OUR CHALLENGES IN PAIN MANAGEMENT IN NEONATES

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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
Premedication before intubation
NICUs in UK

- Written policy 34/239 (14 %)
- Any sedation 88/239 (37%)
  - 18 (8 %) sedation
  - 78 (33 %) opioid ± 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 ± 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 meperidene 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 (\(\downarrow -7\)) \(\mu\)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

Saarenmaa et al J Ped 1999
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)

<table>
<thead>
<tr>
<th></th>
<th>Fentanyl (n=83)</th>
<th>Morphine (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight, g</td>
<td>1720 (1100; 2795)</td>
<td>1580 (1100 ; 2790)</td>
</tr>
<tr>
<td>Gestational age weeks</td>
<td>31.7 (29.4; 37.0)</td>
<td>31.0 (28.9; 35.3)</td>
</tr>
<tr>
<td>Apgar score 1’</td>
<td>7 (5 ; 9)</td>
<td>6 (5 ; 8)</td>
</tr>
<tr>
<td>Cord arterial pH</td>
<td>7.24 (7.19 ; 7.31)</td>
<td>7.28 (7.16 ; 7.34)</td>
</tr>
</tbody>
</table>
### Main diagnoses, n (%)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Fentanyl</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Distress Syndrome, RDS</td>
<td>60 (73)</td>
<td>58 (73)</td>
</tr>
<tr>
<td>Infection</td>
<td>24 (29)</td>
<td>28 (35)</td>
</tr>
<tr>
<td>Persistent Pulmonary Hypertension, PPHN</td>
<td>18 (22)</td>
<td>15 (19)</td>
</tr>
<tr>
<td>Necrotizing EnteroColitis, NEC</td>
<td>10 (12)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Intraventricular Hemorrhage, IVH</td>
<td>7 (8)</td>
<td>4 (5)</td>
</tr>
</tbody>
</table>
## Duration of treatment

<table>
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<th>Fentanyl (n=83)</th>
<th>Morphine (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at start (h)</strong></td>
<td>11 (6; 21)</td>
<td>9 (6; 18)</td>
</tr>
<tr>
<td><strong>Infusion ≤ 1500 g (h)</strong></td>
<td>60 (36; 104)</td>
<td>60 (41; 77)</td>
</tr>
<tr>
<td><strong>Infusion &gt; 1500 g (h)</strong></td>
<td>48 (38; 77)</td>
<td>53 (35; 81)</td>
</tr>
<tr>
<td><strong>Ventilation ≤ 1500 (d)</strong></td>
<td>10 (4; 19)</td>
<td>8 (4; 15)</td>
</tr>
<tr>
<td><strong>Ventilation &gt; 1500 (d)</strong></td>
<td>4 (3; 5)</td>
<td>4 (3; 6)</td>
</tr>
<tr>
<td><strong>Boluses, n</strong></td>
<td>14 (17%)</td>
<td>21 (26%)</td>
</tr>
</tbody>
</table>
Change of NIPS pain score (mean±SD) in response to tracheal suction

Change in score

<table>
<thead>
<tr>
<th>Duration of infusion</th>
<th>2-12 h</th>
<th>12-24 h</th>
<th>24-48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>Mo</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>3 ± 1</td>
</tr>
</tbody>
</table>
Median (IQR) β-endorphin concentration before, at 2 h, and 24 h of infusion (* p < 0.05)

Baseline 2 h 24 h
Duration of infusion

FE  ● (n=21)
MO  ○ (n=28)
Incidence of adverse effects (**) p< 0.01

- Decreased G-I motility
- Urinary retention

** 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)

Saarenmaa et al 2000
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

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
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 $\uparrow$
    - $\rightarrow$ lower Mo requirement

- Catechol-O-methyltransferase (COMT):
  - decreased activity $\rightarrow$ $\mu$ receptor concentr $\uparrow$
  - $\rightarrow$ 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
- Ns 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 µg/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↑
    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
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