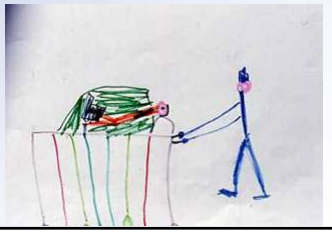
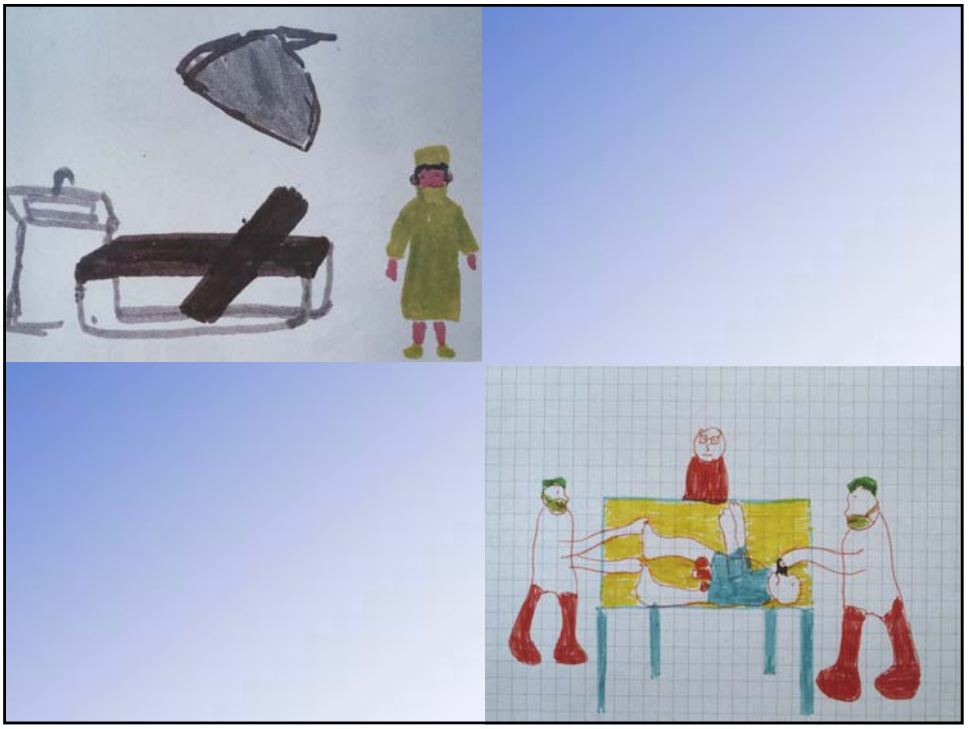
Treatment of postoperative pain

Hannu Kokki, PhD, docent
Kuopio University Hospital and University of Kuopio
Special competence in paediatric anaesthesia
Special competence in pain management

Paediatric postoperative pain

- It has been popular misconception:
  - that young children do not feel pain as severely as adults
  - that the magnitude and duration of its impact is less than in adults






TIZIANO

Paediatric postoperative pain

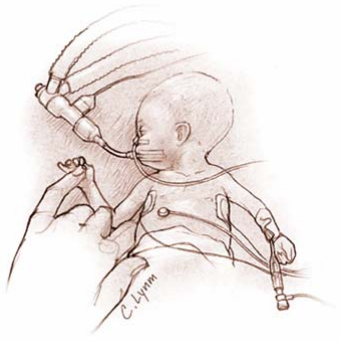
- Now it is known that acute pain in infants and children may induce long-lasting behavioural changes
- Effective management of neonatal pain prevent the development of hyperalgesia, conditioned pain, and conditioned pain behaviours.

Paediatric postoperative pain

- Acute pain in children is still under treated
- This is related mainly to organizational aspects and no to the lack of information
  - the new knowledge about the safe and effective management of pain in children has not been widely or effectively translated into routine clinical practice

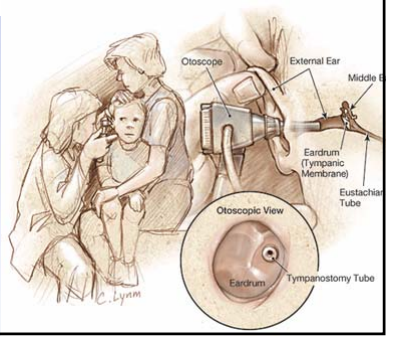
Paediatric postoperative pain

- For ethical and humanitarian reasons pain should be effectively controlled in all age groups



Paediatric postoperative pain

- Pain is a common symptom after surgery also in children
  - Half of the children had significant pain after myringotomy and placement of ventilating tubes



Paediatric postoperative pain

- After adenoidectomy, herniotomy and squint surgery postoperative pain last 2-3days
  - 80% needs analgesic treatment after discharge
- After more extensive surgery, such as orthopaedic surgery and tonsillectomy, almost all children have considerable pain that may last longer than 7 days

Paediatric Anaesthesia 2000 10: 413–417

Recovery after paediatric daycase herniotomy performed under spinal anaesthesia

HANNU KOKKI MD*, MARJA HEIKKINEN MD† AND RIITTA AHONEN PHD (PHARM)‡

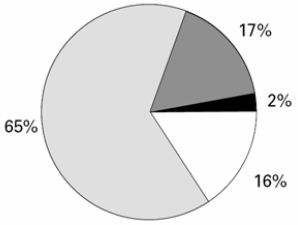


Figure 1
Pain at home following herniotomy.

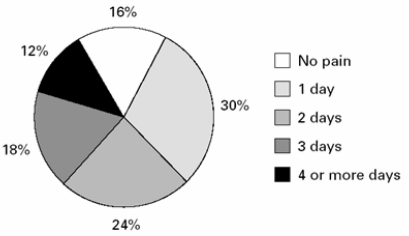


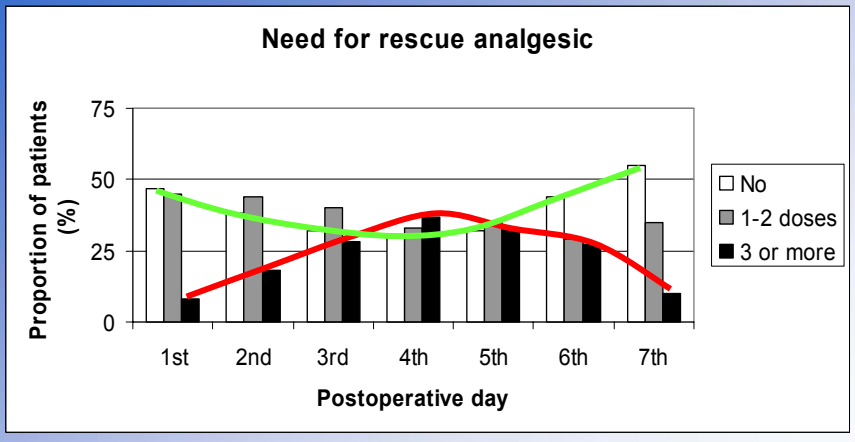
Figure 2
Duration of postoperative pain following herniotomy. Median with 10th and 90th percentiles: 2 (0–4) days.

Paediatric postoperative pain

- Postoperative pain after tonsillectomy

The effect of ketoprofen on recovery after tonsillectomy in children: a 3-week follow-up study

Aarre Salonen [a,b], Hannu Kokki [c,*], Juhani Nuutinen [a]



Paediatric postoperative pain

- Pain following surgery is best managed by providing medication on a regular basis preventing the pain from recurring.

Paediatric postoperative pain

- The concept of **<u>proactive pain management</u>** is best achieved
  - when the drug is administrated as early as possible
  - before the pain has broken through
  - is continued on regular basis for as long as the pain is expected to last

Rather than a single pain treatment, effective relief may require an arsenal

Paediatric postoperative pain

- **Multimodal analgesia** consists of a combination of analgesic regimens to provide more effective analgesia while reducing the incidence and severity of adverse events.

Multimodal analgesia consists:

- Non-opioid analgesics:
  - NSAIDs with or without paracetamol
- Local anaesthetics
  - Central or peripheral block
- Opioids
- Adjuvants
  - Ketamine, clonidine

Paediatric postoperative pain

ADMINISTRATION ROUTES

- In children the choice of formulation can be more important than the choice of drug

ADMINISTRATION ROUTES

- Children dislike suppositories

They hate intramuscular shots

ADMINISTRATION ROUTES

- Intravenous route
  - as long as an intravenous line
  - accurate and practical
- Thereafter by mouth
  - cheap, pleasant and effective
  - small tablets or a mixture.

Paediatric Anaesthesia 2000 **10**: 531–535

The feasibility of pain treatment at home after adenoidectomy with ketoprofen tablets in small children

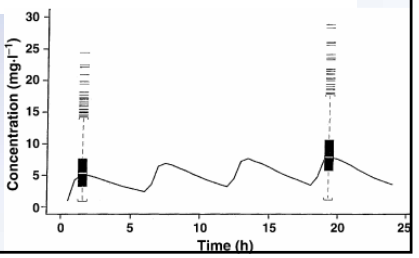
HANNU KOKKI MD*, ELINA NIKANNE MD† AND RIITTA AHONEN PhD (PHARM)‡

Table 2
Problems in administering ketoprofen tablets to children reported by the parents: % (number of children) (n = 555)

Did not receive ketoprofen tablets	6 (23)
Difficulty in swallowing the tablet	12 (65)
Tablet bad-tasting	5 (27)
Difficult to swallow the tablet and bad taste	1 (8)
Pain during swallowing	<1 (2)
Reluctance	<1 (2)
No problems	80 (418)

Paediatric postoperative pain

- Paracetamol (acetaminophen)
  - long record of efficacy and safety for paediatric analgesia
  - now i.v. preparation available
  - suppositories produce highly variable plasma concentrations



Anderson Ped Anesth 2004.
High variability is demonstrated for the maximum concentrations after the first and fourth doses

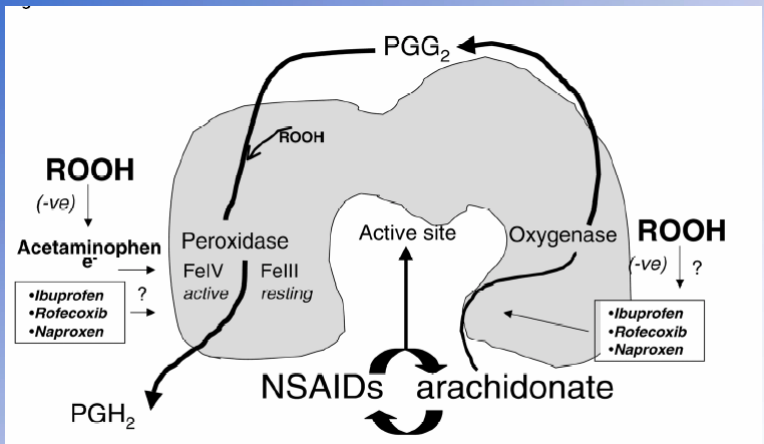
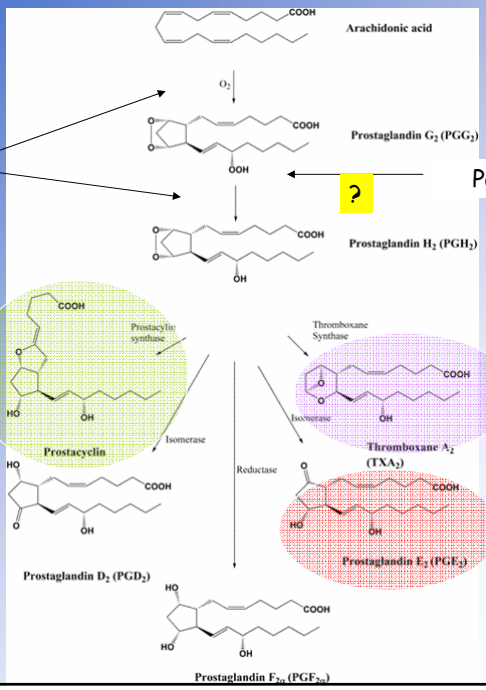


Figure 6. Mechanisms of action of acetaminophen and NSAIDs on cyclo-oxygenase-2 activity. Traditional

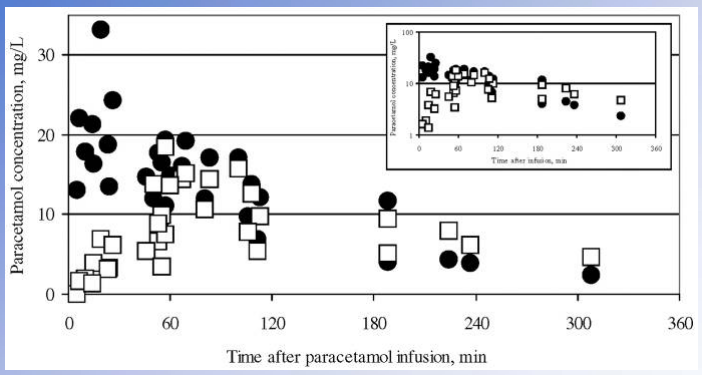
NSAIDs

Paracetamol

?



Plasma (circles) and CSF (squares) paracetamol concentrations after a single intravenous injection of paracetamol 15 mg/kg



Kumpulainen, E. et al. Pediatrics 2007;119:766-771

ORIGINAL RESEARCH ARTICLE

Clin Drug In
1173-256

Ketoprofen for Add-On Pain Treatment to Paracetamol after Strabismus Surgery in Children

Hannu Kokki,[1,2] *Sinikka Purhonen*,[2] *Markku Teräsvirta*[3] and *Paula Ylönen*[2]

1 Department of Pharmacology and Toxicology, University of Kuopio, Kuopio, Finland
2 Department of Anaesthesiology and Intensive Care, Kuopio University Hospital, Kuopio, Finland
3 Department of Ophthalmology, Kuopio University Hospital, Kuopio, Finland

Kokki H et al. I.v. intraoperative ketoprofen in small children during adenoidectomy: a dose-finding study. Br J Anaesth 1998;81:870-4

	Ketoprofen i.v.			
	3 mg/kg	1 mg/kg	0.3 mg/kg	Placebo
Need for rescue analgesia	53%	62%	65%	82%
Mean of fentanyl doses	0.7	0.9	1.1	1.7

Pediatric postoperative pain

- NSAIDs
  - useful because surgery causes both pain and inflammation
  - the analgesic activity result principally from a peripheral inhibition of prostaglandin synthesis
  - seems to have also a central analgesic action

Paediatric Anaesthesia 2002 **12**: 313–316

Diffusion of ketoprofen into the cerebrospinal fluid of young children

HANNU KOKKI MD, PHD*, MARKO KARVINEN MD* AND ANTTI JEKUNEN MD, PHD†

Paediatric postoperative pain

- NSAIDs
  - effective analgesics in mild and moderate pain
  - in severe pain should be given with paracetamol and opioids
  - use of appropriate regional analgesic technique should be considered

Paediatric postoperative pain

- NSAIDs
  - Most extensively evaluated in children: ibuprofen, diclofenac, flurbiprofen, ketoprofen, ketorolac
  - Significant opioid sparing effect
  - Enhance analgesia especially during activity

Nonsteroidal Anti-Inflammatory Drugs for Postoperative Pain

A Focus on Children

Hannu Kokki

Pediatr Drugs 2003; 5 (2): 103-123

Table I. Suggested dosages of some NSAIDs for postoperative pain mana

Agent	Single doses (mg/kg)	Frequency (hourly)	Maximal daily dose (mg/kg)
Diclofenac	1	8–12	3
Ibuprofen	10	6–8	4
Flurbiprofen	1	8–12	5
Ketoprofen	1–2	6–8	5
Ketorolac	0.3–0.5	6–8	2

a The same doses may be used intravenously, by mouth, and rectally.

ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2003; 42 (4): 373-379
0312-5963/03/0004-0373/$30.00/0

Pharmacokinetics of Intravenous and Rectal Ketoprofen in Young Children

Hannu Kokki,[1] *Marko Karvinen*[1] and *Pekka Suhonen*[2]

1 Department of Anaesthesiology and Intensive Care, Kuopio University Hospital, Kuopio, Finland
2 Department of Pharmaceutics, University of Kuopio, Kuopio, Finland

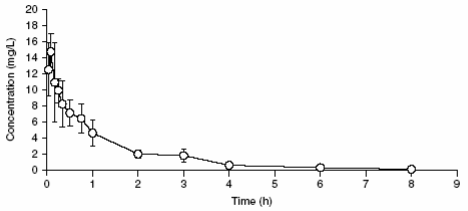


Fig. 1. Mean (SD) plasma concentrations of ketoprofen obtained after single intravenous administration of ketoprofen 1 mg/kg to young children.

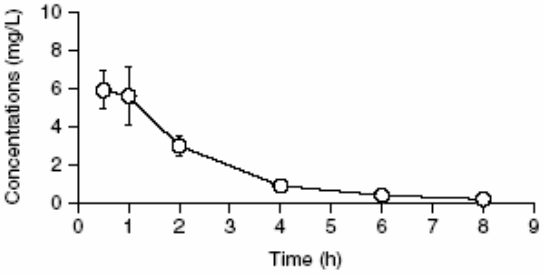
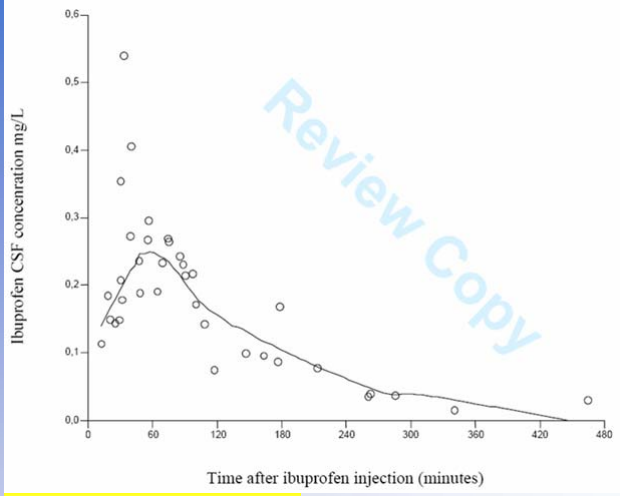


Fig. 2. Mean (SD) plasma concentrations of ketoprofen (dose-normalised to 1 mg/kg) obtained after single rectal administration of ketoprofen to young children.

Bioavailability of ketoprofen 73%

CNS penetration



Ibuprofen 10 mg/kg iv

CNS penetration

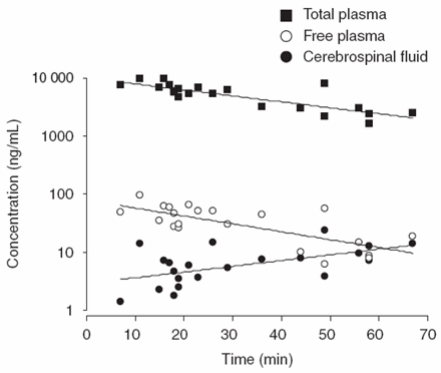


Fig. 1. Concentrations of ketoprofen after intravenous administration (1 mg/kg) from each patient.

Cerebrospinal Fluid Distribution of Ketoprofen after Intravenous Administration in Young Children

Anne Mannila,[1] Hannu Kokki,[2,3] Marja Heikkinen,[4] Merja Laisalmi,[2] Marko Lehtonen,[1] Hanna L. Loukilsto,[3] Tomi Järvinen[1] and Jouko Savolainen[1]

CNS penetration

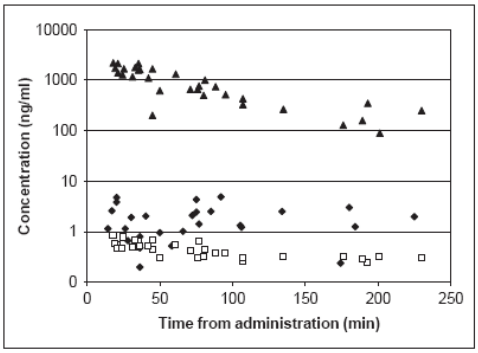
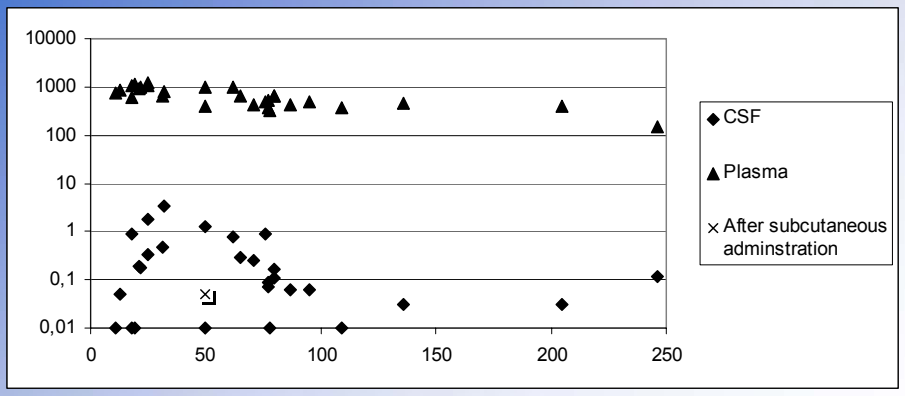


Figure 1. CSF (◆), protein-free plasma (□), and total plasma (▲) concentration of indomethacin in children after intravenous administration (0.35 mg/kg).

Plasma and Cerebrospinal Fluid Concentrations of Indomethacin in Children After Intravenous Administration

Anne Mannila, MSc, Elina Kuanpalainen, BM, Marko Lehtonen, MSc, Marja Heikkinen, MD, Merja Laisalmi, MD, Terhi Salo, Jarkko Bautio, PhD, Jouko Savolainen, PhD, and Hannu Kokki, MD, PhD

CNS penetration

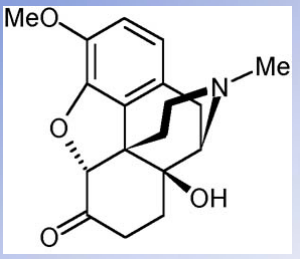


Ketorolac 0.5 mg/kg i.v.

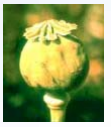
Opioids

- Opioids
  - Highly effective in the management of severe pain
  - Unfortunately opioid receptors so widely distributed in the body
    - Adverse effects common
      - Excessive sedation
      - Respiratory depression
      - Protracted nausea and vomiting
      - Constipation
      - Urinary retention
      - Pruritus

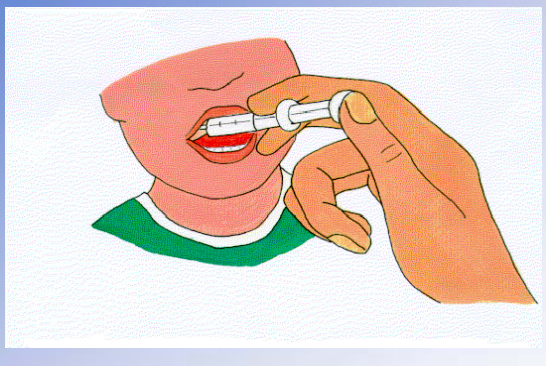
Bladder Retention of Urine as a Result of Continuous Intravenous Infusion of Fentanyl: 2 Case Reports. PEDIATRICS 2001



Oxycodone



Paediatric postoperative pain



Poor man PCA

Administration of Oxycodone to Oral Mucosa in Children

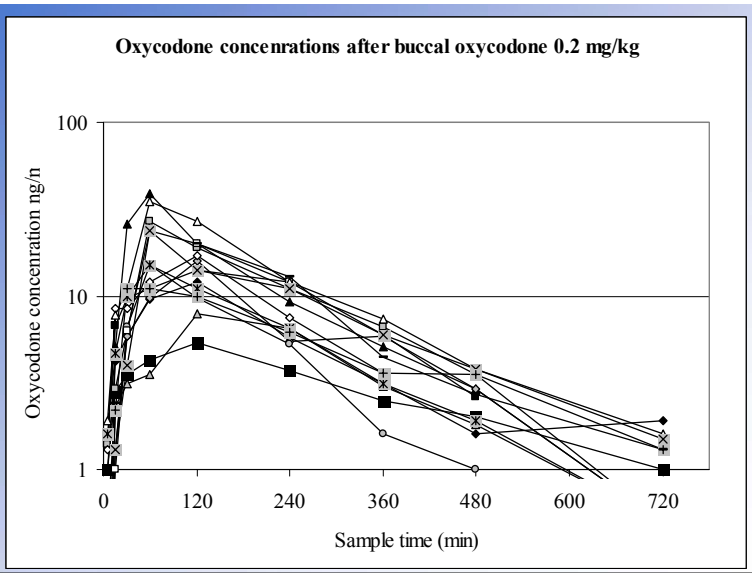
Kokki H, Rasanen I, Laisalmi M, Lehtola S, Vanamo K, Ojanperä I

- Kuopio University Hospital
- University of Kuopio
- University of Helsinki, Finland

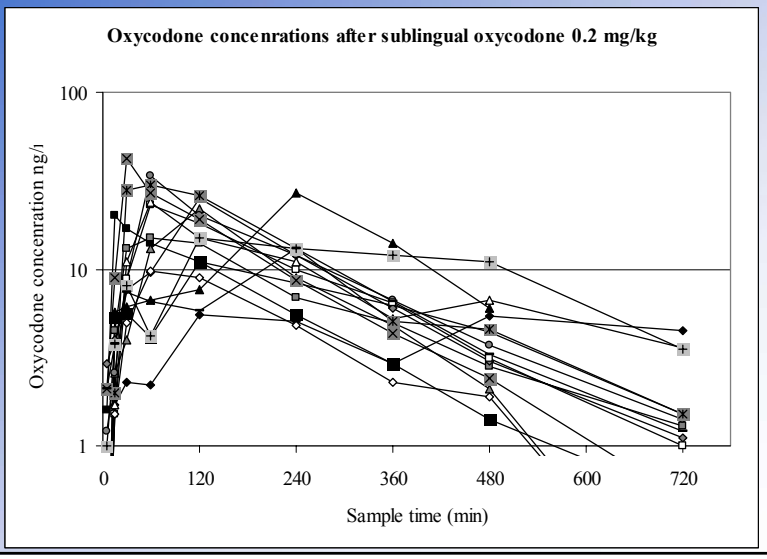
- Oxycodone 10 mg/ml liquid
  - Easy and accurate dosing
  - Small volume
  - Neutral taste
  - Bioavailability from oral mucosa 55%

- The criteria for successful oxycodone administration:
  - Child kept oxycodone in her/his mouth at least for 60 seconds before swallowing.

Buccal group



Sublingual group



Results

- 12 out of 15 children in both groups developed analgesic plasma concentration of oxycodone 12 ng/ml
- Plasma oxycodone concentration > 12 ng/ml
  - sublingual group: 4–236 min (mean 163 min)
  - buccal group: 15–239 min (mean 126 min)

Conclusions:

- Oxycodone 0.2 mg/kg given buccally or sublingually:
- If the child does not swallowed or spit out the drug
  - Analgesic concentration is achieved in 30 to 60 minutes
  - Analgesic concentration is sustained for 2-3 hours

Conclusions:

- If the child swallows
  - The rate of absorption is slower
  - But the extent of absorption is not decreased
- If the child spits out the drug
  - A repeated dose of 0.1 mg/kg may be given

Conclusions:

- Instillation to the mouth is a feasible route for oxycodone administration in children
- Sublingual administration is easy and it provides fast and reliable absorption

Paediatric postoperative pain

- Changing parents knowledge
- Giving appropriate and clear instructions to caregivers
  - verbal and written, pictograms
  - contact numbers
- Apparently improves the quality of pain management

Explain to the child

And avoid intramuscular shots in awake children

Postoperative Behavioral Changes in Children After Adenoidectomy

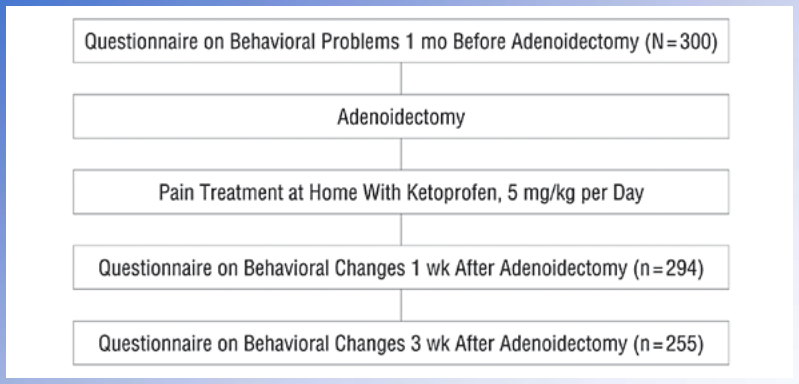
Protocol

- At discharge, parents were instructed about the postoperative care and pain management.
- A proactive pain treatment: 5 mg/kg/day of ketoprofen.
- To be given on a regular basis for at least 72 hours.
- Hospital contact telephone numbers
- All verbal information was reinforced with written instructions.

Tuomilehto, H. et al. Arch Otolaryngol Head Neck Surg 2002;128:1159-1164.

Paediatric postoperative pain

Flowchart of the present study



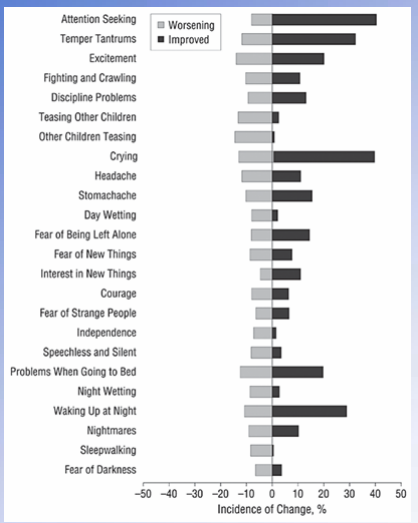
Tuomilehto, H. et al. Arch Otolaryngol Head Neck Surg 2002;128:1159-1164.

Paediatric postoperative pain

- A total of 285 children (97%) received ketoprofen at home, the mean number of doses was 6

Tuomilehto, H. et al. Arch Otolaryngol Head Neck Surg 2002;128:1159-1164.

The incidence of improvement and worsening in behavioral changes for each item 1 week after surgery



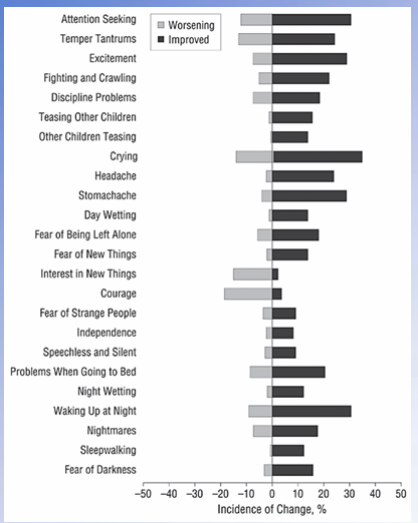
Tuomilehto, H. et al. Arch Otolaryngol Head Neck Surg 2002;128:1159-1164.

Table 4. Magnitude of Behavioral Changes in 294 Patients 1 Week After Surgery

	No. (%) of Cases				
Domain	Large Improvement	Moderate Improvement	No Change	Moderate Worsening	Large Worsening
Emotional distress	4 (1)	36 (13)	183 (64)	48 (17)	13 (5)
Physical symptoms	27 (10)	47 (18)	124 (47)	39 (15)	26 (10)
Day function disturbances	2 (1)	27 (9)	241 (85)	10 (4)	3 (1)
Sleep disturbances	4 (1)	23 (8)	223 (79)	23 (8)	11 (4)

Table 4. Magnitude of Behavioral Changes in 294 Patients 1 Week After Surgery

The incidence of improvement and worsening of behavioral changes for each item 3 weeks after surgery



Tuomilehto, H. et al. Arch Otolaryngol Head Neck Surg 2002;128:1159-1164.

Table 5. Magnitude of Behavioral Changes in 255 Patients 3 Weeks After Surgery

	No. (%) of Cases				
Domain	Large Improvement	Moderate Improvement	No Change	Moderate Worsening	Large Worsening
Emotional distress	3 (1)	30 (12)	184 (73)	25 (10)	9 (4)
Physical symptoms	31 (13)	45 (20)	122 (53)	26 (11)	7 (3)
Day function disturbances	2 (1)	21 (8)	214 (85)	14 (5)	1 (1)
Sleep disturbances	1 (1)	21 (8)	195 (77)	32 (13)	3 (1)

Table 5. Magnitude of Behavioral Changes in 255 Patients 3 Weeks After Surgery

Paediatric postoperative pain

Key issues

- Severe pain may induce long-lasting harm to mind and body
- Postoperative pain is common in children
- After minor surgery pain last for 2-3 days and after major surgery for 1-3 weeks
- Little research has been performed in the pharmacokinetics and pharmacodynamics of analgesics in children

Paediatric postoperative pain

Key issues

- In most situations sufficient pain relief may be achieved using the existing treatment options
- Titration of rescue analgesic is essential in each patient for optimal pain relief
- Peripheral and central block should be considered in all children undergoing surgery

Key issues

- Children hate intramuscular injections and dislike suppositories
- Alternative administration routes should be used for conscious children

Let they be children

"Don't believe, that 3-years old could not decide between different treatment options."
A Bösenberg, APA, Manchester, 8.3.2007