

## Kliiniline küsimus nr 9

Kas patsiendi postoperatiivse ägeda valu ravis mõjutab ravimite<sup>1</sup> manustamise viis i/v vs i/m vs enteraalne valuravi tulemust?

<sup>1</sup>paratsetamool, NSAIDid, opiaadid

**Tulemusnäitajad:** valu tugevus, valu vähenemine, aeg valuvaigistava toime saabumiseni, lisavaluvaigisti vajadus, aeg esimese lisavaluvaigisti vajaduseni, valuvaigisti toime kestus, postoperatiivsete tüsistuste esinemissagedus, valuvaigistitest tingitud kõrvaltoimed, rehospitalseerimine valu tõttu, patsiendi (eestkostja) rahulolu valuraviga, meetodi ohutus

### Ravijuhendid

#### Kokkuvõte:

Manustamisviiside otsesid omavahelisi võrdlusi on vähe.

**nsNSAID ja koksiiidid:** parenteraalsel ja enetraalsel manustamisel ei ole vahet efektiivsuses ja kõrvaltoimete esinemissageduses (Level I soovitus), kuid on oluline hinnavahe.

**Paratsetamool:** p/o manustamisel vahetus postop perioodis ja rektaalsel manustamisel üldiselt on biosaadavus väga varieeruv ning osadel patsientidel võib seetõttu olla kontsentratsioon vereplasmas subterapeutiline.

**Opioidid:** i/v püsiinfusiooniga suurem hingamisdepressiooni oht kui teiste manustamisviisidega (Level IV soovitus). Opioidide i/m vajadusel manustamisel on valuravi kvaliteet halvem kui i/v PCA-ga (Level I soovitus). Võrdluses i/m ja s/c on s/c manustamine patsientide poolt eelistatud, muid erinevusi ei ole.

**i/m manustamine:** ei ole soovitatav (Level I soovitus)

### 1.“Behandlung acuter perioperativer und postraumatischer Schmerzen” 2009 (DE-07)

#### The grading system of the guideline

Degree of recommendation	Level of evidence	
<b>A</b>	<b>1a</b>	Systematic review of controlled randomized clinical trials
	<b>1b</b>	Controlled randomized clinical trials with a strict confidence interval
	<b>1c</b>	“All or nothing” therapeutic results
<b>B</b>	<b>2a</b>	Systematic review of cohort studies
	<b>2b</b>	Cohort studies (including lesser quality randomized clinical trials)
	<b>2c</b>	Observation of therapeutic results (outcomes research).
	<b>3a</b>	Systematic review of case-control studies
	<b>3b</b>	Case-control study
<b>C</b>	<b>4</b>	Case report (including cohort or case-control of poor quality)
	<b>5</b>	Specialists' opinions lacking critical evaluation or based on basic matters (physiological study or study with animals)

- I/m administration of analgesics is not recommended. GoR: A
- I/m injections are painful (LoE: 4) (Cupitt und Kasipandian, 2004).
- I/m injections – risk of nerve damage, risk of haematomas (LoE: 4) (Greenblatt und Koch-Weser, 1976; Muller-Vahl, 1983; Tong und Haig, 2000).

#### Children:

- At the acute postoperative phase i/v administration should be preferred (GoR: B) RCT showed reduced analgetics need if non-opioids were given i/v compared to oral administration, but there were no difference in the intensity of pain (LoE: 1b) (Tuomilehto et al., 2000).

Two studies found no difference when oral administration was compared to the rectal administration of non-opioids (LoE: 1b) (Kokki et al., 2000; Tuomilehto und Kokki, 2002).

- I/m administration of analgesics is not recommended. GoR: A  
i/m administration is for children particularly traumatic (Hunseler et al., 2005).
- For enteral administration NSAIDs offer benefit over paracetamol GoR: B ((LoE: 5) Anderson (2004)
- Parenteral paracetamol gave compared to placebo significantly better analgetic effect (LoE: 1b) (Granry et al., 1997).

## 2. Acute Pain Management: Scientific Evidence 2010 (AU10)

Levels of evidence	
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-controlled studies or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test and post-test
<b>Clinical practice points</b>	
<input checked="" type="checkbox"/>	Recommended best practice based on clinical experience and expert opinion

Administration of systemic analgesic drugs (opioids, nsNSAIDs and coxibs) - direct comparisons between oral and other routes of administration are limited.

#### Key messages:

- NSAIDs (nsNSAIDs and coxibs) given parenterally or rectally are not more effective and do not result in fewer side-effects than the same drugs given orally (U) (Level I (Cochrane review).
- Early postoperative p/o paracetamol results in highly variable plasma concentrations that may remain subtherapeutic in some patients (N) (Level II)
- Rectal administration of single doses of paracetamol results in highly variable plasma concentrations that often remains subtherapeutic (N) (Level II)

- Intermittent s/c morphine injections are as effective as i/m injections and have better patient acceptance (U) (Level II)
- Continuous i/v infusions of opioids in the general ward setting is associated with an increased risk of respiratory depression compared with other methods of parenteral opioid administration (U) (Level IV)
- Intermittent i/m injections are distressing for children and are less effective for pain control than i/v infusions (U) (Level III-1)

### Conclusions based on clinical experience and expert opinion:

- Other than in the treatment of severe acute pain, and providing there are no contraindications to its use, the oral route is the route of choice for the administration of most analgesic drugs (U).
- Controlled-release opioid preparations should only be given at set time intervals (U).
- Immediate-release opioids should be used for breakthrough pain and for titration of controlled-release opioids (U).
- The use of controlled-release opioid preparations as the sole agents for the early management of acute pain is discouraged because of difficulties in short-term dose adjustments needed for titration (U).

### Opioids

#### p/o

- Morphine liquid 20mg every 4h provides better pain relief after hip surgery than im morphine 5-10mg prn (McCormack et al 1993 **Level II**)

#### i/m

- Incidence of resp. depression from 0.8 (0.2-2.5)% to 37 (22.6-45.9)% using respiratory rate and oxygen saturation, respectively, as an indicators. (review by Cashman and Dolin 2004) **Level IV**
- Quality of pain relief was less with intermittent im regimes than with iv PCA (Hudcova et al 2005) **Level I**
- In children, there was no difference in rate of onset, analgesic effect and side effects when s/c morphine compared with i/m, significantly higher patient preference for the s/c route (Cooper et al 1996 **Level II**; Lamacraft et al. 1997 **Level IV**).
- i/m and s/c morphine after Cesarean section -no significant difference in side effects, patient satisfaction or pain relief at rest, but lower pain scores after s/c administration at 12, 16, 20h after surgery (Safavi and Honarmand 2007 **Level III**).
- Comparison of same morphine dose single s/c or i/v inj - i/v resulted in more rapid onset of analgesia (5 min i/v; 20 min s/c) and better pain relief between 5 min and 25 min after injection, but also led to higher sedation scores up to 30 min after injection and higher PCO2 levels (Tveita et al. 2008 **Level II**).
- Intermittent s/c morphine inj are as effective as i/m and have better patient acceptance (**Level II**)
- In children there was no difference in rate of onset, analgesic effect and side effects when s/c injections of morphine were compared with i/m morphine injections and there was a significantly higher patient preference for the s/c route

(Cooper 1996; Lamacraft et al. 1997).

#### **i/v**

- i/v tramadol was more effective than same dose given p/o after dental surgery, difference in bioavailability of single dose of tramadol may be up to 30% (Ong et al. 2005; **Level II**)
- Large i/v doses of tramadol can result in a high incidence of emetic symptoms (Pang et al 2000, **Level II**).
- Compared with PCA, continuous iv opioid infusions in a general ward setting resulted in a 5-fold increase in the incidence of respiratory depression (Schug and Torrie, 1993, **Level IV**).

#### **Rectal**

- In cancer pain patients – no difference in pain relief or ADRs between po and rectal tramadol (Mercadante et al 2005, **Level II**)

#### **Intranasal**

In children, intranasal fentanyl at a dose of 1.7 mcg/kg was shown to be as effective as iv morphine 0.1mg/kg in children presenting to an emergency department with an acute fracture (Borland et al 2007, **Level II**) and equivalent to oral morphine for pain relief during burn wound dressing changes (Borland et al 2005 **Level II**).

#### **nsNSAID**

##### **p/o**

- No good evidence that nsNSAIDs given parenterally or rectally are more effective or result in fewer side effects than the same drugs given orally for the treatment of postop pain (Tramer et al. 1998 **Level I**).

##### **i/m**

- Limited number of nsNSAIDs/ coxibs available for i/m inj. Ketorolac and parecoxib i/m are effective analgesic agents (Smith et al 2000 **Level I**; Lloyd et al 2009 **Level I**).

##### **i/v**

- In single doses as the sole analgesic agent, parecoxib iv 20 to 40mg has shown to be effective (Lloyd et al 2009, **Level I**)
- In most cases the route of administration does not seem to alter efficacy. Iv nsNSAIDs and coxibs are more expensive although their efficacy and likelihood of side effects is similar (Tramer et al. 1998, **Level I**)
- Comparison of rectal diclofenac and iv parecoxib showed no difference in pain relief, side effects or rescue analgesic requirements (Ng et al. 2008; **Level II**).
- Efficacy and times to onset of analgesia were similar with iv and im parecoxib (Daniels et al, 2001, **Level II**)

#### **Rectal**

- No advantage in using nsNSAID if the oral route is available (Tramer et al. 1998,

## Level I)

### Paracetamol

#### p/o

- Oral bioavailability is good (63-89% Oscier and Milner 2009), but early postop oral administration can result in highly variable plasma concentrations and may be subtherapeutic (Holmer and Pettersson et al. 2004, [Level II](#)).
- In the same doses p/o paracetamol was less effective and of slower onset than i/v, but more effective and faster onset than per/rect.
- Paracetamol effervescent tablets were absorbed significantly faster than ordinary paracetamol (Rygnestad et al. 2000, [Level II](#)).

#### i/v

- I/v – faster onset than same dose given orally (Moller, Sindet-Pedersen et al 2005, [Level II](#)), but more expensive.
- Due to the good bioavailability and tolerability of p/o paracetamol, the use of iv form should be limited to clinical circumstances where enteral route is not appropriate.

#### Rectal

- Paracetamol is effective when given p/rect (Romsing et al. 2002, [Level I](#)), although rectal absorption of paracetamol is slower and less predictable than p/o (bioavailability 24-98%, Oscier and Milner 2009).
- In children, similar results have been noted. Initial administration of doses of 25mg/kg achieved average blood concentrations at the lower end of the therapeutic range and large variations in absorption were reported (Hahn, Henneberg et al. 2000)
- Less effective when same dose administered p/o (Anderson et al 1996, [Level II](#), Anderson et al 1999, [Level IV](#))
- Doses of 1g per/rect after cardiac surgery (Holmer Pettersson et al 2006 [Level II](#)) and hysterectomy (Kvalsvik et al 2003 [Level II](#)) as well as 2g rectally after laparoscopic gynecological surgery (Hahn, Morgensen et al. 2000 [Level II](#)) also resulted in subtherapeutic blood levels. The levels may increase to within therapeutic range after repeated administration (Holmer Pettersson et al 2006 [Level II](#)).
- When available, the oral route is preferable.

## Süsteematilised ülevaated ja meta-analüüsid

**Kokkuvõte:** Otsingu tulemusena leiti üks meta-analüüs, kus võrreldakse ennetavaks või postoperatiivseks valu raviks ühekordse annusena manustatud iv paratsetamooli või per os paratsetamooli. Meta-analüüsi tulemusena selgus, et statistilist erinevust kahe manustamise viisi vahel ei ole või oli see kliiniliselt ebaoluline.

- **McNicoll, E.D. et al (2011) „Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis“** British Journal of Anaesthesia 106 (6): 764–75

**Summary.** Paracetamol is the most commonly prescribed analgesic for the treatment of acute pain. The efficacy and safety of i.v. formulations of paracetamol is unclear. We performed a systematic search (multiple databases, bibliographies, any language, to May 2010) for single-dose, randomized, controlled clinical trials of propacetamol or i.v. paracetamol for acute postoperative pain **in adults or children**. Thirty-six studies involving 3896 patients were included. For the primary outcome, 37% of patients (240/367) receiving propacetamol or i.v. paracetamol experienced at least 50% pain relief over 4 h compared with 16% (68/527) receiving placebo (number needed to treat<sup>1</sup>44.0; 95% confidence interval, 3.5–4.8). The proportion of patients in propacetamol or i.v. paracetamol groups experiencing at least 50% pain relief diminished over 6 h. Patients receiving propacetamol or paracetamol required 30% less opioid over 4 h and 16% less opioid over 6 h than those receiving placebo. However, this did not translate to a reduction in opioid-induced adverse events (AEs). **Similar comparisons between propacetamol or i.v. paracetamol and active comparators were either not statistically significant, not clinically significant, or both.** AEs occurred at similar rates with propacetamol or i.v. paracetamol and placebo. **However, pain on infusion occurred more frequently in those receiving propacetamol compared with placebo (23% vs 1%). A single dose of either propacetamol or i.v. paracetamol provides around 4 h of effective analgesia for about 37% of patients with acute postoperative pain.** Both formulations are associated with few AEs, although patients receiving propacetamol have a higher incidence of pain on infusion.

## Children

**1. Goldstein,** Lee Hilary, et al. "Effectiveness of oral vs rectal acetaminophen: a meta-analysis." *Archives of pediatrics & adolescent medicine* 162.11 (2008): 1042-1046.

**Objective** To determine, on the basis of published studies, the efficacy of rectal vs oral acetaminophen as treatment of fever and pain.

**Data Sources** MEDLINE, PubMed, and the Cochrane database as well as major pharmacologic textbooks and the references of all included studies were searched for studies comparing oral and rectal administration of acetaminophen.

**Study Selection** Randomized and quasi-randomized controlled studies **comparing rectal and oral administration of acetaminophen** were included. Reviews, letters, and studies that compared combined treatments or additional drugs were excluded.

**Main Exposure** Oral vs rectal acetaminophen.

**Main Outcome Measures** Standardized measures of temperature and pain reduction.

**Results** **We did not perform a meta-analysis comparing rectal and oral acetaminophen for pain reduction because only 1 study** (Anderson B Kanagasundarum S Woollard G Analgesic efficacy of paracetamol in children using tonsillectomy as a pain model. *Anaesth Intensive Care* 1996;24 (6) 669- 673) **fulfilled the inclusion criteria.**

**Conclusions** Rectal and oral acetaminophen are comparable with respect to temperature reduction. The American Academy of Pediatrics recommendation to refrain from rectal acetaminophen in children should possibly be revised.

## RCTs

### Kokkuvõte:

**Paratsetamool** Otsingu tulemusena leiti kaks RCT-d, mis ei anna täpset vastust uuringuküsimusele. Uuringud käsitlevad pre- või intraoperatiivses perioodis manustatud paratsetamooli iv või po, kuid mõõdavad postoperatiivse valu tugevust. Uuringu tulemusest selgus, ennetava analgeesia paratsetamooli manustamise viis ei mõjuta postoperatiivse valu tugevust. (Fenlon et al 2013, Brett et al 2012 ).

**nsNSAID** Otsingu tulemusena ei leitud ühtegi RCT-d, mis vastaks konkreetset uuringuküsimusele. Leidus uuringuid, mis käsitlevad valuvaigistitest tingitud kõrvaltoimeid (primaarne ja sekundaarne veritsus ja PONV).

**Koksiibid** Otsingu tulemusena ei leitud ühtegi RCT-d, mis vastaks konkreetset uuringuküsimusele. Leidus uuringuid, mis käsitlevad valuvaigistitest tingitud kõrvaltoimeid (veritsus ja PONV).

**Opioidid:** Leidus ainult 1 värske (viimase 10 a jooksul avaldatud) RCT, mis vastas uuringuküsimusele. Võrreldi 10mg i/v ja 10mg i/m morfiini. i/v – oluliselt kiirem analgeetilise toime algus kui i/m (5 vs 20 min) ja suurem valu vähenemine samas ka veidi suurem paCO<sub>2</sub> tõus ja tugevam sedatiivne toime (Tveita et al. 2008)

## Paracetamol

PubMed search for **Paracetamol**:

**Filters** activated: Meta-Analysis, Randomized Controlled Trial, Systematic Reviews, published in the last 5 years, Humans.

**MeSh terms** used:

"analgesia/methods"

"paracetamol"

"acetaminophen"

"route of administration"

"intravenous"

"postoperative pain"

"adverse effects"

"pain/prevention and control"

"hepatotoxicity"

"treatment outcome"



1. "paracetamol"[All Fields] AND "acetaminophen"[All Fields] AND ((Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "2009/10/08"[PDat] : "2014/10/06"[PDat] AND "humans"[MeSH Terms]) Results: 224

2. "paracetamol"[All Fields] AND "acetaminophen"[All Fields] AND ((Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "2009/10/08"[PDat] : "2014/10/06"[PDat] AND "humans"[MeSH Terms]) Results: 425 (filter 10 years)

3. "paracetamol administration"[All Fields] AND ((Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "2009/10/08"[PDat] : "2014/10/06"[PDat] AND "humans"[MeSH Terms]) Results: 15

- **Fenlon, S. et al (2013) „Oral vs intravenous paracetamol for lower third molar extractions under general anaesthesia: is oral administration inferior?‘‘** British Journal of Anaesthesia 110 (3): 432–7

**Background.** Paracetamol formulations provide effective analgesia after surgery [Duggan ST, Scott LJ. Intravenous paracetamol (acetaminophen). Drugs 2009; 69: 101–13; Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. Cochrane Database Syst Rev 2008; CD004602]. I.V. paracetamol is superior to oral for pain rescue (Jarde O, Boccard E. Parenteral versus oral route increases paracetamol efficacy. Clin Drug Invest 1997; 14: 474–81). By randomized, double-blinded trial, we aimed to determine whether preoperative oral paracetamol provides inferior postoperative analgesia to preoperative i.v. paracetamol.

**Methods.** One hundred and thirty participants received either oral paracetamol and i.v. placebo (Group OP), or oral placebo and i.v. paracetamol (Perfalgan™) (Group IP). Oral preparations were given at least 45 min before surgery; i.v. preparations after induction of anaesthesia. Pain was assessed by a 100 mm visual analogue scale (VAS) 1 h from the end of surgery. Rescue analgesia was given on request.

**Results.** A total of 128 patients completed the study. There were no significant differences in baseline characteristics or intraoperative variables between the groups. The study was designed to reveal whether OP is inferior to IP, with an inferiority margin of 20%. The number of patients reporting satisfactory analgesia at 1 h with VAS ≤30 mm were 15 (OP) and 17 (IP), respectively. The secondary outcome measure of the mean (standard deviation) VAS (mm) for the whole of each group was 52 (22) for OP and 47 (22) for IP. **Analysis of confidence intervals indicates that oral paracetamol is not inferior to i.v. paracetamol. The median survival (90% CI) to rescue analgesia request was 54.3 (51.2– 57.4) min in Group OP and 57.3 (55.4–59.2) min in Group IP; there was no significant difference in this measure.**

**Conclusions.** In this study of lower third molar extraction, **oral paracetamol is not inferior to i.v. for postoperative analgesia.**

- **Brett, C. N., S. G. Barnett, and J. Pearson.** "Postoperative plasma paracetamol levels following oral or intravenous paracetamol administration: a double-blind randomised controlled trial." Anaesthesia and intensive care 40.1 (2012): 166-171.



**Aim:** double-blind RCT, which method of administration achieves therapeutic plasma levels most effectively in the early postoperative period.

**Methods:** 30 patients undergoing day case arthroscopy of the knee were randomised to receive either 1g oral paracetamol 30 to 60 min preoperatively (20 patients) or 1g i/v paracetamol intraoperatively (10 patients). Plasma paracetamol levels were measured 30 min after arrival in the recovery room. Secondary outcomes included postop pain scores, rescue analgesia requirements and duration of stay in the recovery room.

**Results:** All patients receiving the i/v preparation had plasma levels above the analgesic level compared to less than half (7/20) in the oral group. Mean plasma paracetamol levels were 88.6 $\mu$ mol/l for the i/v group and 53.2 $\mu$ mol/l for the oral group (P=0.0005). There were trends towards reduced rescue analgesia and duration of stay in the recovery room for the intravenous group although not reaching statistical significance. There was **no difference in pain scores between groups**.

**Conclusion:** Intraoperative administration of 1g of i/v paracetamol more reliably achieved effective paracetamol levels in the early postoperative period compared to an equal dose given orally preoperatively. Only a minority of patients receiving the 1g oral dose preoperatively had plasma levels in the therapeutic analgesic range.

## Children:

1. **Capici**, F., et al. "Randomized controlled trial of duration of analgesia following intravenous or rectal acetaminophen after adenotonsillectomy in children." *British journal of anaesthesia* 100.2 (2008): 251-255.

**Background.** Doses of acetaminophen 40 mg kg<sup>-1</sup> rectally and 15 mg kg<sup>-1</sup> i.v. produce similar effect-site concentrations. However, the clinical effectiveness of these routes has not been compared.

The **aim** of this study was to compare duration and efficacy of analgesia in children following adenotonsillectomy after acetaminophen either 40 mg kg<sup>-1</sup> rectally or 15 mg kg<sup>-1</sup> i.v.

**Methods.** Fifty children aged between 2 and 5 yr were recruited. They received a standardized anaesthetic, including 2 mg kg<sup>-1</sup> of fentanyl. Children were randomized to receive either rectal or i.v. acetaminophen. Postoperative pain was assessed regularly with the Children and Infants Postoperative Pain Scale score and rescue analgesia provided if scores were 4 or greater. The primary outcome measure was time to first analgesia. Results were plotted with a Kaplan–Meier analysis and median time to rescue analgesia compared between the groups.

**Results.** The protocol was successfully completed in 46 children. Forty-five children required rescue medication. **The time to first rescue analgesia was longer in children receiving rectal acetaminophen (median 10 h, inter-quartile range 9–11 h) compared with those receiving i.v. acetaminophen (7, 6–10 h) with a P-value of 0.01 by log-rank test for equality in survivor function.**

Few children in either group required rescue analgesia within the first 6 h with differences between the groups being most prominent in the period from 6 to 10 h.

**Conclusions.** Rectal acetaminophen 40 mg kg<sup>-1</sup> provides longer analgesia for moderately painful procedures when compared with 15 mg kg<sup>-1</sup> acetaminophen i.v.

2. **Owczarzak**, Vicki, and Joseph Haddad. "Comparison of oral versus rectal administration of acetaminophen with codeine in postoperative pediatric adenotonsillectomy patients." *The Laryngoscope* 116.8 (2006): 1485-1488.

**Objective:** To examine whether acetaminophen with codeine administered per rectum is an effective alternative for pain control compared with oral administration after an adenotonsillectomy.

**Study Design:** A prospective, randomized control study.

**Methods:** Seventy-five children aged 1 to 5 were recruited for this study. Each child was assigned randomly to receive either rectal or oral postoperative pain medication. A journal with eight questions was kept for 10 days after the operation, and an overall survey of five questions was filled out at the first postoperative visit.

**Results:** Postoperative pain was adequately controlled in those patients receiving suppositories when compared with those patients receiving oral pain medication. Adverse effects and total number of doses given per day were similar. Parents found the suppositories easy to administer, and more parents would switch or consider switching from oral pain medication to suppositories if given the choice.

**Conclusions:** The suppositories achieved equivalent pain control as oral medication with few side effects and good tolerance. Furthermore, many parents preferred the suppositories to oral medication in maintaining postoperative pain control because of ease of administration. If given the choice for future surgeries, many parents would switch or consider switching from oral pain medication to suppositories.

3. **Prins**, Sandra A., et al. "Pharmacokinetics (PK) and analgesic effects of intravenous propacetamol vs rectal paracetamol in children after major craniofacial surgery." *Pediatric Anesthesia* 18.7 (2008): 582-592.

**Background:** The PK and analgesic effects of iv and rectal paracetamol were compared in nonventilated infants after craniofacial surgery in a double-blind placebo controlled study.

**Methods:** During surgery all infants (6 months–2 years) received a rectal loading dose of 40 mg/kg<sup>-1</sup> paracetamol 2 h before anticipated extubation. On admittance to the pediatric surgical ICU, the children were randomized to receive either a 15 min iv infusion of 40 mg/kg<sup>-1</sup> propacetamol, a prodrug of paracetamol, or 20 mg/kg<sup>-1</sup> or paracetamol rectally every 6 h. A population PK analysis of the paracetamol plasma concentration time-profiles was undertaken using nonlinear mixed effects models. The visual analogue scale (VAS) (score 0–10 cm) and COMFORT Behavior scale (score 6–30) were used to monitor analgesia in the 24-h period following surgery.

**Results:** 12 infants received iv propacetamol and 14 paracetamol suppositories. Paracetamol PK were described according to a two-compartmental model with linear disposition. PK parameters were standardized to a 70 kg person using allometric '1/4 power' models. Parameter estimates were: absorption half-life from the rectum 4.6 h, propacetamol hydrolysis half-life 0.028 h, clearance 12 l/h/70 kg<sup>-1</sup>, intercompartmental clearance 116 l/h/70 kg<sup>-1</sup>, central and peripheral volume of distribution 7.9 and 44 l/70 kg<sup>-1</sup>, respectively. During the 24-h study period 22 infants exhibited VAS scores <4 cm, which was considered a cutoff point. On single

occasions four patients, two in each group, exhibited a VAS score  $\pm$ 4 cm. Nine patients in the rectal treatment group and three patients in the intravenous treatment group received midazolam for COMFORT-B scores exceeding 17 (  $P < 0.05$ ).

**Conclusions:** Iv propacetamol proved to be more effective than rectal paracetamol in infants after craniofacial surgery. Midazolam was more frequently administered to patients receiving paracetamol suppositories, indicating that these children experienced more distress, possibly caused by pain.

PubMed search for **nsNSAIDs/coxibs**:

**Filters** activated: Randomized Controlled Trial, published in the last 5 years, Humans.

**MeSh terms** used:

"analgesia/methods"  
"administration"  
"route of administration"  
"intramuscular"  
"intravenous"  
"postoperative pain"  
"adverse effects"  
"pain/prevention and control"  
"respiration/drug effects"  
"nausea/drug therapy"  
"sedation/analgesia"  
"treatment outcome"

PubMed search for **OPIOIDS**:

**Filters** activated: Randomized Controlled Trial, published in the last 5 years, Humans.

**MeSh terms** used:

"analgesia/methods"  
"opioid administration"  
"route of administration"  
"intramuscular"  
"intravenous"  
"postoperative pain"  
"morphine/adverse effects"  
"pain/prevention and control"  
"respiration/drug effects"  
"nausea/drug therapy"  
"sedation/analgesia"  
"treatment outcome"

- Tveita, T., et al. "A controlled comparison between single doses of intravenous and intramuscular morphine with respect to analgesic effects and patient safety." *Acta anaesthesiologica Scandinavica* 52.7 (2008): 920-925.

**Aim:** to compare patient safety and analgesic efficacy of a single and high dose of morphine given IM or IV for postop pain management.

**Materials and methods:** 38 patients with postop pain following hip replacement surgery were given IM or IV morphine 10 mg at a specified pain level. The study was randomized and double blinded. Time to onset of analgesic effect (11-point numeric rating scale), respiratory function ( $p_a\text{CO}_2$ ,  $p_a\text{O}_2$ , and respiratory rate), level of sedation (5-point verbal rating scale), and hemodynamic function were recorded.

**Results:** In the IV group there was a slight but significant increase in  $p_a\text{CO}_2$  after 5, 10, and 15 min compared with the IM group (5.2 vs. 4.8, 5.4, vs. 5.0 and 5.5 vs. 5.1 kPa, respectively). The IV group had a significantly faster onset of analgesic effect than the IM group (5 vs. 20 min). Between 5 and 25 min after morphine administration, pain status in the IV group was significantly improved compared with the IM group. Patients in the IV group were slightly more sedated than the IM group 5 and 10 min after morphine.

**Conclusion:** A 10 mg bolus dose of IV morphine given to patients with moderate pain after surgery does not cause severe respiratory depression, but provides more rapid and better initial analgesia than 10 mg given IM. IV morphine even at a dose as high as 10 mg IV is well tolerated if there is a certain level of pain at its administration. The safety of IV morphine on the general ward needs to be further explored in adequately controlled studies.

## Children

**1. Kokki**, Hannu, et al. "Pharmacokinetics (PK) of oxycodone after intravenous, buccal, intramuscular and gastric administration in children." *Clinical pharmacokinetics* 43.9 (2004): 613-622.

**Objective:** To evaluate the PK of four administration routes of oxycodone parenteral liquid (10 mg/mL), single iv and im injections and buccal and gastric administration, in children.

**Patients and participants:** 40 generally healthy children, aged 6–93 months, undergoing inpatient surgery.

**Methods:** After induction of anaesthesia, children received a single dose of oxycodone 0.1 mg/kg iv (n = 9), im (n = 10), buccally (n = 11) or via an orogastric tube into the stomach (n = 10). Regular blood samples were collected up to 12 hours, and plasma was analysed for oxycodone using gas chromatography-mass spectrometry (limit of quantification 1 µg/L).

**Results:** The peak drug concentration observed was 57–110 (mean 82) µg/L after iv administration, 23–54 (34) µg/L after im administration, 3.9–14 (9.8) µg/L after buccal administration and 1.7–15 (9.2) µg/L after gastric administration. The time to peak concentration was 2–30 (16) minutes in the im group, 30–480 (221) minutes in the buccal group and 60–360 (193) minutes in the gastric group. The terminal elimination half-lives were closely similar in the four groups: 124–208 (163) minutes

in the iv group, 162–227 (150) minutes in the im group, 73–234 (150) minutes in the buccal group and 80–246 (147) minutes in the gastric group. Area under the concentration-time curve (AUC) was 5037–8954 (6612)  $\mu\text{g} \cdot \text{min/L}$  in the intravenous group, 3084–5524 (4473)  $\mu\text{g} \cdot \text{min/L}$  in the intramuscular group, 1444–5560 (3658)  $\mu\text{g} \cdot \text{min/L}$  in the buccal group and 692–3843 (2436)  $\mu\text{g} \cdot \text{min/L}$  in the gastric group. The estimated bioavailability (AUC/mean intravenous AUC) of intramuscular oxycodone was 0.47–0.84 (0.68), that of buccal oxycodone 0.22–0.84 (0.55) and that of gastric oxycodone 0.10–0.58 (0.37).

**Conclusion:** The PK of intravenous oxycodone in children aged 6–93 months are fairly similar to those reported in adults. Im administration provides relatively constant drug absorption, but after buccal and gastric administration the interindividual variation in the rate and extent of absorption is large.