

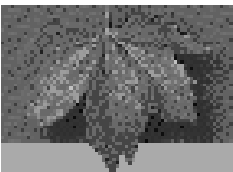
OUR CHALLENGES IN PAIN MANAGEMENT IN NEONATES

Vineta Fellman

Professor of Neonatology

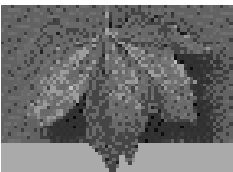
**Lund University, Sweden and
University of Helsinki, Finland**





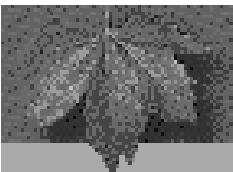
Questions

- Does the newborn feel pain?
- How should we measure pain?
- How should we prevent distress and pain?
- Pharmacological treatment?
 - Which drug?
 - How should we assess the beneficial effects?
 - How should we assess adverse effects ?
- Non-pharmacological ways to decrease pain?



Does the newborn infant feel pain?

- **Nociceptive pathways II trimester (1970-80's)**
- **Fentanyl anaesthesia for surgery in preterms**
 - **Anand et al 1987**
- **Heal prick pain in newborn mouse /infant**
 - **Fitzgerald**
- **Behavioural pain scales (1980-90's)**
- **Longterm effects**
 - **Fitzgerald and Beggs 2001, Grunau 2002**



How should we measure pain?

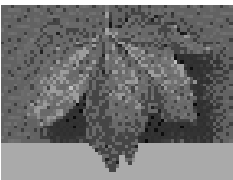
- **Univariate pain scales**
 - Face: FACS, NFCS, MAX
 - Whole body: IBCS, MBPS, LIDS, RIPS

- **Multidimensional scales for acute pain**
 - NIPS, PIPP, PAT, CRIES, DSVNI, SUN, Comfort...
Anand, Stevens, McGrath: Pain in neonates 2ed, 2000

- **Continuous distress and prolonged pain**
 - EDIN (Echelle Douleur Inconfort Nouveau-Né)
neonatal pain and discomfort scale,
ArchDisChild 2001;85:F36

Pain?!



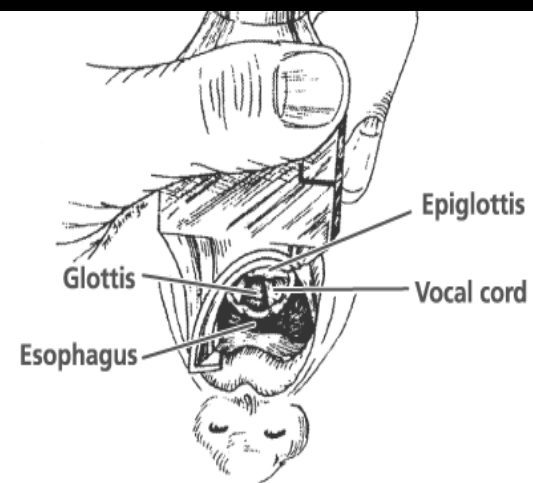
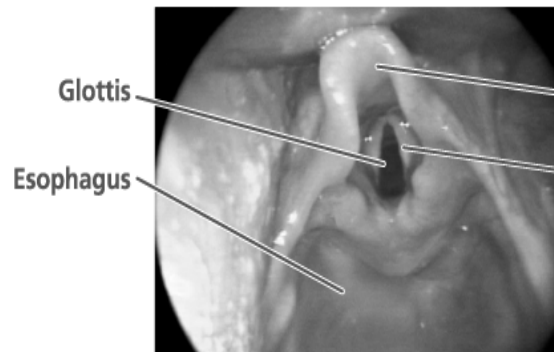


Painful situations

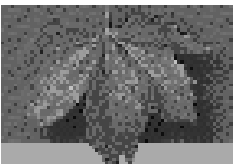
- 1. Procedural pain: Intubation ?**
- 2. Postoperative pain ?**
- 3. Mechanical ventilation ?**

1. Is intubation painful?

- Considered painful in children and adults
- If no premedication:
 - less success rate, longer duration
 - physiological changes
 - increased intracranial pressure



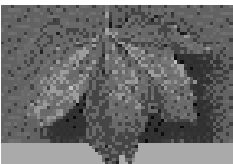
Photograph and drawing of laryngoscopic view of glottis and surrounding structures



Premedication before intubation NICUs in UK

- **Written policy 34/239 (14 %)**
- **Any sedation 88/239 (37%)**
 - 18 (8 %) sedation
 - 78 (33 %) opioid $\pm$ other
 - 8 (3 %) fentanyl
- **Premedication ineffective**
 - slow onset
 - long duration

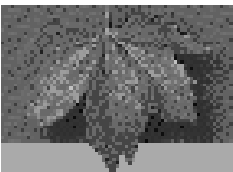
Whyte et al ADC 2000;82:F38



Premedication for intubation France

- **10-day period, 97% of intubations**
- **Analgesia $\pm$ sedation in**
 - **37 % of neonates**
 - **67 % of infants**
 - **92 % of children**

Simon et al Crit Care Med 2004;32:565



Neonatal intubation - opinions

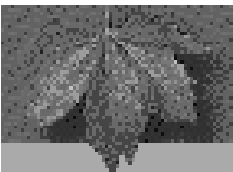
- **”Should we reconsider awake neonatal intubations?”**

Duncan et al Paediatr Anaesth 2001;11:135

- **”Tracheal intubation in neonates: is there a right way?”**

reluctance to use premedication due to lack of familiarity with drugs, mask bagging, and difficult intubations

Anand Crit Care Med 2004;32:614



Few intubation RCTs in neonates

■ Thiopental (5-6 mg/kg) vs placebo

- Physiological changes ↓
- Time for intubation ↓

Can J Anaesth 1994;41:281

Arch Dis Child 2000;82 F34

■ Alfentanil 20 µg/kg vs meperidine 1 mg/kg

- Duration of hypoxia less with alfentanil

Acta Paediatr 1994;83:151

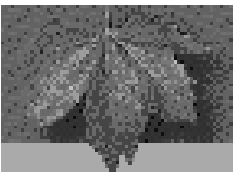
■ Morphine, atropine, succinylcholine vs placebo

- Faster, less physiological changes, and injury

J Paediatr Child Health 2002;38:146

Challenge: well-designed and well-executed intubation RCT with follow-up





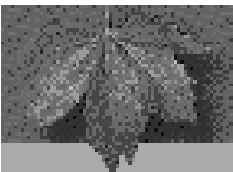
2. Postoperative pain

- **Analgesia needed**
- **Analgesia given**
 - **More if systematic pain assessment**

Eur J Clin Pharmacol 2003;59;87

- **Analgesia and reaction to vaccination**
 - **n.s vs controls**

Pediatrics 2003;111:129



Treatment for postoperative pain

■ Morphine drug of choice

- bolus = infusion
- 10-12 (↓ -7) $\mu\text{g/kg/}$

Br J Anaesth 2003;90:643

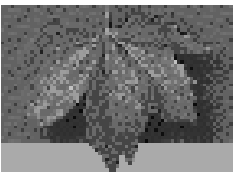
■ NSAID

- Ketorolac 1 mg/kg over 10 min
- Pain relief in 17/18 (94%) – NIPS

Pediatric Anaesth 2004;14:487

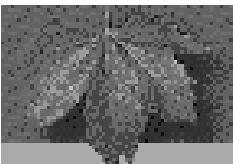
3. Mechanical ventilation painful?





Is mechanical ventilation painful?

- **YES: Continuous pain**
 - Inflammation due to disease
- **YES: Procedural pain**
 - Tracheal suctioning
 - Gavage tube insertion
 - Arterial/Venous line insertion
 - Heel lancing
 - Dressing change
- **NO: Modern synchronized ventilation!?**



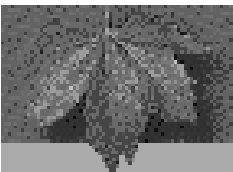
Randomized controlled opioid trial

■ Aim

- To compare efficacy and adverse effects of fentanyl and morphine on days 0-2

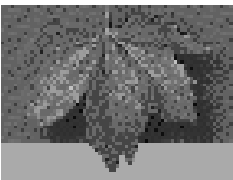
■ Hypothesis: Fentanyl superior

- Shorter onset and duration
- Less adverse effects ?
 - does not stimulate histamine release



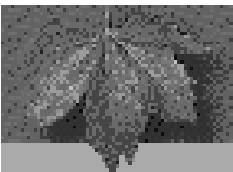
Inclusion criteria

- **Need for mechanical ventilation > 1d**
- **Clinical need for pain relief on day 0**
- **No major malformation**
- **Gestational age > 24 weeks**



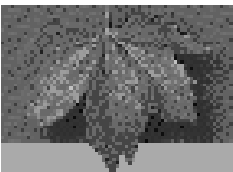
Design

- **One center study**
- **Randomization with envelopes**
- **Stratification by bw < or > 1500 g**
- **Blinded administration**
- **Standard painful routine procedures**



Protocol

- **2-day infusion started on day one**
 - **FE: loading 10.5 µg/kg 1 h,
then 1.5 µg/kg/h**
 - **MO: loading 140 µg/kg 1 h,
then 20 µg/kg/h**
 - **Additional boluses (1 h dose)
if needed 1- 4/d**
- **Pain assessment at procedures**



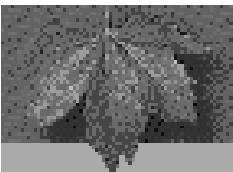
Methods of assessment

■ Pain

- physiological parameters (HR, MABP)
- modified NIPS pain scale (score 0-8)
- hormonal (Adr, NorAdr, β -endorphin)

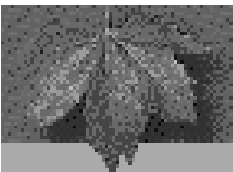
■ Adverse effects

- urine retention (ultrasound)
- decreased gastrointestinal motility



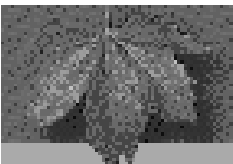
Birth data, median (IQR)

	Fentanyl (n=83)	Morphine (n=80)
Birthweight, g	1720 (1100; 2795)	1580 (1100 ; 2790)
Gestational age weeks	31.7 (29.4; 37.0)	31.0 (28.9; 35.3)
Apgar score 1'	7 (5 ; 9)	6 (5 ; 8)
Cord arterial pH	7.24 (7.19 ; 7.31)	7.28 (7.16 ; 7.34)



Main diagnoses, n (%)

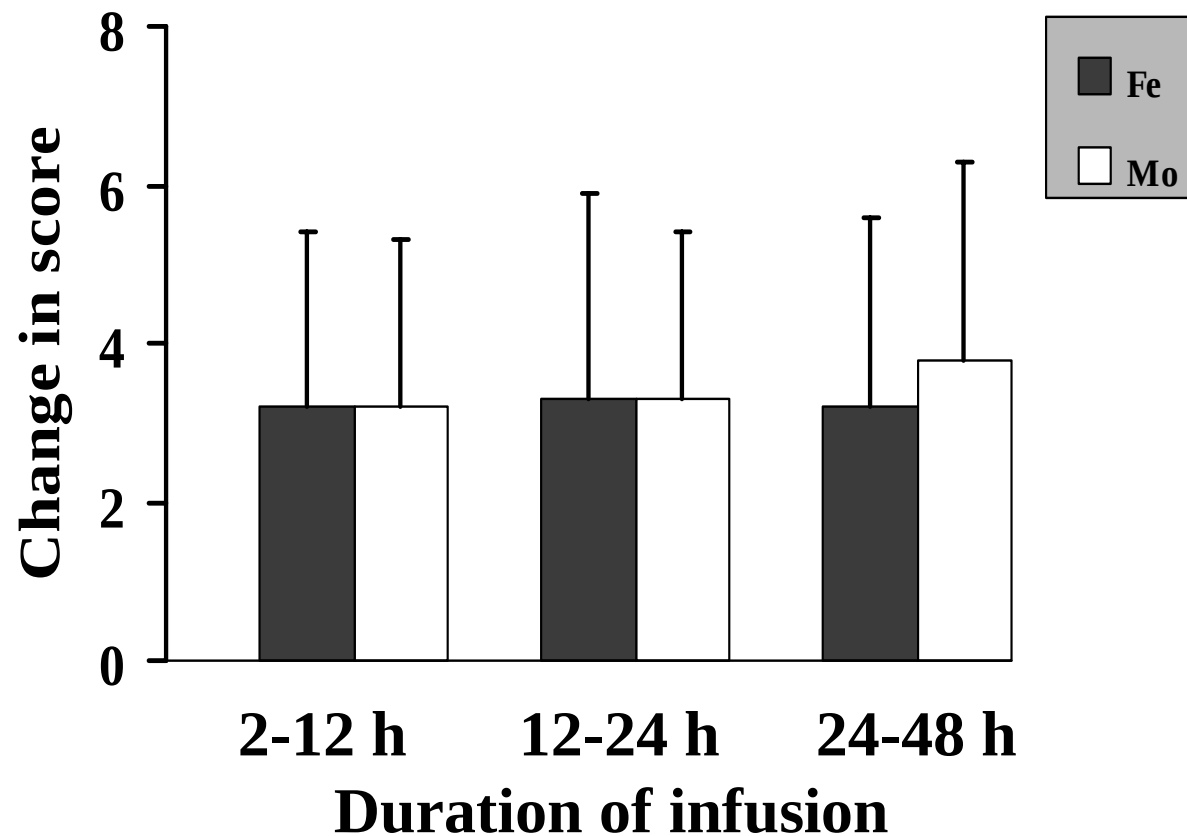
	Fentanyl	Morphine
Respiratory Distress Syndrome, RDS	60 (73)	58 (73)
Infection	24 (29)	28 (35)
Persistent Pulmonary Hypertension, PPHN	18 (22)	15 (19)
Necrotizing Enterocolitis, NEC	10 (12)	8 (10)
Intraventricular Hemorrhage, IVH	7 (8)	4 (5)



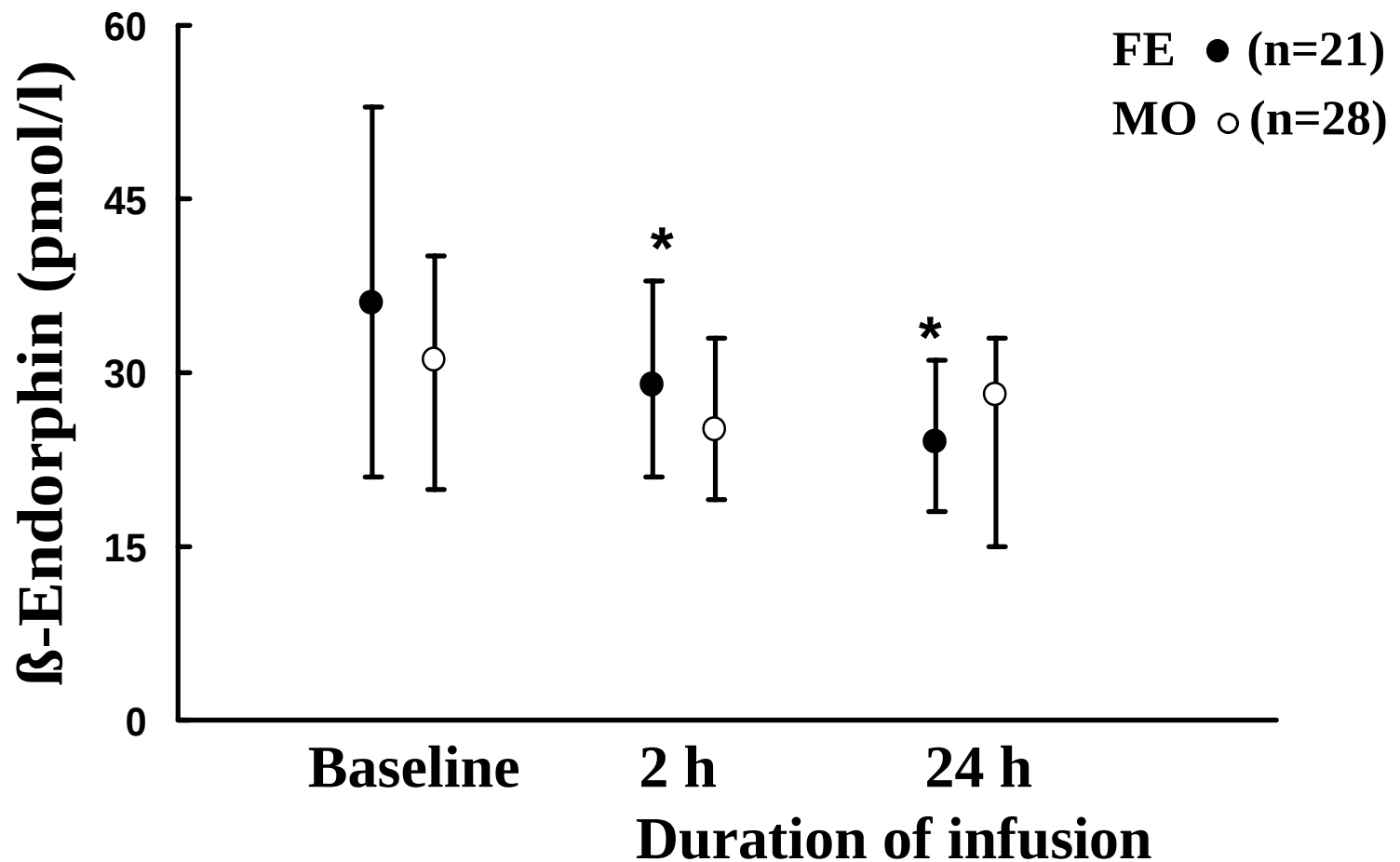
Duration of treatment

	Fentanyl (n=83)	Morphine (n=80)
Age at start (h)	11 (6; 21)	9 (6; 18)
Infusion ≤ 1500 g (h) > 1500 g	60 (36 ; 104) 48 (38 ; 77)	60 (41 ; 77) 53 (35 ; 81)
Ventilation ≤ 1500 (d) > 1500	10 (4 ; 19) 4 (3 ; 5)	8 (4 ; 15) 4 (3 ; 6)
Boluses, n	14 (17%)	21 (26%)

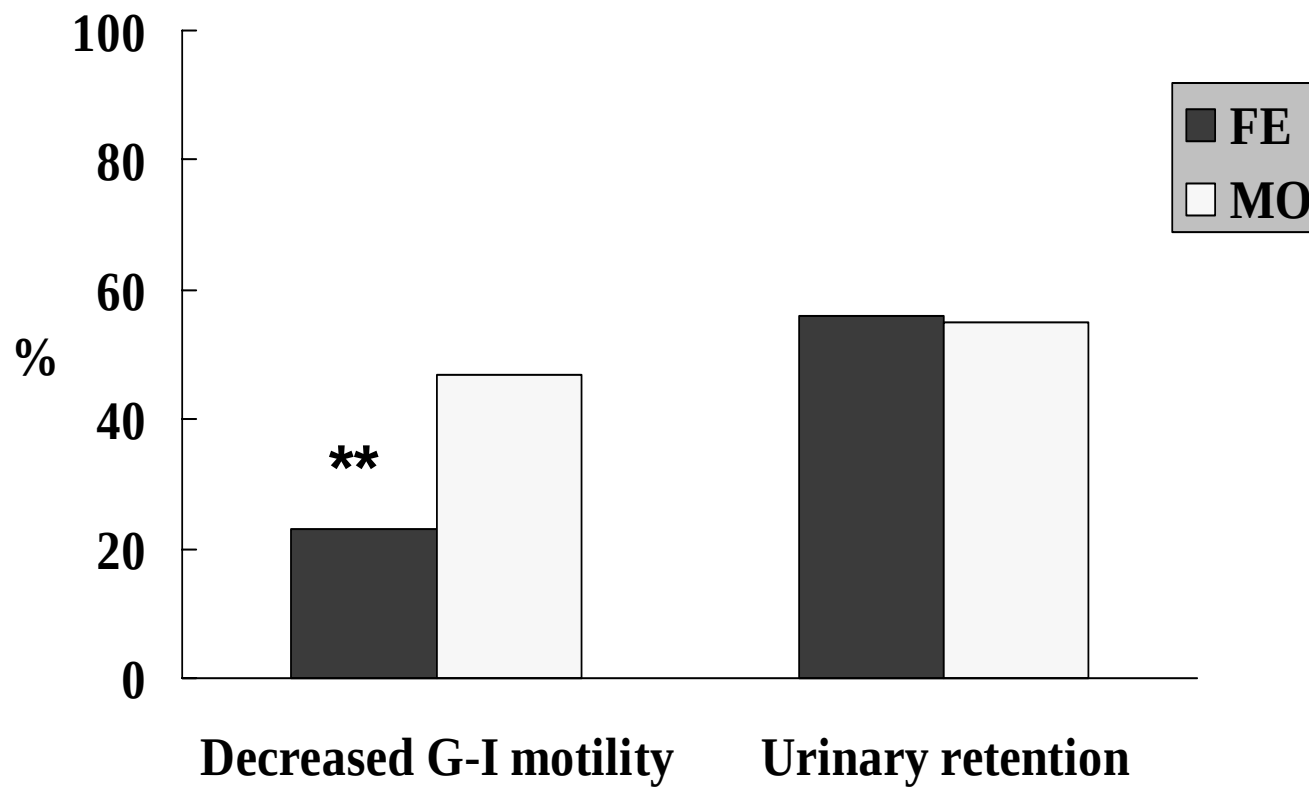
Change of NIPS pain score (mean $\pm$ SD) in response to tracheal suction

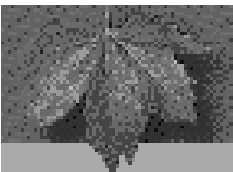


**Median (IQR) β -endorphin concentration before,
at 2 h, and 24 h of infusion (* p <0.05)**



Incidence of adverse effects (** p< 0.01)

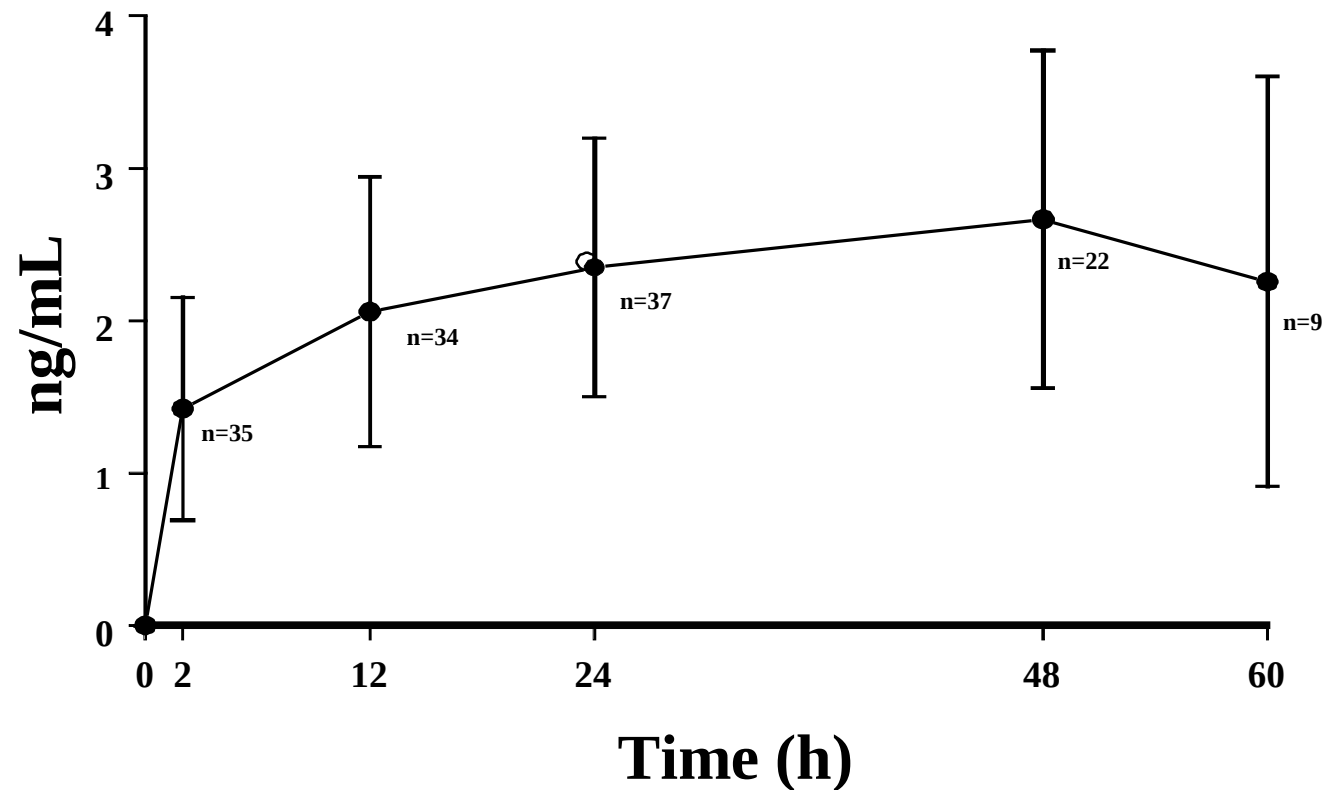




Conclusion

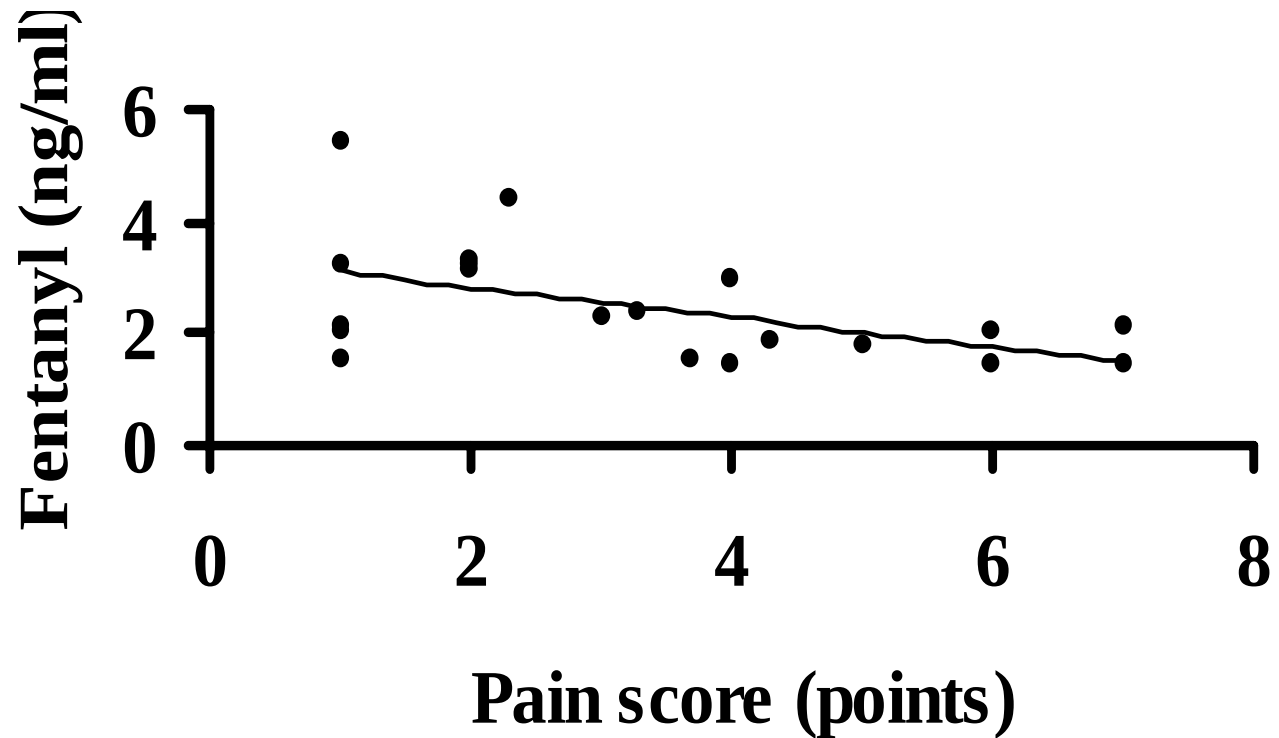
- **Efficacy similar**
 - β -endorphin response favors FE
 - Adrenalin, noradrenalin ns difference
- **Adverse effects**
 - less GI-motility decrease in FE
 - effect on a. pulmonary pressure ND

Fentanyl concentrations after IV loading of 10 µg/kg/1h and maintenance 1.5 µg/kg/h

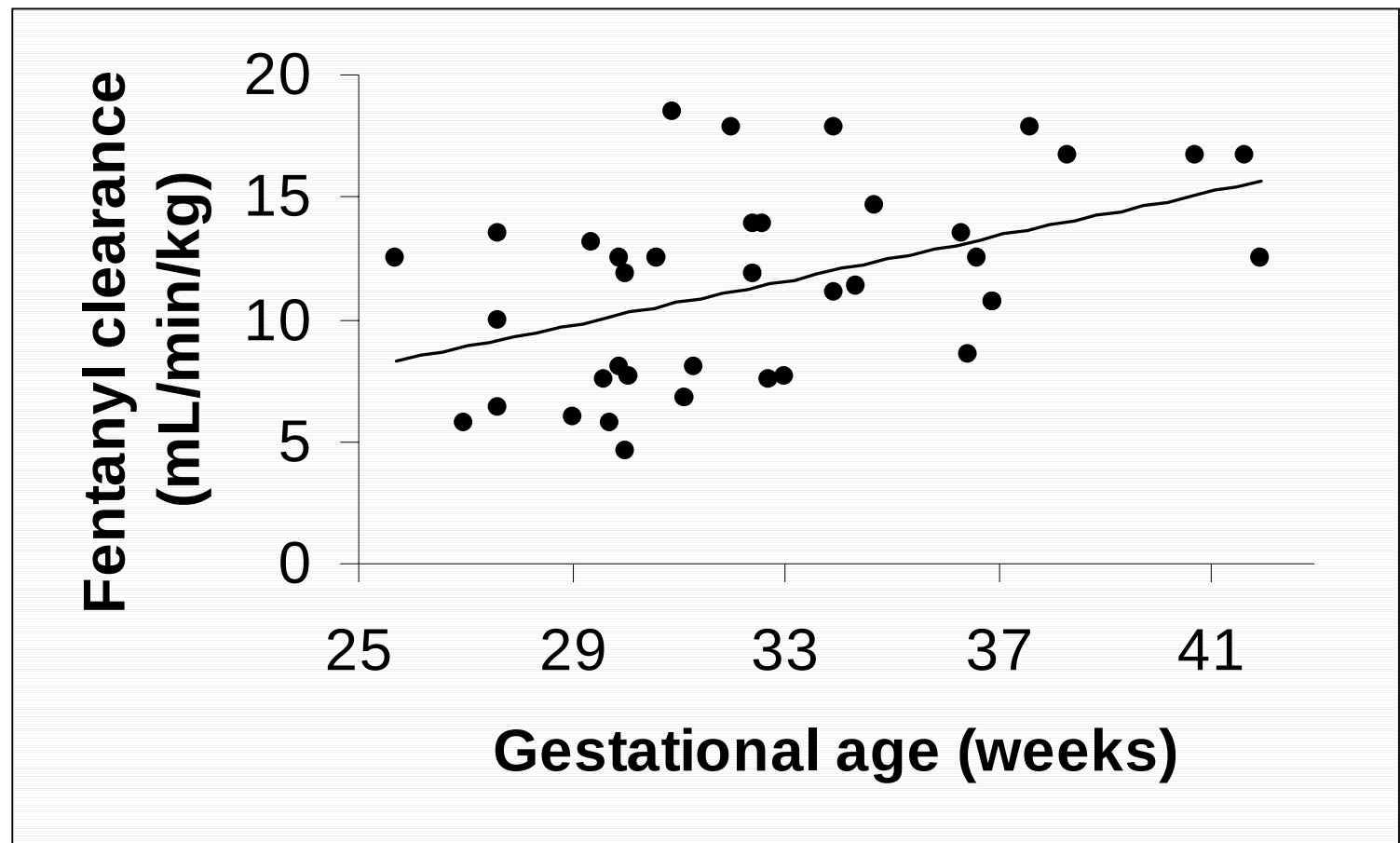


Saarenmaa et al J Ped 2000

**Fentanyl steady state concentration correlates
with 2-day pain score ($r=-0.57$, $p<0.01$)**

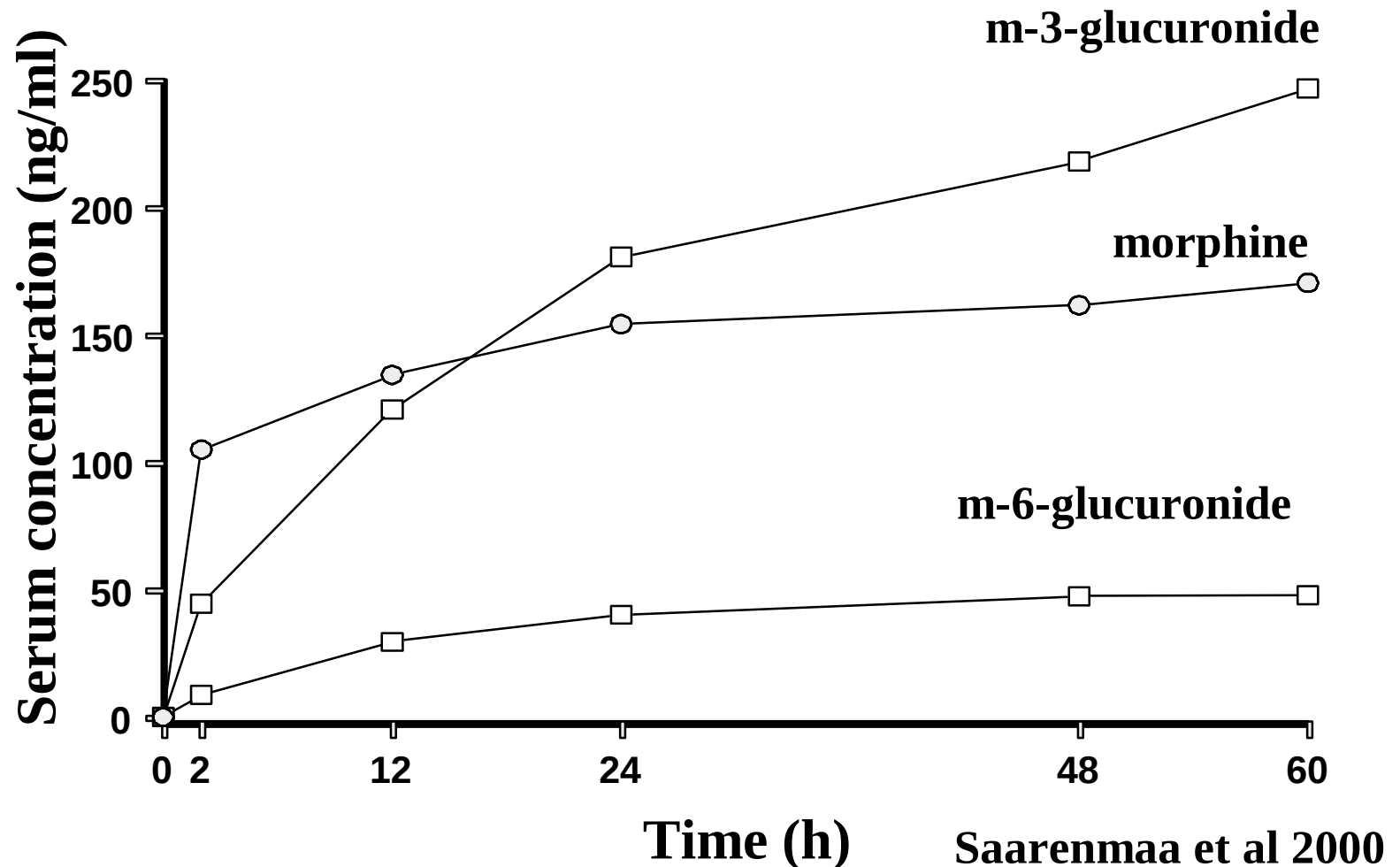


Plasma clearance of fentanyl correlates with gestational age ($r= 0.456$, $p<0.01$) and birth weight ($r= 0.482$, $p<0.01$)

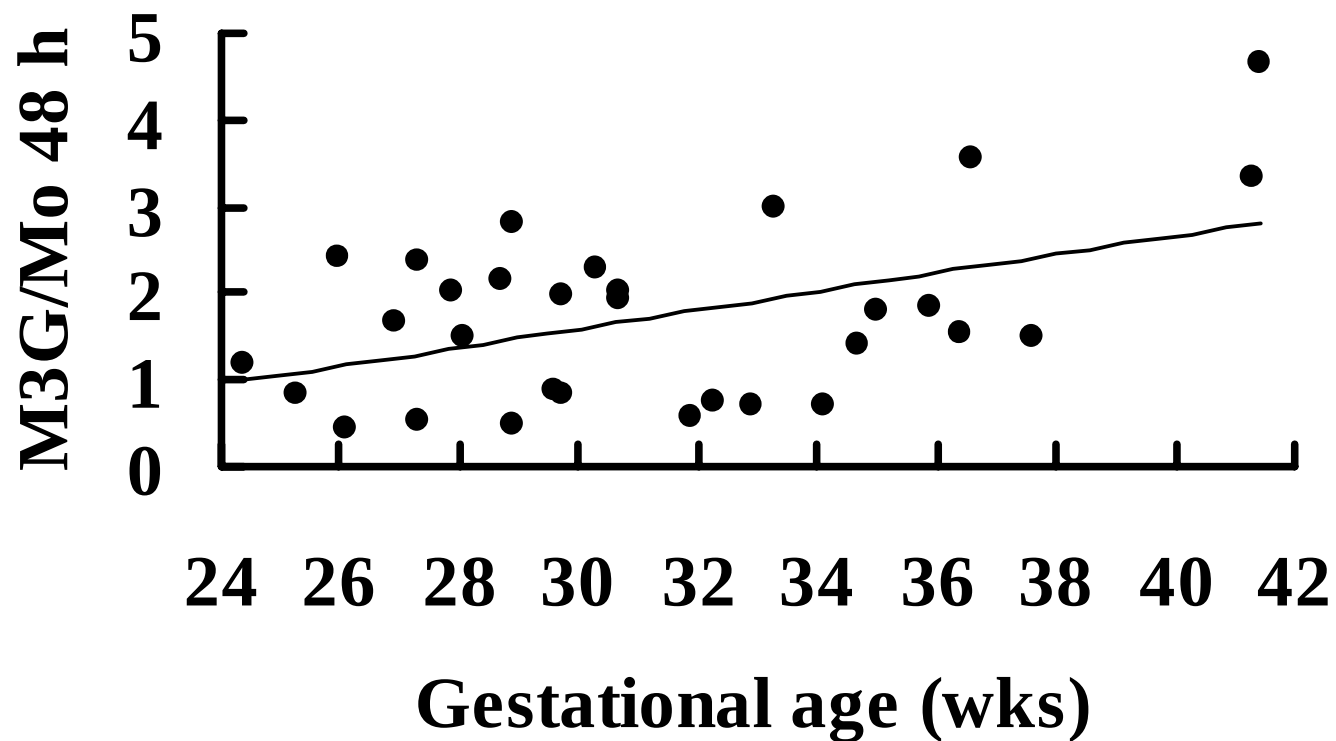


Saarenmaa et al J Ped 2000

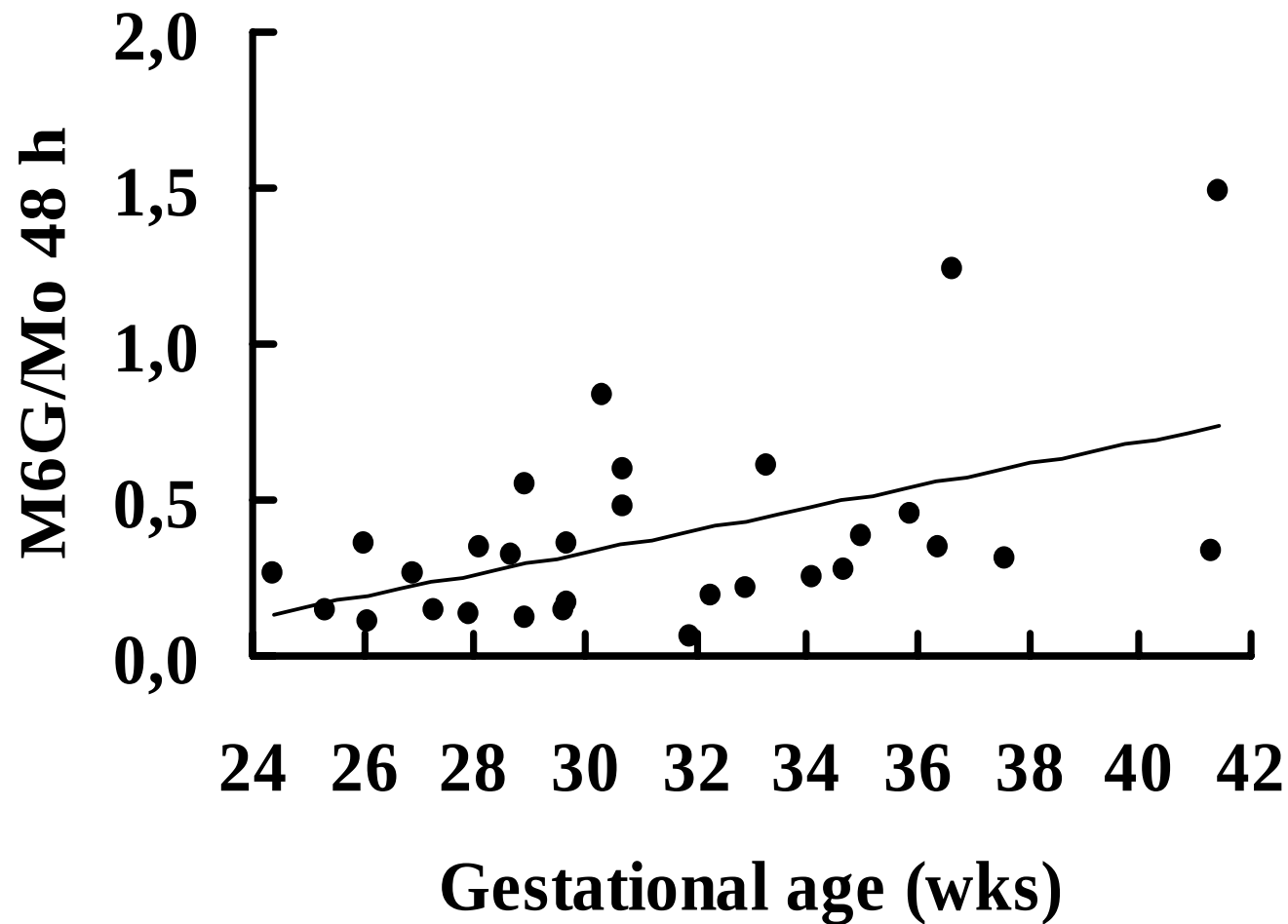
**Concentrations of morphine and its metabolites
after IV loading of 140 µg/kg/1h and maintenance
20 µg/kg/h (n=30)**



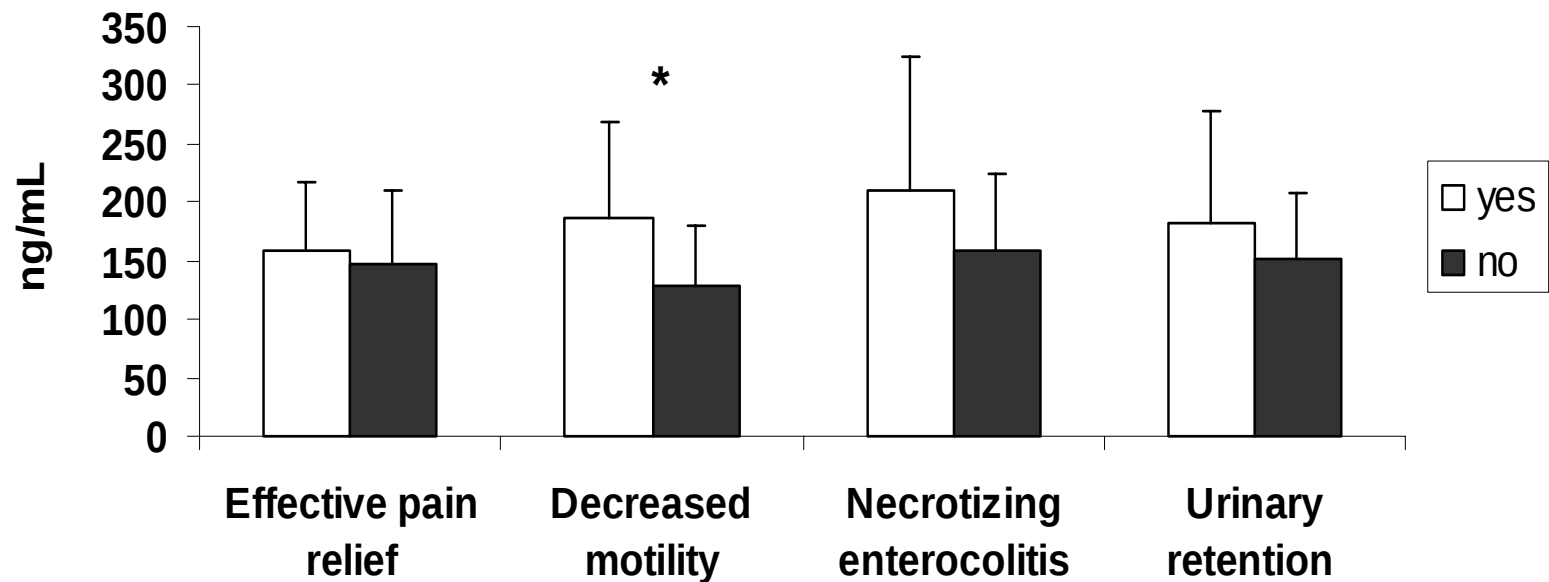
Ratio of morphine-3-glucuronide to morphine at 48 h correlates with gestational age ($r=0.50$, $p<0.01$)



Ratio of morphine-6-glucuronide to morphine at 48 h correlates with gestational age ($r=0.49$, $p<0.01$)

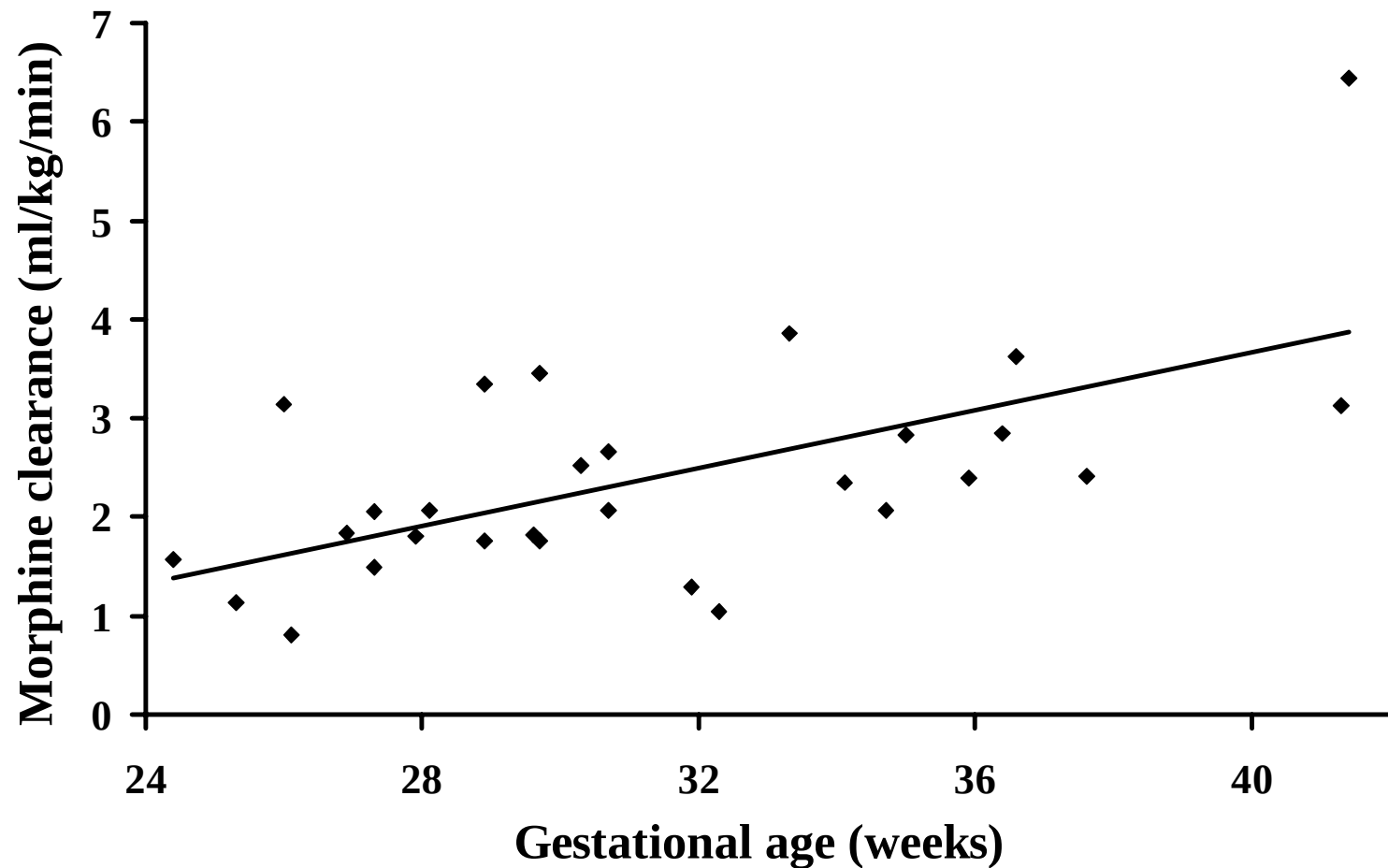


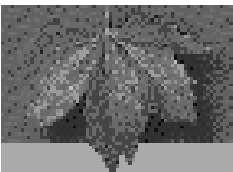
Morphine concentration at steady state in relation to pain relief and adverse effects



Saarenmaa et al Clin Pharmacol Ther 2000

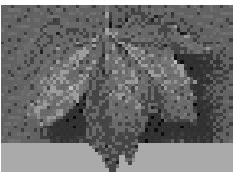
Morphine clearance in relation to gestational age ($r=0.60$, $p<0.01$)





Conclusions

- **Clearance correlates with immaturity**
 - FE: 5-15 ml/min/kg
 - MO: 1-4 ml/min/kg
- **Steady state concentration**
 - FE: moderate correlation to pain relief
 - MO: no correlation to pain relief (M-3-G, M-6-G!)
 - FE/MO: relates to adverse effects
- **Volume of distribution, T1/2, protein binding**
 - ND, varies with gestational and postnatal age
 - Taddio Clin Perinat 2002, Wood NEJM Oct 2002



Controversies in NICU opioid use

■ Which opioid?

- Fentanyl used in Helsinki, USA
- Morphine used in Europe

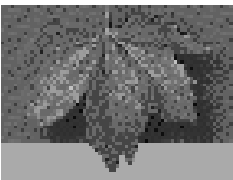
■ When?

- Routine infusion when mechanical ventilation...
- Do they really need it ?
- No analgesia to 40 % with painful procedures

Arch Pediatr Adolesc Med 2003;157:1058

■ No consensus on pain assessment?

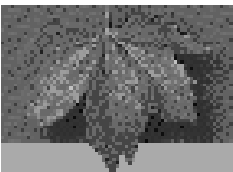
■ Hazards of opioid treatment neglected?



Morphine vs placebo

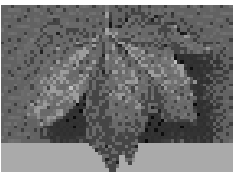
- **2-center RCT (n=73 vs n=77)**
- **100 µg/kg + 10 µg/kg/h vs placebo, ad 7 d**
- **NIPS, PIPP, VAS: ns**
- **IVH decrease in Morphine infants**
 - **23% vs 40% p=.04**

Simons JAMA 2003;290:2419



Pharmacogenetics

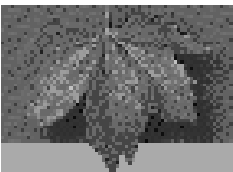
- **Effect related to polymorphism in**
 - **Opioid receptor gene (OPRM):**
 - binding ↑**
 - lower Mo requirement**
 - **Catechol-O-methyltransferase (COMT):**
 - decreased activity → μ receptor concentr ↑**
 - increased sensitivity to pain**



NEOPAIN

- **Multicenter RCT**
- **Ventilation >8h, < 72 h age, 23-32 gw**
 - **Morphine 100 µg/kg + 10 µg/kg/h (n=449)**
 - **Placebo (n=449)**
 - **If clinically needed, open-label morphine**
- **No difference Mo vs placebo**
 - **Open-label Mo: worse outcome**

Anand et al Lancet 2004;363:1673



Withdrawal symptoms

- **Clinical reports – do we care?**

- fentanyl ≥ 415 $\mu\text{g/kg}$ (70% sensit, 78% specif)

Ann Pharmacother 2003;37:473

- **Experimental data on morphine:**

- hypersensitivity upon opioid withdrawal

Pain. 2004;110:269 & 281

- **Experimental data on fentanyl**

- inhibition of GABAergic effects - parasymp $\uparrow$

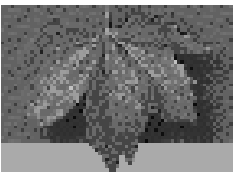
Brain Res 2004;1007:109

Nonpharmacological interventions

- Individualized developmental care (NIDCAP)
- Subgroup of items indicate pain

Pediatrics 2004;114:65



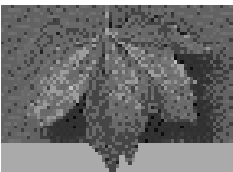


Recommendations

- **Individualized care – prevent pain !**
 - routine, repetitive pain assessments
 - low dose opioid infusion with boluses
 - NSAID
- **If pharmacological treatment, consider:**
 - gestational age
 - postnatal age
 - disease
 - pharmacogenetics
- **More research, RCT!**

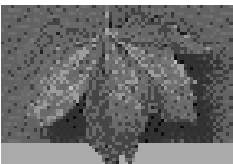
The goal: normal development





Acknowledgements

- Elina Saarenmaa, MD PhD, Dpt Pediatrics
- Pentti Neuvonen Dpt Clin Pharmacol
- Per Rosenberg Dpt Anesthesiology
- University of Helsinki
- Pirkko Huttunen Dpt Forensic Medicine
- Juhani Leppäluoto Dpt Physiology
- University of Oulu
- NIDCAP-group Neonatal unit
- Lund University



Thank you !

