular and rectal routes. The bioavailability of rectal and intramuscular ketoprofen is about the same after oral administration (Ishizaki et al. 1980, Martindale 1996). The absorption after rectal administration may, however, be delayed and erratic, as shown with acetaminophen (Morton and O'Brien 1999).

When ketoprofen is used in injectable form, a rapid onset of analgesic action is achieved (Ishizaki et al. 1980, Kostamovaara et al. 1998). Due to rapid absorption, peak plasma levels of intramuscular ketoprofen is attained within 30 minutes in adults (Wollheim et al. 1981). In children, intramuscular ketoprofen also performs well (Alam and Takrouri 1999). Furthermore, according to clinical observations, administration of a single intravenous ketoprofen bolus suppresses pain within 5 to 30 minutes (Debruyene et al. 1987).

2.6.2.2. Metabolism and excretion

In the circulation, ketoprofen is 99% bound to protein, mostly to albumin. Ketoprofen is extensively metabolised by microsomal enzymes in the liver and the drug follows a simple metabolic pathway (primarily glucuronidation), leading to the formation of an unstable glucuronic ester that is excreted in the urine (Kantor 1986, Veys 1991).

Despite being mostly protein bound, ketoprofen does not appear to alter the pharmacokinetics of other highly protein-bound drugs. However, drug interactions with probenecid, aspirin and methotrexate have been described (Jamali and Brocks 1990, Veys 1991). Ketoprofen is a feasible drug for continuous intravenous infusion in acute pain treatment in children without evidence of accumulation after 24 hours of infusion and therefore an effective and safe non-opioid analgesic also for children (Kokki et al. 2001, Salonen et al. 2002).

The elimination of ketoprofen is rapid and independent of the route of administration (Ishizaki et al. 1980, Debruyne et al. 1987). The elimination half-life in plasma is about 1.5-4 hours (Ishizaki et al. 1980, Kokki et al. 2000a).

2.6.3. Pharmacodynamics

In children ketoprofen possesses a good anti-inflammatory effect, and ketoprofen is potent compared to some other NSAIDs (Guyonnet and Julou 1976). Ketoprofen's anti-inflammatory properties are related to its inhibitory effects on mediators of inflammation. Ketoprofen is an effective and safe drug in the treatment of juvenile rheumatoid arthritis (Zutshi and Mason 1976, Brewer et al. 1982).

Ketoprofen has proved to be a potent analgesic, also when compared with other NSAIDs or paracetamol (Fossgren 1976). Ketoprofen is one of the most powerful inhibitors of cyclo-oxygenase, in addition, ketoprofen inhibits the lipoxygenase pathway of the arachidonic acid cascade, as well as it is a powerful bradykinin inhibitor (Kantor 1986). At the dosage of 0.3 mg/kg, ketoprofen has been shown to have a significant analgesic effect, however, it may be used safely up to dose of 5 mg/kg/d (Brewer et al. 1982, Maunuksela 1993, Kokki et al. 1998). Moreover, continuous intravenous ketoprofen improved pain after major surgery in children receiving an epidural opioid, reducing the need for the opioid (Kokki et al. 1999b). Recently there is accumulating evidence that ketoprofen has also a central action (Ossipov et al. 2000).

NSAIDs are also commonly used in children in the treatment of fever. In children, ketoprofen has an antipyretic effect when given as an oral dose of 0.5 mg/kg. However, the antipyresis was significantly better at a dose of 1.0 mg/kg (Keinänen-Kiukaanniemi et al. 1980).

2.6.4. Toxicology

Ketoprofen and other propionic acid derivatives have low toxicity. There was no evidence of carcinogenicity or mutagenicity in standard screening assays, and the drug appeared to have no effect on protein, DNA or RNA synthesis (Kantor 1986). No embryotoxic or teratogenic effects have been demonstrated for ketoprofen and the drug has not been shown to affect fetal or postpartum developments. The average lethal dosage in the different animals ranged between 100 mg/kg to 200 mg/kg. In humans, no toxic effects have been found in adults with doses up to 4 mg/kg/d (70 kg adult) and 5 mg/kg/d in children (Fossgren 1976, Kantor 1986, Kokki et al. 2000b).

2.6.5. Clinical usage

Ketoprofen was introduced for clinical use in 1973 in France and the United Kingdom (Kantor 1986) and is available as oral, rectal, i.v., i.m. and topical gel formulations. Ketoprofen is used in mild to moderate pain or as in concurrent use with opioids in severe pain in postoperative pain situations (Morton 1999, Joshi 1999). Intravenous and intramuscular ketoprofen has proved to be a safe and effective analgesic for postoperative pain both in adults (Hommeril et al. 1994), and also in paediatric patients (Nikanne et al. 1997, Kokki et al. 1998, Kokki et al. 1999a, Alam and Takrouri 1999). In adults, ketoprofen is also used in musculoskeletal and joint disorders such as ankylosing spondylitis, rheumatoid arthritis, in peri-articular disorders such as bursitis and tendinitis and in other pain and inflammatory conditions such as acute gout or soft-tissue disorders (Fossgren 1976, Veys 1991, Martindale 1996).

In children a ketoprofen dosage of 5 mg/kg/day has proved to be an effective and safe analgesic in postoperative pain management at home (Kokki et al. 2000). Intravenously ketoprofen has been safely studied up to dosage of 3 mg/kg without an increase in adverse events. However, for routine use a dose of 1 mg/kg is recommended (Kokki et al. 1998, Alam and Takrouri 1999). Since the half-life of ketoprofen is relatively short the dose may be repeated up to three or four times a day or a continuous infusion may be used

(Maunuksela 1993, Salonen et al. 2001). In children ketoprofen has proved not to only produce good analgesia but also to reduce the consumption of opioids and the incidence of adverse events such as nausea and vomiting after surgery (Kokki et al. 1999a).

2.6.6. Adverse events

2.6.6.1. Gastrointestinal adverse events

Clinical trials of long term treatment have demonstrated that ketoprofen is well tolerated. Ketoprofen compared with other NSAIDs performs well in the incidence of the adverse events (Veys 1991). In adults, commonly reported adverse drug events of ketoprofen are gastrointestinal complaints such as nausea, dyspepsia, epigastric discomfort, gastritis or gastric ulcer. The cause of gastrointestinal adverse reactions is related to ketoprofen's inhibition of prostaglandin synthetase and the subsequent depletion of prostaglandins. Prostaglandins inhibit the secretion of gastric acid and have other protective actions such as stimulation of mucus and bicarbonate secretion and gastric mucosal blood flow (Day et al. 1987, Ivey 1988). Based on different studies an estimate of the frequency of these adverse events is 9% in both adults and children (Fossgren 1976, Kokki et al. 2000b). According to studies among adults it seems that the gastrointestinal adverse events are dose related, but not time dependent (Kantor 1986, Garcia and Hernandez-Diaz 2001).

2.6.6.2. Renal adverse events

Transient depression of renal function (increased blood urea nitrogen and serum creatinine) is characteristic of NSAIDs. Renal functional changes induced by NSAIDs, whether asymptomatic or accompanied by edema, are reversible on withdrawal of the drug (Kantor 1986) .

The inhibition of prostaglandin production is thought to cause depression of renal function, especially if the patient has a previous high renin state (e.g. heart failure, volume depletion, chirrrosis) or pre-existing renal insufficiency (Henrich 1983). Much less

common but more severe nephrotoxic reactions that can be associated with NSAIDs are intestinal nephritis and renal papillary necrosis (Rocha et al. 2001).

2.6.6.3. Effect on platelet function and bleeding time

It is known that NSAIDs inhibit biosynthesis of tromboxane A₂. The reduced production of tromboxane A₂ prevents platelet aggregation and may increase blood loss during and after surgery (Vane and Botting 1996, Fitzgerald and Patrono 2001). An intravenous bolus (1.4 mg/kg) of ketoprofen has been reported to impair platelet aggregation and to prolong bleeding time measured two hours after infusion. The medians of the bleeding time, however, remained within the normal range, and after 24 hours the values were normalised (Niemi et al. 1997). The use of ketoprofen did not increase postoperative blood loss after total hip or knee replacement (Kostamovaara et al. 1998). Moreover, with ketoprofen an increase of blood loss peri- and intraoperatively during adenoidectomy in children seems to be minimal (Kokki et al. 1998, Nikanne et al. 1999, Kokki et al. 2001).

2.6.6.4. Other adverse events

Ketoprofen appears to have a low potential for allergic manifestations, apart from cross-reactivity in aspirin-intolerant patients (Kantor 1986). In patients with aspirin intolerance ketoprofen can cause a life-threatening bronchoconstriction (Frith et al. 1978). There has been shown some adverse effect on the CNS such as cephalgia in 0.6%, vertigo in 0.5% and somnolence in 0.5% of patients using ketoprofen (Fossgren 1976). Dermatological effects such as exanthema, urticaria, pruritus, muco-cutaneous reactions, contact dermatitis and photosensitivity have been reported in less than one percent of patients using ketoprofen (Fossgren 1976).

Hepatic effects due to ketoprofen are rare, but include slightly elevated transaminases and a elevation in alkaline phosphatase (Fossgren 1976). However, no cases of liver injury attributable to ketoprofen have been reported (Kantor 1986). Ketoprofen may cause pain at the injection site when administrated as an intramuscular injection, or local irritation when used as suppositories (Martindale 1996).

Nikanne (1999) evaluated adverse events in a study concerning the use of ketoprofen for postoperative pain management in children. In hospital every fifth child had an adverse events, the most common (34%) being nausea and/or vomiting. However, only 1 % of children needed treatment because of these adverse events. There were no significant differences between children receiving ketoprofen or placebo, except children who received ketoprofen experienced significantly less excessive somnolence compared to the children who received placebo ($P < 0.001$). In the same study two thirds of the children were reported to have one or more adverse events at home. However, only 2 % of children needed treatment for adverse events, and furthermore, there were no differences between ketoprofen and placebo groups in the proportion of children with one or more adverse events or in the number of adverse events at home.

2.7. Postoperative behavioural changes in children

Changes in children's behaviour have been seen following both day and inpatient surgery (Campbell et al. 1988) and also after hospitalisation (Vernon et al. 1966). Day surgery has been considered to be psychologically beneficial for minor paediatric surgery for the majority of children and families (Scaife and Johnstone 1990). However, in spite of the increasing tendency to perform surgery on an ambulatory basis, the incidence of behavioural changes has remained around 50% since the 1950s (Kain et al. 1996, Kotiniemi et al. 1997). The changes observed have been mostly transient, lasting only for a few days or weeks, but some children may show behavioural problems several months or years following surgery (Vernon et al. 1966, Kain et al. 1996).

Nevertheless, it should be emphasised that length of stay is only one of many factors related to admission, which may adversely affect a child's emotional response. It should not assumed that these other factors can be ignored simply because admission is on a day basis (Scaife and Johnstone 1990, Kain et al. 1996).

Vernon and co-workers (1966) used factor analysis, in which the 27 items in the post-hospital behavioural questionnaire were divided into six categories: general anxiety and regression, separation anxiety, anxiety about sleep, eating disturbances, aggression towards authority and apathy-withdrawal. Since the changes in children's behaviour have been evaluated in most studies by parents using a structured questionnaire, either a post-hospital behavioural questionnaire or its derivate.

Behavioural changes are thought to be the result of an interaction between the distress the child experiences during the perioperative period and the individual personality characteristics of the child (Kain et al. 1999). Distress can be reduced by simple experiences of creating a suitable children's environment, avoiding separation from the parents by adequate explanation and reassurance from the staff experienced in the care of children, and by minimising pain (Scaife and Johnstone 1990).

Moreover, behavioural changes are common in children also after day surgery, specially in young children, less than 4 years of age. Postoperative pain has proved to be an important factor in occurrence of these changes. Pain on the day of the operation predicts occurrence of behavioural problems up to the 4th week, 2-4 weeks longer than the duration of pain itself (Kotiniemi et al. 1997).

Other predictors identified for the occurrence of negative postoperative behavioural changes are the temper of the child and the state and trait anxiety of the parents. Also a high anxiety level during induction has been demonstrated to develop postoperative negative behavioural changes (Kain et al. 1999). On the other hand, a well-managed surgical intervention of underlying infectious disease itself may improve the quality of life of children (Rosenfeld et al. 2000).

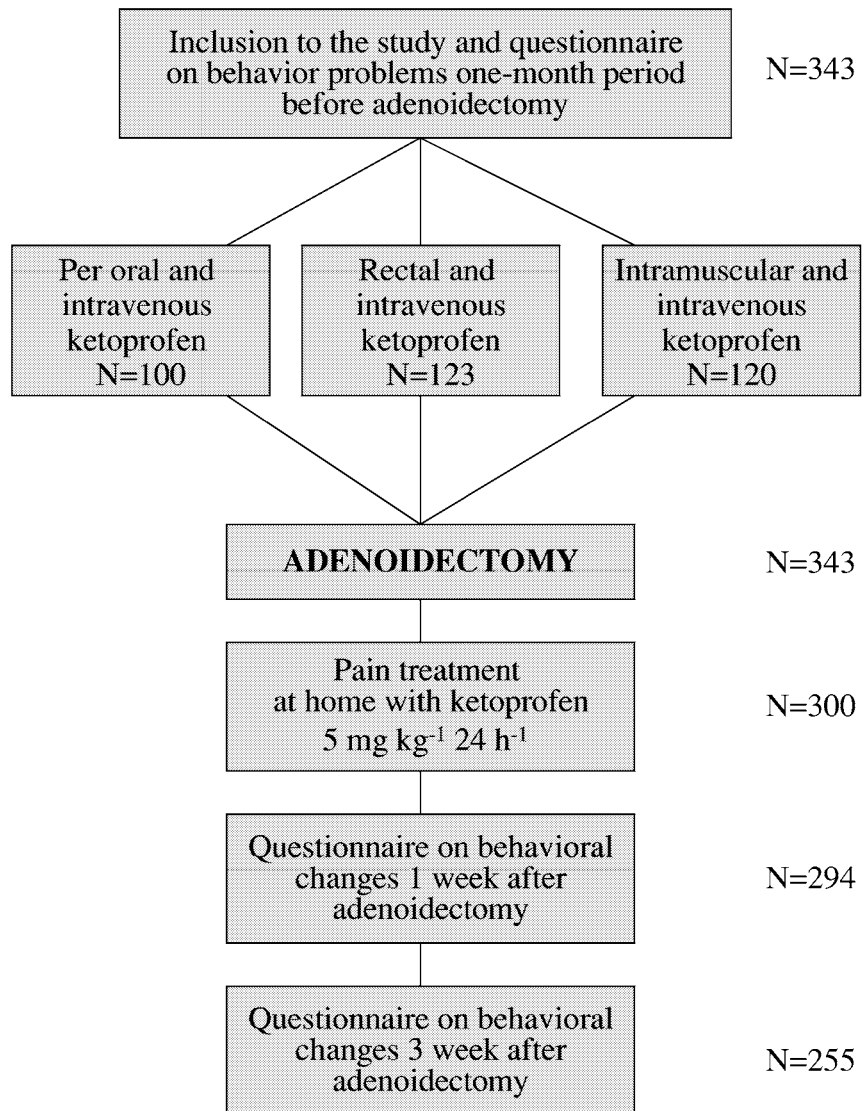
3. PURPOSE OF THE PRESENT STUDY

1. To evaluate perioperative and postoperative pain in children following a day-case adenoidectomy with a special reference to oral, rectal, intramuscular and intravenous administration of ketoprofen. (Studies I-III)
2. To determine the pharmacokinetics of ketoprofen in young children after a single oral and intramuscular administration. (Study IV)
3. To assess postoperative behavioural changes in children aged 1-10 years one and three weeks after day-case adenoidectomy when a proactive pain treatment was used. (Study V)

4. PATIENTS AND METHODS

4.1. Patients

A total of 363 children were included in the studies; 343 of them were studied in the Department of Otorhinolaryngology and Anaesthesia and Intensive Care of Kuopio University Hospital, and 20 children were studied in the Department of Paediatric Surgery and Anaesthesia and Intensive Care during 1999-2000. Studies I-III included 343 children who all underwent a day-case adenoidectomy. Pharmacokinetics of ketoprofen was evaluated in study IV, when 20 patients had surgery below the umbilicus under spinal anaesthesia. In study V, the recovery of the first consecutive 300 children during a three-week period after the operation was reported. Patients were excluded if they had a known allergy to ketoprofen or other non-steroidal anti-inflammatory drugs, asthma, haemorrhagic diathesis, kidney or liver dysfunction, or had any other known contraindication for NSAIDs. All patients were ASA (American Society of Anaesthesiologists' physical status grading) I or II, and the parents and children old enough were informed and gave written consent. In studies I-III the study design was prospective, randomised, double-blind, double dummy with a placebo control and differed from each other by the administration route of ketoprofen. In study IV and V the study design was prospective, longitudinal and open. Fig. 1 presents a flow-chart of study V. In study V the number of returned questionnaires postoperatively after one week was 294 (98%) and after three weeks 255 (85%).



4.2. Surgical technique of adenoidectomy

The adenoids were removed using a curettage technique under indirect visual control. The operations were performed by ENT-resident surgeons working in the day surgery center. At the time of this trial there were five residents in the Department of Otorhinolaryngology and the present author being one of them. All residents had sufficient experience in adenoidectomy. The removal of adenoid tissue for all the children was performed by curettage under indirect vision with a mirror. Haemostasis was controlled with temporary nasopharyngeal packs and suction-electrocautery. After the operation children were transferred to the PACU for continuous monitoring of vital signs and assessment of pain and adverse events.

4.3. Anaesthesia technique

A standard anaesthetic technique, as described in the original publication, was used. In studies I-III each child was premedicated with diazepam 0.5 mg kg^{-1} orally up to a maximum of 10 mg, 30 minutes before induction. EMLA[®]cream (Astra, Södertälje, Sweden) was used at the venous puncture site. Atropine 0.01 mg kg^{-1} and fentanyl $1 \text{ } \mu\text{g kg}^{-1}$ was given intravenously and anaesthesia was induced with thiopenthal 5 mg kg^{-1} i.v. To facilitate tracheal intubation cis-atracurium 0.1 mg kg^{-1} was given i.v. Anaesthesia was maintained with 2-3% sevoflurane (inspired concentration) in 65 % nitrous oxide in oxygen with intermittent positive pressure ventilation. On completion of the procedure muscle relaxation was reversed with neostigmine $50 \text{ } \mu\text{g kg}^{-1}$ and glycopyrrolate $10 \text{ } \mu\text{g kg}^{-1}$. All children received fentanyl $1 \text{ } \mu\text{g kg}^{-1}$ at the induction and no more opioids were allowed during surgery. For intraoperative fluid maintenance all children were given 0.9 % saline $5\text{-}10 \text{ ml kg}^{-1} \text{ h}^{-1}$. In study IV surgery was performed under spinal anaesthesia with light general anaesthesia.

4.4. Assessment of postoperative pain

4.4.1. In hospital

Postoperative pain was assessed using the Maunuksela pain scale (Maunuksela et al. 1987), modified by Nikanne et al. (1997) (0 = no pain, 1-3 = mild pain, 4-6 = moderate pain, 7-9 = severe pain, 10 = worst pain).

In the PACU, specially trained nurses continuously assessed the pain experienced by the child at rest and during swallowing and recorded it every hour up to three hours. If the child was in pain with a pain score at rest ≥ 3 , fentanyl $0.5 \mu\text{g kg}^{-1}$ i.v. was given. The dose was repeated at 5-10 minutes intervals until the pain had diminished to slight (pain score < 3). No more than four doses were allowed in one hour. No other analgesic medication was permitted during the study. The last pain assessment and recording was made just before discharge. At the same time the worst pain at rest and during swallowing during the PACU stay was noted.

4.4.2. After discharge

Postoperative pain at home was assessed by the parents. The questionnaire completed by the parents consisted information about the pain intensity at home experienced by the child, pain duration and medication requirements. At home the pain intensity was assessed using a 4-point verbal rating scale (VRS). The VRS was used because it is a generally accepted, simple and sensitive method for pain assessment (Littman et al. 1985). In the scale used 1 = no pain, 2 = mild pain, 3 = moderate pain, 4 = worst pain. The questionnaire was filled in and returned one and three weeks after the operation.

4.5. The treatment of pain

Study I

A total of 100 patients were studied; patients were randomly allocated either to receive ketoprofen or placebo. Forty children received ketoprofen 1.0 mg kg⁻¹ by mouth as a mixture (Orudis[®] 1 mg/ml mixture, Rhône-Poulenc Rorer, Cedex, France) 30 minutes before the operation and placebo i.v. at induction (10 ml 0.9 % normal saline) injected over 10 minutes (ORAL-group). Forty children were given a placebo mixture 30 minutes before operation and ketoprofen intravenously at induction 1.0 mg kg⁻¹ in 10 ml 0.9% normal saline i.v. injected over 10 minutes (Orudis[®] 50 mg/ml injection, Rhône-Poulenc Rorer, Helsinki, Finland) (IV-group), and 20 children received a placebo mixture and normal saline injection (PLACEBO-group).

Study II

A total of 123 patients were studied; patients were randomly allocated either to receive ketoprofen or placebo. Forty-two children received ketoprofen rectally 25 mg as a suppository (Ketorin[®] 25 mg supp., Orion, Espoo, Finland) after induction but before the surgery and placebo intravenously (10 ml 0.9 % normal saline) (SUPPOSITORY-group) and 42 children were given placebo suppository and ketoprofen 25 mg in 10 ml 0.9% normal saline injected i.v. over 5 minutes (Ketorin[®] 50 mg/ml injection, Orion, Espoo, Finland) (IV-group), and 39 children received a placebo suppository and a normal saline injection i.v. (PLACEBO-group).

Study III

A total of 120 patients were studied; patients were randomly allocated either to receive ketoprofen or placebo. Forty children received ketoprofen intramuscularly 2 mg kg⁻¹ (Ketorin[®] 50 mg/ml injection, Orion, Espoo, Finland) in the left deltoideus muscle and placebo i.v. 10 ml (0.9 % normal saline) after induction of anaesthesia but before surgery (IM-group). Forty children received 0.4 –0.8 ml 0.9% normal saline intramuscularly and ketoprofen 2 mg kg⁻¹ in 10 ml 0.9% normal saline i.v. injected over 5 minutes (IV-group), and 40 children received i.m. and i.v. injections of normal saline (PLACEBO-group).

4.6. The pharmacokinetics of ketoprofen

Study IV

A total of 20 patients were studied. Two parallel groups of young children received a single intramuscular or oral dose of ketoprofen. In the intramuscular group ten children received a single intramuscular administration of ketoprofen (Ketorin 50 mg ml⁻¹, Orion, Espoo, Finland). Ketoprofen was injected into the deltoid muscle at a dose of 1 mg kg⁻¹. In the tablet group six children, weight 12 to 17 kg, received a single oral administration of 12.5 mg ketoprofen tablet and four children, weight 18 to 23 kg, received a single oral administration of 25 mg ketoprofen (Ketorin 25 mg tablet, Orion, Espoo, Finland).

4.7. Postoperative behavioural changes

Study V

The recovery of 300 patients who had taken part in the first three stages of the study, see studies I-III, were included in study V. After discharge the study design was prospective, longitudinal and open. At discharge, parents were instructed about the postoperative care of their child and pain management at home. A proactive pain treatment protocol was used at home with ketoprofen 5 mg kg⁻¹ 24h⁻¹, divided in two or three doses. Medication was obtained by parents at discharge and they were enforced to give the children ketoprofen on a regular basis at least for 72 hours after surgery starting at the same day depending on the time of discharge and continued thereafter when needed.

To evaluate the changes in the child's postoperative behaviour the caregivers completed a questionnaire containing 24 items adapted from the Posthospital Behavioural Questionnaire modified by Kotiniemi (1997). Data concerning the behavioural changes at home were collected on three consecutive times; at the day of operation before surgery, at one week and at three weeks after surgery. A total of 213 children received the first dose of ketoprofen before surgery (PREOP-group); either an oral mixture 30 minutes before surgery, or as a suppository or intramuscular and intravenous injection at induction. Eighty-seven children received placebo (POSTOP-group). This allowed us to compare

these two groups to observe if ketoprofen had any pre-emptive effect. At discharge all children were given ketoprofen 1 mg kg⁻¹ i.v.

4.8. Intraoperative bleeding and adverse events

At the end of surgery, the surgeon estimated the amount of bleeding using a five-point scale (1 = no bleeding, 2 = less than average, 3 = average, 4 = more than average, 5 = profuse bleeding). In the PACU nurses recorded all adverse events and postoperative bleeding for each patient. At home, adverse events and postoperative bleeding were reported by the parents.

4.9. Discharge criteria

Patients were discharged when they were awake, were able to walk unaided, had stable vital signs for at least 1 hour, had no pain or only mild pain, had not vomited for one hour, were able to tolerate clear fluid, and had no bleeding. The anaesthetist and surgeon who had performed the operation checked all patients before discharge. The discharge was defined as delayed if it took place later than 5 hours after surgery.

4.10. Statistical methods

Statistical methods are described in the original papers I-V.

In studies I-III the statistical analysis of continuous variables was performed using the Kruskal-Wallis test, and for post hoc analysis, the Mann-Whitney test with Bonferonni correction was used. For the categorical variables, the chi-square test was used. $P < 0.05$ was considered statistically significant.

In study V change scores after surgery (at one week and at three weeks) for each domain was compared to the scores obtained at baseline using repeated measures analysis of variance (ANOVA) The internal consistency of the survey was assessed to determine

reliability. The calculation of Cronbach α was used for the instrument as a whole and with removal of each domain. The reliability coefficient $\alpha > 0.7$ was considered evidence of good reliability. The measure of agreement between two different rating-methods to measure the change in postoperative behaviour consecutively after one week and three weeks for each domain was assessed by Spearman rank correlation and Kappa-test. A P-value of less than 0.05 was considered statistically significant.

In study IV the pharmacokinetic parameters were calculated by noncompartmental analysis using the WinNonlin software installed on a personal computer (WinNonlin Version 1.1-Scientif. Consulting, Inc. 8509 Burnside Drive Apex; NC 27502 USA).

4.11. Ethical aspects

The studies were approved by the Ethics Committee of Kuopio University Hospital and was conducted in accordance with the latest revision of Declaration of Helsinki (World Medical Association Declaration of Helsinki. 52nd WMA General Assembly, Edinburgh, Scotland, 2000). The National Agency for Medicines was notified of the use and doses of ketoprofen in children younger than 12 years. All the parents and children old enough were informed and gave written consent. This study was financially supported by the EVO-grant of Kuopio University Hospital. Orion Pharma, Espoo and Aventis Pharma (former Rhône-Poulenc Rorer), Helsinki kindly provided ketoprofen used in the present studies, but made no contribution to the trial plan or to the analysis of the results.

5. RESULTS

5.1. Comparison of different administration routes of ketoprofen

Studies I-III compared different administration routes of ketoprofen.

5.1.1. Patients characteristics

In studies I-III among the 343 children there were more boys than girls, however, the difference was not significant. Age, weight and height were similar in all groups. All the children were ASA physical status 1, except the two children (ASA 2) receiving ketoprofen intravenously. (Table 1)

There were neither protocol deviations nor dropouts likely to interfere with the results. Moreover, all children who were asked, participated in the study. The suction-electrocautery was used for haemostasis in almost all (96%) of the operations.

Table 1. Patient characteristics. Data represent number of cases or median (10th /90th percentiles), n= 343.

	Ketoprofen n= 244	Placebo n= 99
Sex (boys/girls)	147/97	58/41
Age (months)	39 (16-91)	38 (16-87)
Height (cm)	98 (79-127)	97 (80-128)
Weight (kg)	15 (11-29)	15 (11-28)
ASA 1	242	99
2	2	-

5.1.2. Occurrence of pain in PACU

When the patient was transferred to the PACU for continuous monitoring of vital signs, the study nurses assessed the pain continuously and recorded it every hour for up to three hours, both at rest and when swallowing by using the Maunuksela pain scale. In studies I-III children receiving ketoprofen had significantly lower pain scores according to the Maunuksela pain scale than children receiving placebo after the first postoperative hour at rest ($P= 0.04$) and for swallowing ($P= 0.005$) and for the worst pain measured on swallowing during the PACU- stay ($P= 0.03$). The observed Maunuksela pain scores did not differ significantly between the ketoprofen groups. (Table 2)

Table 2. Maunuksela pain scores in the study groups. In the pain score 0 = “no pain “, 1-3 = “ slight pain “, 4-6 = “ moderate pain “, 7-9 = “ severe pain “, 10 = “ worst possible pain “. Data are expressed as median (10th /90th percentiles), n= 343.

	Ketoprofen n= 244	Placebo n= 99
<u>Pain at 1 hour</u>		
At rest	3 (0-7) *	5 (0-8)
On swallowing	4 (0-8) **	6 (0-8)
<u>Pain at 2 hour</u>		
At rest	0 (0-4)	1 (0-5)
On swallowing	0 (0-5)	1 (0-5)
<u>Worst pain in PACU</u>		
At rest	4 (0-7)	5 (0-8)
On swallowing	5 (0-8) ***	6 (0-8)
<u>Pain at discharge</u>		
At rest	0 (0-2)	0 (0-1)
On swallowing	0 (0-2)	0 (0-2)

* $P= 0.04$, ** $P= 0.005$, *** $P= 0.03$ (Mann-Whitney test with Bonferonni correction).

5.1.3. Intraoperative bleeding

The surgeon estimated the intraoperative bleeding at the end of the operation. According to the results, the use of ketoprofen did not increase the incidence of intraoperative bleeding in the present study. Furthermore, there were no significant differences between the groups in studies I-III combined. It seems that the use of ketoprofen does not increase intraoperative bleeding after adenoidectomy. (Table 3)

Table 3. The intraoperative bleeding estimated by the surgeon, Data represent number of cases, n= 343.

	Ketoprofen n= 244	Placebo n= 99
Less than normal	18	5
Normal	190	88
More than normal	36	6

5.1.4. Need for rescue analgesic

In PACU the children were administered fentanyl $0.5 \mu\text{g kg}^{-1}$ i.v., if the pain score was assessed ≥ 3 at rest. The dose was repeated at 5-10 minutes intervals until the pain had diminished to slight (pain score < 3).

In the present study a total of 249 children needed rescue analgesic in the PACU; 166 (68%) children who had received ketoprofen and 83 (84%) children who had received placebo. There was a significant difference in the need for rescue analgesics between the children receiving ketoprofen, and those receiving placebo, ($P= 0.003$) (chi-square test). The proportion of children needing rescue analgesics and the requirement for rescue analgesics was similar between the different administration routes of ketoprofen. However, as detected in study I, among those children who needed rescue analgesics, the requirement for rescue analgesics was significantly less in those children receiving i.v. ketoprofen than those receiving oral ketoprofen, ($P= 0.024$) (Mann-Whitney test with Bonferonni correction). (Table 4)

Among those children who needed fentanyl, three out of four children receiving ketoprofen needed only one or two doses of fentanyl, but every other child receiving placebo needed three or more doses of fentanyl ($P= 0.009$). (Table 5)

Table 4. Children who received fentanyl in the PACU in studies I-III combined. Data represent number of cases (%), n= 343.

	Ketoprofen n= 244	Placebo n= 99
No fentanyl	78 (32)	16 (16)
Needed fentanyl	166 (68) *	83 (84)

*P= 0.003 (chi-square test)

Table 5. Children who received 1-2 or > 3 doses of fentanyl in the PACU in studies I-III combined. Data represent number of cases (%), n= 249.

	Ketoprofen n= 166	Placebo n= 83
1-2 doses of fentanyl	126 (76)	48 (58)
> 3 doses of fentanyl	40 (24)	35 (42) *

*P= 0.009 (chi-square test)

5.1.5. Adverse events in PACU

The study nurses recorded all adverse events and postoperative bleeding for each patient in the PACU. There was no difference between the study groups in the incidence of adverse events in studies I-III combined. (Table 6)

The most common adverse events were nausea, retching and vomiting, observed in 59 out of 343 children (17%). In the suppository group no ano-rectal adverse events were noticed. In the ketoprofen group (n= 244) four children [with i.v. ketoprofen (n= 122) three children] had pain at the infusion site at hand, and likewise in the placebo group (n= 99), four children had pain at the infusion site at hand. The discharge was delayed for 15 (6%) children receiving ketoprofen and for seven (7%) children receiving placebo, because of excessive sedation, severe pain or protracted vomiting. Altogether, five children (1%), four receiving ketoprofen and one receiving placebo, were admitted overnight to the hospital because of excessive sedation, protracted vomiting or on a decision of a surgeon due to a child's history of snoring and apnoeas at nights. There was no difference between the groups in surgeon-assessed bleeding. Sedation at discharge was similar in all groups.

Table 6. Adverse events in the PACU. Data are expressed as number of cases (total %).

	Ketoprofen n= 244	Placebo n= 99
Nausea, retching, vomiting	40	19
Pain at the infusion site at hand	4	4
Difficulty in passing urine	3	2
Somnolence	7	3
Swelling in eyelids	1	1
Shivering	1	-
Agitated	1	-
Upper abdominal pain	-	-
Children with adverse events	48 (20%)	19 (19%)

5.1.6. Pain after discharge

The questionnaire regarding postoperative pain after discharge was given to the first consecutive 300 children out of 343 children participating in studies I-III. The questionnaire consisted of information concerning pain intensity at home experienced by the child, pain duration and medication requirements, and it was filled in by the parents.

Recovery after adenoidectomy was painful for most children, because 268 (91 %) patients had pain at home. However, most children had just mild or moderate pain, severe pain being reported in 109 (37%) children. The most intense pain occurred on the first postoperative day. The mean time for pain cessation was 3 days (range 0 to 8 days).

The original scheme was to continue the proactive pain treatment for three postoperative days. A total of 285 (97 %) children received ketoprofen at home and the mean number of doses was 6 doses as planned in the original scheme, however some children seemed to need more pain medication, because the maximum number of given doses was 24 doses.

Because there were no significant differences in pain intensity, number of analgesic or duration of pain at home between patients who received the first dose of ketoprofen before surgery or at discharge, no pre-emptive effect of ketoprofen was detected.

5.1.7 Adverse events after discharge

Adverse events after discharge were reported by the parents with a questionnaire one week after surgery. Altogether, 213 (72%) of the children had some kind of adverse event reported after discharge. However, there were no differences in adverse events at home between the children who had received ketoprofen and those who had received placebo during surgery. The most common adverse event was somnolence, occurring in two out of five children. Other common complaints were fever (29%), stomach-ache (18%), nausea, retching and vomiting (15%). Thirty-four children [15 children in the intravenous group (n= 122) and 19 children in the placebo group (n= 99)] had pain at the infusion site on the hand, but no significant difference was seen between the groups. Only 11 out of 294 children had any kind of postoperative bleeding at home. However, none of them needed any surgical intervention due to postoperative bleeding. Moreover, none of the children required admission to hospital or any other intervention. As a conclusion, no difference was seen in the incidence of adverse events after discharge in children who received ketoprofen or placebo in hospital. (Table 7)

Table 7. Adverse events at home. Data are expressed as number of cases.

	Study patients n= 294
Somnolence	126
Nausea, retching, vomiting	45
Pain at the infusion site at hand	34
Headache	31
Fever	84
Stomach-ache	54
Diarrhoea	19
Constipation	17
Dizziness	33
Bleeding	11
Skin rash	4
Children with adverse events	213

5.2. Pharmacokinetics of oral and intramuscular ketoprofen

In study IV the pharmacokinetic properties of oral and intramuscular ketoprofen were determined. However, there was no significant difference detected between these two different administration routes of ketoprofen. Ketoprofen was absorbed well because the maximal plasma concentration was achieved in 30 minutes in both groups, and the maximal plasma concentration ranged between 3.6 and 7.4 $\mu\text{g ml}^{-1}$ after intramuscular administration of ketoprofen, and between 2.8 and 8.2 $\mu\text{g ml}^{-1}$ after oral administration. The terminal half-life was comparable in both study groups, $t_{1/2}$ ranged between 0.8 and 2.2 h in the intramuscular group, and between 0.9 and 2.1 h in the tablet group. The relative bioavailability of ketoprofen was about 100% between oral and intramuscular administration. After intramuscular administration of ketoprofen the apparent clearance rate ranged between 0.07 and 0.11 $\text{l h}^{-1} \text{kg}^{-1}$ [mean $\text{Cl}/F = 0.09 (0.02) \text{l h}^{-1} \text{kg}^{-1}$], and the mean retention time between 1.4 and 2.4 h [mean 1.9 (0.3) h]. The results did not significantly differ from those that were detected after oral administration of ketoprofen. The apparent clearance after oral administration of ketoprofen was between 0.07 and 0.12 $\text{l h}^{-1} \text{kg}^{-1}$ [mean $\text{Cl}/F: 0.09 (0.02) \text{l h}^{-1} \text{kg}^{-1}$], and the mean retention time ranged between 1.8 and 2.7 h [mean 2.1 (0.3) h].

According to the pharmacokinetic properties detected in study IV, there were no significant differences between ketoprofen administered by mouth or intramuscularly.

5.3. Postoperative behavioural changes

In the present study data concerning behavioural changes were collected at three consecutive times; at the day of operation before surgery, which constituted baseline data, and at one week and at three weeks after the surgery. The response rates for questionnaires were high. A total of 294 out of 300 questionnaires were returned at one week (response rate 98%) and 255 questionnaires at three weeks (response rate 85%).

At baseline emotional distress and day-time function disturbances were the domains of greatest impact, followed by sleep disturbances and physical symptoms. None of the children had any developmental disabilities or mental disorders. Overall, at baseline some minor behaviour disturbances were noted, but those are considered to be normal during childhood.

At one week after surgery most of the children did not show any postoperative behavioural changes, and when changes were observed they were equally, in the range of 1 % to 18 %, improvements or worsening in any domain. Only a few children had large improvement or worsening in behaviour after surgery. As expected, the largest degree of changes occurred in physical symptoms, headache and stomach-ache.

At three weeks after surgery more positive than negative behavioural changes compared with the baseline were noticed, and only 1 % to 4 % of the children had significant worsening in any behavioural domain. However, most of the children did not have any behavioural changes at all.

When factors affecting behavioural changes in the postoperative period were evaluated, the age of child was a significant factor ($P < 0.05$) for all domains. Although differences were statistically significant, the actual changes in each domain during the follow-up were rather minimal. Other significant factors affecting behavioural changes were; the worst pain at rest ($P= 0.04$) and during swallowing ($P= 0.02$) observed in the PACU for day-time function disturbances. Fear of separation from parents ($P= 0.03$) was a significant factor

implicating sleep disturbances. The gender of children did not influence the results. According to the present study it is concluded that in children a day-case adenoidectomy with proactive pain treatment results in only negligible incidence of behaviour troubles.

6. DISCUSSION

6.1. Pain treatment with different administration routes of ketoprofen

6.1.1. Analgesic effect of ketoprofen

In hospital ketoprofen provided a sufficient background analgesia after adenoidectomy without any increase in adverse effects. Children who received ketoprofen needed significantly less rescue analgesics than children receiving placebo did. The proportion of the children who needed rescue analgesic was smaller in those who had received ketoprofen compared to those who had received placebo. Furthermore, three out of four children who received ketoprofen needed just one or two doses of rescue analgesic compared with every other child who received placebo. This supports the opioid-sparing effect of ketoprofen and other propionic acid derivatives detected in earlier studies (Maunuksela 1992a, Kokki et al. 1994, Nikanne et al. 1997).

When different administration routes of ketoprofen were compared, no significant difference in the number of children needing or in need for rescue analgesics was discovered in the present study. This could be due to a rapid absorption of ketoprofen following administration by all administration routes included in the study (Ishizaki et al. 1980, Kantor 1986, Kokki et al. 2000a). This assumption was supported in the present study, since the rate and extent of absorption, and the elimination of ketoprofen were comparable after intramuscular and oral administration in young children. However, among those children who needed rescue analgesics, the requirement for rescue analgesics was less for those children receiving ketoprofen intravenously than those receiving ketoprofen by mouth.

Despite the comparable results between the different administration routes of ketoprofen few principles should be kept in mind when choosing the route of administration. The intramuscular route of administration should be avoided in awake children because of the injection pain. Also it should be remembered that awake children dislike suppositories. Obviously, the oral route cannot be used immediately after operation because children are

sedated or otherwise non co-operative, for example if they experience nausea or vomiting (Van der Marel et al. 2001). There is no justification to administer ketoprofen by intramuscular injection in awake children with i.v.-line in place or who can swallow.

Children receiving ketoprofen had significantly less pain than children receiving placebo both at rest and on swallowing during the hospital-stay. Pain can be expected to be most intense during swallowing after throat surgery. The pain scores did not differ significantly between the ketoprofen groups. However, the major mechanism of NSAIDs is through their inhibition on prostaglandin biosynthesis (Vane 1971), and hence the onset of the analgesic efficacy may be delayed (Maunuksela et al. 1992b). In addition to a peripheral action, ketoprofen is expected to have also a rapid central analgesic action (Willer et al. 1989, Ossipov et al. 2000). To support this, Debruyne and co-workers (1987) has shown that administration of a ketoprofen bolus i.v. suppresses pain within 5 to 30 minutes. Therefore when a rapid and effective analgesia is needed ketoprofen i.v. seems to be practical choice.

Proactive pain management seems to perform well in children after day surgery. It is known that postoperative pain is common also after minor surgeries (Finley et al. 1996, Kokki et al. 1997). The present study confirms that the recovery after adenoidectomy is painful for children, because nine out of ten patients were reported to have pain at home. However, most children had just mild or moderate pain. The somewhat analogous findings concerning the postoperative pain after discharge in the present study and those reported by Nikanne and co-workers (1997) point out the fact that the most intense pain occurs on the first postoperative day, and the mean time for pain cessation is 3 days.

The present study failed to show a pre-emptive effect of ketoprofen. There were no significant differences in pain intensity, proportion of children needing rescue analgesics, number of analgesic doses or duration of pain at home between patients who received the first dose of ketoprofen before the surgery and those who received the first dose at discharge. The theory of pre-emptive analgesia is based on preventing the central hypersensitisation by blocking of afferent input before the surgery. However, so far also

other studies have failed to confirm this theory (Dahl and Kehlet 1993, McQuay 1995, Salonen et al. 2001, Salonen et al. 2002).

6.1.2. Adverse events in hospital

Ketoprofen seems to result a low incidence of adverse events when used as a pain management after day-case adenoidectomy (Nikanne 1999). In the present study every fifth children who received ketoprofen had an adverse events in hospital, however there were no significant differences between children receiving either ketoprofen or placebo. This result agrees well with the studies by Nikanne (1999) who reported adverse events in 18% of children receiving ketoprofen. Nausea and vomiting are common after paediatric day-case surgery (Karlsson et al. 1990). However, in a recent study by Kokki and co-workers (1999) it was noted that children who received ketoprofen as a background analgesic experienced significantly less vomiting than children receiving placebo after strabismus surgery. In the present study also the most common adverse events for the children receiving ketoprofen in hospital were nausea and vomiting, the incidence being 17%, which agrees well with the previous findings of Nikanne (1999) and those reported by Kokki and co-workers (1999).

One of the major concerns about NSAIDs is their effect on haemostatic mechanism. It is known in adults that NSAIDs inhibit biosynthesis of tromboxane A₂. The reduced production of tromboxane A₂ prevents platelet aggregation and may increase blood loss during and after surgery (Vane and Botting 1996). However, in the present study none of children required any intervention due to postoperative bleeding. It seems that during adenoidectomy in children there is no risk of increase of blood loss peri- and intraoperatively when ketoprofen is used as an analgesic. However, intraoperative bleeding was estimated by the surgeon using a five-point scale. This is obviously not an accurate method to detect minor differences.

For day surgery to be effective the admission rate of patients into hospital must be low. In the present study five children (1%) were admitted overnight to hospital due to an

adverse event, which is well acceptable according the recommendation of The Royal College of Anaesthetists (1998). Children were admitted to the hospital because of excessive sedation, protracted vomiting or on a decision of surgeon due to a child's history of snoring and apnoeas at nights.

6.1.3. Adverse events after discharge

Today an increasing number of children are undergoing day surgery. A consequence of this is that caregivers are more and more responsible for the postoperative care of their children. Therefore, pain medication at home must be both effective and safe to use. In the present study the incidence of adverse events at home was 72%, the most common adverse event being somnolence, which occurred in two out of five children. However, in the present study, there was no significant difference between children who had received ketoprofen or placebo during surgery. In the study by Kokki and co-workers (2000) two out of three of the children were reported to have adverse events. The most common adverse event was again somnolence that was reported in 36% of the children. The incidence of somnolence in these studies was apparently lower than reported earlier (70%) by Kotiniemi (1997). In the present study 11 children (4%) had bleeding at home, but none of them required any intervention and there was no significant difference between children who had received ketoprofen or placebo during surgery. Opioids are known to cause drowsiness and somnolence, and in children, ketoprofen has proved not to only produce good analgesia but also to reduce the consumption of opioids and the incidence of adverse events caused by opioids (Kokki et al. 1999a).

6.2. Pharmacokinetics of ketoprofen

The pharmacokinetic properties of ketoprofen appears not to be affected by the children's age (Kokki et al. 2000a). Moreover, it seems that pharmacokinetic profiles are quite similar in children with those reported in adults (Ishizaki et al. 1980). However, knowledge of pharmacokinetics of different administration routes of ketoprofen in children is still scanty. Due to a relatively short half-life (around two hours), it seems that there is no risk

of drug accumulation when ketoprofen is used for short term pain treatment. In the present study, when ketoprofen was administered either by mouth or intramuscularly, the rate and extent of absorption, and the elimination of ketoprofen were comparable in young children. Therefore, there is no justification from the pharmacological point of view to use intramuscular administration of ketoprofen in awake children.

6.3. Postoperative behavioural changes after proactive pain treatment

In the present study proactive pain treatment with ketoprofen after adenoidectomy performed well. The incidence of significant behavioural problems was surprisingly rare in our study. However, the timing of the first dose of ketoprofen did not affect the incidence of negative behavioural changes. Overall, the incidence and type of postoperative behavioural changes has remained similar, approximately 50 % or over, in most studies over the years. In a recent study, Kotiniemi and co-workers (1997) detected a substantial incidence of problematic behavioural changes in children at one week after minor day case surgery. In their study the significant factors predicting problematic changes in behaviour after surgery were severity of postoperative pain and the age of child (more negative changes among children less than 3 yr.), and previous bad experience of health care.

In the present study at one week after surgery most children did not show any postoperative behavioural changes, and when changes were observed they were equally, in the range of 1% to 18%, improvements or worsening. The age of the child was a significant factor also in present study. Although the difference was significant, the actual changes during the follow-up were rather minimal. Other significant factors affecting behavioural changes were the worst pain at rest and during swallowing observed in PACU, and fear of separation from parents. Therefore, it is vital to provide an adequate pain treatment for children, and also to inform and prepare caregivers sufficiently for their children's operation and postoperative care to avoid any unnecessary suffering.

In the study by Kotiniemi (1997) the incidence of problematic changes decreased from 47% to 9% during a four weeks follow-up, but at the same time, the frequency of beneficial changes decreased from 17% to 9%. In the present study, the incidence of worsening in behavioural domains was lower and the incidence of improvements was higher than reported by Kotiniemi (1997). Moreover, in the present study at three weeks after surgery, more positive than negative behavioural changes, compared with the baseline, were noticed. Furthermore, only 1 to 4 % of the children showed large worsening in any behavioural domain, and most children not showing any behavioural changes at all.

The most common complaints after surgery in the present study were physical symptoms, headache and stomach-ache. This was expected, because headache is a common symptom in children after throat surgery (Kotiniemi et al. 1997). Moreover, stomach-ache and headache are common during childhood: it has been found that half of the children in Finland have suffered from headache by the age of 7 years (Sillanpää et al. 1996).

The effect of disease itself on behavioural problems cannot be underestimated, and it has been shown that an improvement in the child's medical condition has a beneficial effect on the quality of life. Rosenfeld and co-workers (2000) evaluated the effect of surgical procedures on children's postoperative behavioural changes, and found that the insertion of tympanostomy tubes improves the children's subjective well-being and therefore their quality of life.

6.4. Limitations of the present study

A fairly wide age range of the children, varying from one to ten years, can be seen as a limitation of the present study. Children at different developmental stages respond to stress by different defence mechanisms and with different cognitive potential. Children under the age of three years are at risk for exhibiting more adverse postoperative behaviour (McGraw 1994).

Nikanne and co-workers (1999) noted in their study that younger children aged less than four years, seemed to experience more pain than older children. However, the duration of pain in younger children was shorter compared to older children. These findings, may indicate the complexity of pain assessment in young children which can be considered as another limitation of our study. Pain assessment in small children is difficult because of their limited verbal abilities and understanding, developmental level and emotional stress. Several other factors such as anxiety, excitement, operation stress, fatigue and residual effects of anaesthetic agents can cause postoperative distress for children (Wolf 1999, Morton 1999). Consequently, for small children pain scales with assessment based on multiple variables are recommended. The Maunuksela pain scale, used in the present study, is a multidimensional assessment based on physiologic, behavioural and contextual indicators, and it has been validated for the use in children from 1 to 18 years (Maunuksela et al. 1987).

The response rate for the questionnaires was high, however the opinions of the non-returned might have had some importance for the further quality control of children's day surgery.

The blood loss intraoperatively was estimated by the surgeon using a five-point scale. This obviously is not accurate method to detect minor differences. Furthermore, the number of patients in the present study was too small to make any definitive conclusions about possible rare adverse events of surgery or anaesthesia.

The peak ketoprofen plasma concentration was noticed in most patients at 30 minutes. Because we did not collect blood samples within the first 30 minutes of administration by mouth we may have missed the absolutely peak concentration in some patients. However, the blood volume in young children is limited and therefore it is unethical to take too many samples. In the present study the total volume of blood samples was less than 2% of blood volume for each child.

6.5. Recommendations for effective and safe pain management after day-case adenoidectomy

Parents' guidance is essential in children's pain management at home. Giving appropriate and clear instructions to caregivers apparently improves the quality of pain management (Sepponen et al. 1998), and for example, in the present study 97 % of the children received ketoprofen at home. Because the worst pain after adenoidectomy occurs on the first postoperative day, parents should be instructed to continue regular pain medication on arrival home to avoid unwanted break-through of the pain. Moreover, parents need the telephone number of the hospital in case of any problems or questions after discharge.

We believe that the approach used in the present study, where parents were instructed about proactive pain treatment and where all verbal information was reinforced with written instructions, helped and supported the parents in using pain medication with regular and proper doses. Adequate postoperative pain treatment is a part of our hospital's ISO-9002 quality program. In this respect, a constant quality control of the pain management directory is essential.

Perioperative pain treatment should be improved, because despite the present pain management protocol, children experienced pain and needed rescue analgesics. Whether, for example, combining NSAIDs and paracetamol or a weak oral opioid are an effective and safe solutions is worth of further studies.

7. CONCLUSIONS

1. Pain after adenoidectomy in children is common, lasting around three days after discharge with the first postoperative day being the worst. Perioperative pain management with ketoprofen provides significantly better analgesia than placebo. However, between different administration routes of ketoprofen there is no clinically significant difference in the requirement or in the proportion of children needing rescue analgesics.
2. The rate and extent of absorption, and the elimination of ketoprofen are comparable after intramuscular and oral administration in young children. Therefore, there is no justification to administer ketoprofen by intramuscular injection in children with an i.v.-line in place or who can swallow.
3. The incidence of significant behavioural problems after adenoidectomy is rare when proactive pain treatment is used.

8. REFERENCES

- Alam K, Takrouri MS. Analgesic effects of intra-muscular ketoprofen (Profenid) and pethidine for squint surgery in children. *Middle East J Anesthesiol* 1999; 15: 31-8.
- Ambuel B, Hamlett KW, Marx CM, et al. Assessing distress in pediatric intensive care environments. The Comfort scale. *J Pediatr Psychol* 1992; 17: 95-109.
- Anand KJ, Carr DB. The neuroanatomy, neurophysiology, and neurochemistry of pain, stress, and analgesia in newborns and children. *Pediatr Clin North Am* 1989; 36: 795-822.
- Annala P, Lindgren L, Lounamaa P, Dunkel P, Annala I, Yli-Hankala A. ECG T-wave amplitude changes during thiopentone induction with or without alfentanil. *Acta Anaesthesiol Scand* 1995; 39: 401-5.
- Annala P, Rorarius M, Reinikainen P, Oikkonen M, Baer G. Effect of pre-treatment with intravenous atropine or glycopyrrolate on cardiac arrhythmias during halothane anaesthesia for adenoidectomy in children. *Br J Anaesth* 1998; 80: 756-60.
- Annala P, Viitanen H, Reinikainen P, Baer G, Lindgren L. Induction characteristics of thiopentone/suxamethonium, propofol/alfentanil or halothane alone in children aged 1-3 years. *Eur J Anaesthesiol* 1999; 16: 359-66.
- Bailey AG, Valley RD. Myths in Pediatric Anesthesia. *Problems in Anesthesia* 1991; 5: 483-96.
- Beyer JE, Aradine CR. Patterns of pediatric pain intensity: a methodological investigation of a self-report scale. *Clin J Pain* 1987; 3: 130-41.
- Bonica JJ. Physiology of pain. In: *The management of pain*. Philadelphia: Lea & Febiger, 1990; 28-94.
- Brandom BW, Meretoja OA, Simhi E, Taivainen T, Wolfe SR, Woelfel SK, Gronert BJ, Cook DR. Age related variability in the effects of mivacurium in paediatric surgical patients. *Can J Anaesth* 1998; 45: 410-6.
- Brennan LJ. Modern day-case anaesthesia for children. *Br J Anaesth* 1999; 83: 91-103.
- Brewer EJ, Giannini EH, Baum J et al. Ketoprofen (Orudis®) in the treatment of juvenile rheumatoid arthritis. A segment I study. *J Rheumatol* 1982; 9: 144-8.
- Broadman LM, Rice LH, Hannallah RS. Testing the validity of an objective pain scale in children. *Anesthesiology* 1988; 69: A770.

- Björkman R. Central antinociceptive effects of non-steroidal anti-inflammatory drugs and paracetamol. Experimental studies in the rat. *Acta Anaesthesiol Scand Suppl* 1995; 39: 1-44.
- Campbell IR, Scaife JM, Johnston JM. Psychological effects of day case surgery compared with inpatient surgery. *Arch Dis Child* 1988; 63: 415-7.
- Castells X, Alonso J, Castilla M, Ribo C, Anto JM. Outcomes and costs of outpatient and inpatient cataract surgery: a randomised trial. *J Clin Epidemiol* 2001; 54: 23-9.
- Clerque F, Auroy Y, Péquignot F, Jouglu E, Lienhart A, Laxenaire AM. French survey of anesthesia in 1996. *Anesthesiology* 1999; 91: 1509-20.
- Clissold SP. Paracetamol and phenacetin. *Drugs* 1986; 32 (Suppl 4): 46-59.
- Coté CJ. Preoperative preparation and premedication. *Br J Anaesth* 1999; 83: 16-28.
- Coté CJ. Pediatric Anesthesia In: Miller RD (ed) *Anesthesia* 5th edition.. Philadelphia: Churchill-Livingstone, 2000; 2088-117.
- Cowan DL, Hibbert J. Tonsils and adenoids. In: Scott-Brown's (ed). *Otolaryngology*. Oxford: Butterworth-Heinemann, Educational and Professional Publishing Ltd, 1997; 18: 1-16.
- Dahl JB, Kehlet H. The value of pre-emptive analgesia in the treatment of postoperative pain. *Br J Anaesth* 1993; 70: 434-9.
- Davis PJ, Greenberg JA, Gendelman M, Fertal K. Recovery characteristics of sevoflurane and halothane in preschool-aged children undergoing bilateral myringotomy and pressure equalization tube insertion. *Anesth Analg* 1999; 88: 34-8.
- Day RO, Graham GG, Williams KM, Champion GD, de Jager J. Clinical pharmacology of non-steroidal anti-inflammatory drugs. *Pharmacol Ther* 1987; 33: 383-433.
- Debruyne D, de Ligny BH, Ryckelynck JP, Albessard F, Moulin M. Clinical pharmacokinetics of ketoprofen after single intravenous administration as a bolus or infusion. *Clin Pharmacokinet* 1987; 12: 214-21.
- Deutsch ES. Tonsillectomy and adenoidectomy. Changing indications. *Pediatr Clin North Am* 1996; 43: 1319-38.
- Finley GA, McGrath PJ, Forward SP, McNeill G, Fitzgerald P. Parent's management of children's pain following 'minor' surgery. *Pain* 1996; 64: 83-7.

- Fisher DM. Neuromuscular blocking agents in paediatric anaesthesia. *Br J Anaesth* 1999; 83: 58-64.
- Fitzgerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001; 345: 433-42.
- Fossgren J. Ketoprofen. A survey of current publications. *Scand J Rheumatology* 1976; (Suppl 14): 7-32.
- Fox AJ, Rowbotham DJ. Recent advances in Anaesthesia. *BMJ* 1999; 319: 557-60.
- Frith P, Dolovich J, Hargrave FE. Life-threatening asthma, urticaria, and angioedema after ketoprofen. *Lancet* 1978; 2: 847-8.
- Funk W, Jakob W, Riedl T, Taeger K. Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. *Br J Anaesth* 2000; 84: 335-40.
- Garcia Rodriguez LA, Hernandez-Diaz S. Relative risk of upper gastrointestinal complications among users of acetaminophen and non-steroidal anti-inflammatory drugs. *Epidemiology* 2001; 12: 570-6.
- Grenier B, Dubreuil M, Siao D, Meymat Y. Paediatric day case anaesthesia: estimate of its quality at home. *Paediatr Anaesth* 1998; 8: 485-9.
- Guyonnet JC, Julou L. Relationship between the inhibitory activity on 'RCS' and prostaglandins synthesis and the anti-inflammatory activity of ketoprofen and several other non-steroidal anti-inflammatory agents. *Rheumatol Rehabil* 1976; 15 (Suppl): 11-4.
- Hatch DJ. New inhalation agents in paediatric anaesthesia. *Br J Anaesth* 1999; 83: 42-9.
- Henrich WL. Nephrotoxicity of nonsteroidal anti-inflammatory agents. *Am J Kidney Dis* 1983; 2: 478-84.
- Hommeril JL, Bernard JM, Gouin F, Pinaud M. Ketoprofen for pain after hip and knee arthroplasty. *Br J Anaesth* 1994; 72: 383-7.
- Huskisson EC. Measurement of pain. *Lancet* 1974; 2: 1127-31.
- Ishizaki T, Sasaki T, Suganuma T, Horai Y, Chiba K, Watanabe M, Asuke W, Hoshi H. Pharmacokinetics of ketoprofen following single oral, intramuscular and rectal doses and after repeated oral administration. *Eur J Clin Pharmacol* 1980; 18: 407-14.
- Ivey KJ. Mechanisms of nonsteroidal anti-inflammatory drug-induced gastric damage. *Actions of therapeutic agents. Am J Med* 1988; 84 (Suppl 2A): 41-8.

- Jamali F, Brocks DR. Clinical pharmacokinetics of ketoprofen and its enantiomers. *Clin Pharmacokinet* 1990; 19: 197-217.
- Joshi GP. Pain management after ambulatory surgery. *Ambulatory Surgery* 1999; 7: 3-12.
- Kain ZN, Mayers LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children. Predictors and outcomes. *Arch Pediatr Adolesc Med* 1996; 150: 1238-45.
- Kain ZN, Wang SM, Mayes L, Caramico LA, Hofstadter MB. Distress during the induction of anesthesia and postoperative behavioral outcomes. *Anaesth Analg* 1999; 88: 1042-1047.
- Kalso E, Pöyhkä R, Onnela P, Tigerstedt I, Tammisto T. Intravenous morphine and oxycodone for pain after abdominal surgery. *Acta Anaesthesiol Scand* 1991; 35: 642-6.
- Kantor TG. Ketoprofen: A review of its pharmacologic and clinical properties. *Pharmacotherapy* 1986; 6: 93-103.
- Karlsson E, Larsson LE, Nilsson K. Postanaesthetic nausea in children. *Acta Anaesthesiol Scand* 1990; 34: 515-8.
- Katoh T, Kobayashi S, Suzuki A, Iwamoto T, Bito H, Sato S. Fentanyl augments block of sympathetic responses to skin incision during sevoflurane anaesthesia in children. *Br J Anaesth* 2000; 84: 63-6.
- Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg* 1993; 77: 1048-56.
- Keinänen-Kiukaanniemi S, Similä S, Kouvalainen K. Oral antipyretic therapy evaluation of the propionic acid derivatives ibuprofen, ketoprofen, fenoprofen and naproxen. *Pädiatr Pädol* 1980; 15: 139-44.
- Khan FA, Memon, GA. Comparison of spontaneous with controlled mode of ventilation in tonsillectomy. *Paediat Anaesth* 2001; 11: 185-90.
- Kokki H, Hendolin H, Maunuksela EL, Vainio J, Nuutinen L. Ibuprofen in the treatment of postoperative pain in small children. A randomized double-blind-placebo controlled parallel group study. *Acta Anaesthesiol Scand* 1994; 38: 467-72.
- Kokki H, Ahonen R. Pain and activity disturbance after paediatric day case adenoidectomy. *Paediatr Anaesth* 1997; 7: 227-31.
- Kokki H, Nikanne E, Tuovinen K. I.v. intraoperative ketoprofen in small children during adenoidectomy: a dose-finding study. *Br J Anaesth* 1998; 81: 870-4.

- Kokki H. Fasting guidelines for paediatric patients in Kuopio University Hospital. ISO-9000 Quality Standard Program in Intranet of Kuopio University Hospital, 1998.
- Kokki H, Homan E, Tuovinen K, Purhonen S. Perioperative treatment with i.v. ketoprofen reduces pain and vomiting in children after strabismus surgery. *Acta Anaesthesiol Scand* 1999a; 43: 13-8.
- Kokki H, Tuovinen K, Hendolin H. Intravenous ketoprofen and epidural sufentanil analgesia in children after combined spinal-epidural anaesthesia. *Acta Anaesth Scand* 1999b; 43: 775-9.
- Kokki H, Le Liboux A, Jekunen A, Montay G, Heikkinen M. Pharmacokinetics of ketoprofen syrup in small children. *J Clin Pharmacol* 2000a; 40: 354-9.
- Kokki H, Nikanne E, Ahonen R. The feasibility of pain treatment at home after adenoidectomy with ketoprofen tablets in small children. *Paediatr Anaesth* 2000b; 10: 531-5.
- Kokki H, Salonen A, Nikanne E. Perioperative intravenous ketoprofen neither prolongs operation time nor delays discharge after adenoidectomy in children. *Paediatr Anaesth* 2001; 11: 59-64.
- Koltai PJ, Kalathia AS, Stanislaw P, Heras HA. Power-assisted adenoidectomy. *Arch Otolaryngol Head Neck Surg* 1997; 123: 685-8.
- Kornblut A, Kornblut AD. Tonsillectomy and adenoidectomy. In: Paparella MM, Shumrick DA (eds) *Otolaryngology*. Philadelphia: W.B. Saunders Company, 1991; 2149-65.
- Kostamovaara PA, Hendolin H, Kokki H, Nuutinen LS. Ketorolac, diclofenac and ketoprofen are equally efficacious for pain relief after total hip replacement surgery. *Br J Anaesth* 1998; 81: 369-72.
- Kotiniemi LH, Ryhanen PT, Moilanen IK. Behavioural changes in children following day-case surgery: a 4-week follow-up of 551 children. *Anaesthesia* 1997; 52: 970-6.
- Leighton SE, Rowe-Jones JM, Knight JR, Moore-Gillon VL. Day-case adenoidectomy. *Clin Otolaryngol* 1993; 18: 215-9.
- Lerman J, Davis PJ, Welborn LG et al. Induction, recovery, and safety characteristics of sevoflurane in children undergoing ambulatory surgery. A comparison with halothane. *Anesthesiology* 1996; 84: 1332-40.

- Linder TE, Marder HP, Munzinger J. Role of adenoids in the pathogenesis of otitis media: a bacteriologic and immunohistochemical analysis. *Ann Otol Rhinol Laryngol* 1997; 106: 619-23.
- Littman GS, Walker BR, Schneider BE. Reassessment of verbal and visual analog ratings in analgesic studies. *Clin Pharmacol Ther* 1985; 38: 16-23.
- Lloyd-Thomas A. Assessment and control of pain in children. *Anaesthesia* 1995; 50: 753-5.
- Mahmoud NA. Day-case adenoidectomy-safety and cost effectiveness. *Ambulatory Surgery* 1995; 1: 31-5.
- Malmsten CL. Prostaglandins, thromboxanes, and leukotrienes in inflammation. *Am J Med* 1986; 80 (Suppl 4B): 11-7.
- Manner T, Kanto J, Iisalo E, Lindberg R, Viinamäki O, Scheinin M. Reduction of pain at venous cannulation in children with a eutectic mixture of lidocaine and prilocaine (EMLA cream): comparison with placebo cream and no local premedication. *Acta Anaesthesiol Scand* 1987; 31: 735-9.
- Martindale. *The Extra Pharmacopoeia*, 31th edition. Royal Pharmaceutical Society, 1996.
- Maunuksela E-L, Korpela R. Double-blind evaluation of a lignocaine-prilocaine cream (EMLA) in children. Effect on the pain associated with venous cannulation. *Br J Anaesth* 1986; 58: 1242-5.
- Maunuksela EL, Olkkola KT, Korpela R. Measurement of pain in children with self-reporting and behavioral assessment. *Clin Pharm Therap* 1987; 42: 137-41.
- Maunuksela EL, Ryhänen P, Janhunen L. Efficacy of rectal ibuprofen in controlling postoperative pain in children. *Can J Anaesth* 1992a; 39: 226-30.
- Maunuksela EL, Kokki H, Bullingham RES. Comparison of intravenous ketorolac with morphine for postoperative pain in children. *Clin Pharm Therap* 1992b; 52: 436-43.
- Maunuksela EL. Nonsteroidal anti-inflammatory drugs in pediatric pain management. In: Schechter NL, Berde CB, Yaster M (eds). *Pain in infants, children and adolescents*. Baltimore: Williams and Wilkins, 1993; 135-43.
- 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.
- McGrath PJ, Johnson GG, Goodman JT et al. CHEOPS: A behavioural scale for rating postoperative pain in children. *Adv Pain Res Ther* 1985; 9: 395-402.

- McGrath PJ, Johnson GG. Pain management in children. Editorial. *Can J Anaesth* 1988; 35: 107-10.
- McGraw T. Preparing children for the operating room: psychological issues. *Can J Anaesth*. 1994; 41: 1094-1103.
- McQuay HJ. Pre-emptive analgesia: a systematic review of clinical studies. *Ann Med* 1995; 27: 249-56.
- McQuay H, Moore A, Justins D. Treating acute pain in hospital. *BMJ* 1997; 314: 1531-5.
- Mitchell RB, Pereira KD, Friedman NR, Lazar RH. Outpatient adenotonsillectomy. Is it safe in children younger than 3 years? *Arch Otolaryngol Head Neck Surg* 1997; 123: 681-3.
- Montgomery CJ, McCormack JP, Reichert CC, Marsland CP. Plasma concentrations after high-dose (45 mg.kg⁻¹) rectal acetaminophen in children. *Can J Anaesth* 1995; 42: 982-6.
- Morton NS. Abolition of injection pain due to propofol in children. *Anaesthesia* 1990; 45: 70.
- Morton NS. Pain assessment in children. *Paediatric Anaesthesia* 1997; 7: 267-72.
- Morton NS. Prevention and control of pain in children. *Br J Anaesth* 1999; 83: 118-29.
- Morton NS, O'Brien K. Analgesic efficacy of paracetamol and diclofenac in children receiving PCA morphine. *Br J Anaesth* 1999; 82: 715-17.
- National Health Service Executive. Report by the day surgery task force 1993. London.
- Niemi TT, Taxell C, Rosenberg PH. Comparison of the effect of intravenous ketoprofen, ketorolac and diclofenac on platelet function in volunteers. *Acta Anaesthesiol Scand* 1997; 41: 1353-8.
- Nieminen P, Tolonen U, Löppönen H. Snoring and obstructive sleep apnea in children: a 6-month follow-up. *Arch Otolaryngol Head Neck Surg* 2000; 126: 481-6.
- Nikanne E, Kokki H, Tuovinen K. I.v. perioperative ketoprofen in small children during adenoidectomy. *Br J Anaesth* 1997; 78: 24-7.
- Nikanne E, Kokki H, Tuovinen K. Postoperative pain after adenoidectomy in children. *Br J Anaesth* 1999; 82: 886-9.
- Nikanne E. Ketoprofen for postoperative pain after day-case adenoidectomy in small children. Kuopio: Kuopio University Publications D. Medical Sciences 173, 1999; 56-67.

- Oikkola KT, Hamunen K, Seppälä T, Maunuksela EL. Pharmacokinetics and ventilatory effects of intravenous oxycone in postoperative children. *Br J Clin Pharmacol* 1994; 38: 71-6.
- Ossipov MH, Jerussi TP, Ren K, Sun H, Porreca F. Differential effects of spinal (R)-ketoprofen and (S)-ketoprofen against signs of neuropathic pain and tonic nociception: evidence for a novel mechanism of action of (R)-ketoprofen against tactile allodynia. *Pain* 2000; 87: 193-9.
- Penson RT, Joel SP, Bakhshi K, Clark SJ, Langford RM, Slevin ML. Randomized placebo-controlled trial of the activity of the morphine glucuronides. *Clin Pharmacol Ther* 2000; 68: 667-76.
- Pestian JP, Derkay CS, Ritter C. Outpatient tonsillectomy and adenoidectomy clinical pathway: an evaluative study. *Am J Otolaryngol* 1998; 19: 45-9.
- Pöyhiä R, Vainio A, Kalso E. A review of oxycone's clinical pharmacokinetics and pharmacodynamics. *J Pain Symptom Manage* 1993; 8: 62-7.
- Rautakorpi P, Manner T, Ali-Melkkilä T, Kaila T, Oikkola K, Kanto J. Pharmacokinetics and oral bioavailability of glycopyrrolate in children. *Pharmacol Toxicol* 1998; 83: 132-4.
- Roberts L, Worden J. Suggested International terminology and definitions. *Ambulatory Surgery* 1998; 6: 3.
- Rocha GM, Michea LF, Peters EM et al. Direct toxicity of nonsteroidal antiinflammatory drugs for renal medullary cells. *Proc Natl Acad Sci* 2001; 9: 5317-22.
- Rosenfeld RM, Bhaya MH, Bower CM, et al. Impact of tympanostomy tubes on child quality of life. *Arch Otolaryngol Head Neck Surg* 2000; 126: 585-92.
- Royal College of Anaesthetists. Clinical Guidelines for the use of Non-Steroidal Anti-Inflammatory Drugs in the Perioperative Period 1998; 6-11.
- Royal College of Surgeons of England. Commission in the Provision of Surgical Services. Guidelines for Day Care surgery 1992. London.
- Rømsing J, Möller-Sonnergaard J, Hertel S, Rasmussen M. Postoperative pain in children: comparison between ratings of children and nurses. *J Pain Symptom Manage* 1996; 11: 42-6
- Salonen A, Kokki H, Tuovinen K. I.v. ketoprofen for analgesia after tonsillectomy: comparison of pre- and postoperative administration. *Br J Anaesth* 2001; 86: 377-81.

- Salonen A, Kokki H, Nuutinen J. The effect of ketoprofen on recovery after tonsillectomy in children: a three weeks follow-up study. *Int J Pediatr Otorhinolaryngol* 2002; 62: 143-50.
- Scaife JM, Johnstone JMS. Psychological aspects of day care surgery for children. In: Healy TEJ (ed). *Baillier's Clinical Anesthesiology*. London: Baillier Tindall, 1990; 4: 760-71.
- Sepponen K, Ahonen R, Kokki H. The effects of a hospital staff training program on the treatment practices of postoperative pain in children under 8 years. *Pharm World Sci* 1998; 20: 66-72.
- Sepponen K, Kokki H, Ahonen R. Training of medical staff positively influences postoperative pain management at home in children. *Pharm World Sci* 1999; 21: 168-72.
- Sillanpää M, Anttila P. Increasing prevalence of headache in 7-year-old schoolchildren. *Headache* 1996; 36: 466-70.
- Silvasti M, Rosenberg P, Seppälä T, Svartling N, Pitkänen M. Comparison of analgesic efficacy of oxycodone and morphine in postoperative intravenous patient-controlled analgesia. *Acta Anaesthesiol Scand* 1998; 42: 576-80.
- Stow PJ, White JB. Anaesthesia for paediatric tonsillectomy. Comparison of spontaneous ventilation and intermittent positive pressure ventilation. *Br J Anaesth* 1987; 59: 419-23.
- Taivainen T, Meakin GH, Meretoja OA, Wirtavuori K, Perkins RJ, Murphy AK, Fisher GR, Waiter MR. The safety and efficacy of cis-atracurium 0.15 mg.kg(-1) during nitrous oxideopioid anaesthesia in infants and children. *Anaesthesia* 2000; 55: 1047-51.
- Tarbell SE, Cohen IT, Marsh JL. The Toddler-Preschooler Postoperative Pain Scale: an observational scale for measuring postoperative pain in children aged 1-5. Preliminary report. *Pain* 1992; 50: 273-80.
- Tigerstedt I, Tammisto T. A modified visual analogue scale (VAS) for evaluation of pain intensity during immediate postoperative recovery. *Schmerz Pain Douleur* 1988; 9: 27-31.
- Tramèr MR, Williams JE, Carroll D, Wiffen PJ, Moore RA, McQuay HJ. Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. *Acta Anaesthesiol Scand* 1998; 42: 71-9.
- Valtonen M, Iisalo E, Kanto J, Rosenberg P. Propofol as an induction agent in children: pain on injection and pharmacokinetics. *Acta Anaesthesiol Scand* 1989; 33: 152-5.

- Vanderberg SJ, Heatley DG. Efficacy of adenoidectomy in relieving symptoms of chronic sinusitis in children. *Arch Otolaryngol Head Neck Surg* 1997; 123: 675-8.
- Van der Marel CD, van Lingen RA, Pluim MA, Scoones G, van Dijk M, Vaandrager JM, Tibboel D. Analgesic effect of rectal versus oral acetaminophen after major craniofacial surgery. *Clin Pharmacol Ther* 2001; 70: 82-90.
- Vane JR. The inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biol* 1971; 231: 232-5.
- Vane JR. Towards a better aspirin. *Nature* 1994; 367: 215-6.
- Vane JR, Botting RM. Overview-mechanism of action of anti-inflammatory drugs. In Vane JR, Botting JH & Botting RM (eds). *Improved non-steroid anti-inflammatory drugs. Cox-2 enzyme inhibitors*. Neatherlands: Kluwer Academic Publishers and USA: William Harvey Press, 1996; 1-27.
- Vernon DTA, Schulman JL, Foley JM. Changes in children's behaviour after hospitalization. Some dimensions of response and their correlates. *Am J Dis Child* 1966; 111: 581-593.
- Veys EM. 20 Years' Experience with Ketoprofen. *Scand J Rheumatol* 1991; 90: 3-44.
- Viitanen H, Annila P, Viitanen M, Yli-Hankala A. Midazolam premedication delays recovery from propofol-induced sevoflurane anesthesia in children 1-3 yr. *Can J Anaesth* 1999a; 46: 766-71.
- Viitanen H, Annila P, Viitanen M, Tarkkila P. Premedication with midazolam delays recovery after ambulatory sevoflurane anesthesia in children. *Anesth Analg* 1999b; 89: 75-9.
- Viitanen H, Baer G, Annila P. Recovery characteristics of sevoflurane or halothane for day-case anaesthesia in children aged 1-3 years. *Acta Anaesthesiol Scand* 2000; 44: 101-6.
- Viitanen H, Annila. Analgesic efficacy of tramadol 2 mgkg(-1) for paediatric day-case adenoidectomy. *Br J Anaesth* 2001; 86: 572-5.
- Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroidal drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: A full in vitro analysis. *Proc Natl Acad Sci* 1999; 96: 7563-8.

- Willer JC, De Broucker T, Bussel B, Roby-Brami A, Harrewyn JM. Central analgesic effect of ketoprofen in humans: electrophysiological evidence for a supraspinal mechanism in a double-blind and cross-over study. *Pain* 1989; 38: 1-7.
- Willoughby DA, Moore AR, Colville-Nash PR. Cox-1, Cox-2, and Cox-3 and the future treatment of chronic inflammatory disease. *Lancet* 2000; 355: 646-8.
- Wolf AR. Tears at bedtime: a pitfall of extending paediatric day-case surgery without extending analgesia. *Br J Anaesth* 1999; 82: 319-20.
- Wollheim FA, Stenberg P, Nilsson B, Mellbin G. Clinical and methodological studies on intramuscular ketoprofen in postoperative rheumatic pain. *Eur J Clin Pharmacol* 1981; 20: 423-5.
- Woolf CJ, Chong MS. Preemptive analgesia--treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993; 77: 362-79.
- World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.
- Zutshi D, Mason M. Ketoprofen in rheumatoid arthritis: its tolerance and therapeutic effect. *Scand J Rheumatol* 1976; (Suppl 14): 77-84.

9. APPENDIX

PAIN MANAGEMENT WITH KETOPROFEN AFTER ADENOIDECTOMY
QUESTIONNAIRE FOR PARENTS (to be filled in one week after the operation).

1. Name of child_____	9. Did your child have any of the following events on way or at home ?
2. Date of operation_____	
3. How many days did your child have postoperative pain?	
1 Severe pain for_____ days	nausea? 1 Yes 2 No
2 Moderate pain for_____ days	vomiting? 1 Yes 2 No
3 Mild pain for_____ days	diarrhoea? 1 Yes 2 No
4 No pain at home	constipation? 1 Yes 2 No
4. How many days did your child have postoperative pain altogether?	somnolence? 1 Yes 2 No
_____ days	sweating? 1 Yes 2 No
5. On which day was the pain worst at home?	bleeding? 1 Yes No
1 Operation day	redness at the puncture site? 1 Yes 2 No
2 1. postoperative day	pain at the puncture site? 1 Yes 2 No
3 2. postoperative day	upper abdominal pain? 1 Yes 2 No
4 3. postoperative day	abdominal pain elsewhere? 1 Yes 2 No
5 4. postoperative day	headache? 1 Yes 2 No
6 5. postoperative day	fever? 1 Yes 2 No
7 6. postoperative day	vertigo? 1 Yes 2 No
6. How many doses of ketoprofen your child was given?	problems in vision? 1 Yes 2 No
_____doses	rash? 1 Yes 2 No
7. Did your child receive any other pain medication?	something else? 1 Yes 2 No
1 No 2 Yes, what? _____	If yes, what? _____
How many doses? _____	_____
8. How many days was your child given pain medication?	
_____ days	

Postoperative behavioural changes in children after adenoidectomy, one week after the operation.

Findings at one week after adenoidectomy

Children cannot always discuss verbally about their experiences, but these experiences are seen in their behaviour and playing in many different ways. Most of the children have every now and then problems concerning their health. We kindly ask you to estimate how often your child has the following problems at one week after the operation. Please circle the most convenient choice.

	never	occasionally	weekly	daily
attention seeking	1	2	3	4
temper tantrums	1	2	3	4
anxiety	1	2	3	4
quarrelling	1	2	3	4
disobedience	1	2	3	4
teasing other children	1	2	3	4
other children teasing	1	2	3	4
crying	1	2	3	4
headache	1	2	3	4
stomach-ache	1	2	3	4
day-wetting	1	2	3	4
problems in going to sleep	1	2	3	4
night-wetting	1	2	3	4
waking up at nights	1	2	3	4
nightmares	1	2	3	4
sleepwalking	1	2	3	4
fear of darkness	1	2	3	4
fear of being left alone	1	2	3	4
fear of new things	1	2	3	4
curiosity	1	2	3	4
courage	1	2	3	4
fear of strangers	1	2	3	4
withdrawal	1	2	3	4
speechlessness	1	2	3	4

Average of _____ hours of sleep

How many times waking up at nights? _____times

Postoperative behavioural changes in children after adenoidectomy, one week after the operation.

Findings at one week, compared with the situation before surgery

We kindly ask you to estimate how often your child has the following problems at one week after the operation compared with the situation before surgery. Please circle the most convenient choice.

	much less	slightly less	the same	slightly more	much more
attention seeking	1	2	3	4	5
temper tantrums	1	2	3	4	5
anxiety	1	2	3	4	5
quarrelling	1	2	3	4	5
disobedience	1	2	3	4	5
teasing other children	1	2	3	4	5
other children teasing	1	2	3	4	5
crying	1	2	3	4	5
headache	1	2	3	4	5
stomach-ache	1	2	3	4	5
day-wetting	1	2	3	4	5
problems in going to sleep	1	2	3	4	5
night-wetting	1	2	3	4	5
waking up at nights	1	2	3	4	5
nightmares	1	2	3	4	5
sleepwalking	1	2	3	4	5
fear of darkness	1	2	3	4	5
fear of being left alone	1	2	3	4	5
fear of new things	1	2	3	4	5
curiosity	1	2	3	4	5
courage	1	2	3	4	5
fear of strangers	1	2	3	4	5
withdrawal	1	2	3	4	5
speechlessness	1	2	3	4	5

THANK YOU FOR ANSWERS AND EFFORT SO FAR!

Postoperative behavioural changes in children after adenoidectomy, three weeks after the operation.

Findings at three week after adenoidectomy

Children cannot always discuss verbally about their experiences, but these experiences are seen in their behaviour and playing in many different ways. Most of the children have every now and then problems concerning their health. We kindly ask you to estimate how often your child has the following problems at three weeks after the operation. Please circle the most convenient choice.

	never	occasionally	weekly	daily
attention seeking	1	2	3	4
temper tantrums	1	2	3	4
anxiety	1	2	3	4
quarrelling	1	2	3	4
disobedience	1	2	3	4
teasing other children	1	2	3	4
other children teasing	1	2	3	4
crying	1	2	3	4
headache	1	2	3	4
stomach-ache	1	2	3	4
day-wetting	1	2	3	4
problems in going to sleep	1	2	3	4
night-wetting	1	2	3	4
waking up at nights	1	2	3	4
nightmares	1	2	3	4
sleepwalking	1	2	3	4
fear of darkness	1	2	3	4
fear of being left alone	1	2	3	4
fear of new things	1	2	3	4
curiosity	1	2	3	4
courage	1	2	3	4
fear of strangers	1	2	3	4
withdrawal	1	2	3	4
speechlessness	1	2	3	4
Average of _____ hours of sleep	How many times waking up at nights? _____ times			

Postoperative behavioural changes in children after adenoidectomy, three weeks after the operation.

Findings at three week, compared with the situation before surgery

We kindly ask You to estimate how often Your child has following problems at three weeks after the operation compared with the situation before surgery. Please circle the most convenient choice.

	much less	slightly less	the same	slightly more	much more
attention seeking	1	2	3	4	5
temper tantrums	1	2	3	4	5
anxiety	1	2	3	4	5
quarrelling	1	2	3	4	5
disobedience	1	2	3	4	5
teasing other children	1	2	3	4	5
other children teasing	1	2	3	4	5
crying	1	2	3	4	5
headache	1	2	3	4	5
stomach-ache	1	2	3	4	5
day-wetting	1	2	3	4	5
problems in going to sleep	1	2	3	4	5
night-wetting	1	2	3	4	5
waking up at nights	1	2	3	4	5
nightmares	1	2	3	4	5
sleepwalking	1	2	3	4	5
fear of darkness	1	2	3	4	5
fear of being left alone	1	2	3	4	5
fear of new things	1	2	3	4	5
curiosity	1	2	3	4	5
courage	1	2	3	4	5
fear of strangers	1	2	3	4	5
withdrawal	1	2	3	4	5
speechlessness	1	2	3	4	5

THANK YOU FOR YOUR ANSWERS!