Pain Management in the NICU
& Iatrogenic Opiate Withdrawal

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Outline

• The balance between adequate analgesia and excessive drug therapy
• Risks of currently used analgesic and sedation medications
• Benefits of multi-modal analgesia
• Novel approaches to optimize pain and sedation management
The Developing Neonatal Brain

- Time of intense dendrite/synapse formation and pruning
- Neuro-plasticity leads to altered pathways
- Very delicate balance of excitatory and inhibitory neurotransmitters for normal cellular and sub-cellular development

Kapellou, Plos Med, 2006

Issues Unique to Neonatal Pain Control

- Lack of evidence leads to highly variable practices between NICUs\(^1\) → makes research difficult
- Limited belief in / use of pain scores to drive treatment
- Lower levels of P-glycoprotein (P-gp) in the developing brain cause longer residence time of opiates in CNS → higher risk of CNS toxicity\(^2\)
- Decreased drug metabolism / clearance increases cumulative exposure → more adverse outcomes

\(^1\) Lago et al, Ped Anesth, 2005
\(^2\) Lam et al, Pediatric Research, 2015
Variability in Opiate Dosing

- Prospective, observational study with 100% accrual of eligible patients
- Seven PICUs in US
- 419 children treated with morphine or fentanyl infusions

Pediatric Pain
Pain vs Excessive Opiates

Risks of Untreated Pain

- Central sensitization
- Subtle abnormalities brain development, associated with worsened school-age cognition\textsuperscript{1}
- Thinner cortex at school-age in multiple brain regions in preterm infants without major impairments\textsuperscript{2}

Risks of Opiates

- Prolonged mechanical ventilation\textsuperscript{3,4}
- Clinically significant hypotension
- Decreased gastrointestinal motility
- ICU acquired Neonatal Abstinence Syndrome

\textsuperscript{1} Doesburg et al, Pain, 2013
\textsuperscript{2} Ranger et al, PLoS One, 2013
\textsuperscript{3} Bhandari et al, Pediatrics, 2005
\textsuperscript{4} Carbajal et al, Lancet Resp Med, 2015

Risks of Opiates

\textit{NEOPAIN STUDY} = 898
preterm (23-32 weeks) infants

Infants Randomized: Morphine vs Placebo

Composite Outcome: Death or Severe IVH

\textsuperscript{1} Anand et al, Lancet, 2004
NEOPAIN Follow-up

- Developmental follow-up of NEOPAIN infants (N = 572) at 36 weeks postmenstrual age found higher popliteal angle cluster scores, indicative of increased tone, in infants randomized to morphine.

- A 5- to 7-year pilot follow-up of a small subset of NEOPAIN infants (N = 19) found no difference in overall intelligence quotient. Morphine-treated children, however, had smaller head circumference, impaired short-term memory, and social problems compared with placebo-treated children.1

1 Ferguson et al, Neurotoxicol Teratol, 2012

Risk of Opiates

Cumulative Morphine Exposure and Cerebellar Growth1

- 136 preterm (24-32 weeks) infants, serial MRI and 18 month developmental testing
- Cumulative morphine dose was significantly associated with cerebellar volume after adjusting for multiple clinical confounders
- Greater morphine exposure also predicted poorer motor (P < .001) and cognitive outcomes (P = .006) at 18 months CA, an association mediated, in part, by slower brain growth overall.

1 Zwicker et al, J Peds, 2016
Opiate Induced Anti-proliferative and Pro-Apoptotic Effects

- Early opioid exposure leads to decreased neuron density and shortened dendritic length
- Early opioid exposure leads to supporting cell death and decreased myelination
- Rodents exposed to postnatal morphine exhibit persistently decreased motor activity and impaired learning ability

Animal data confirm that prolonged early opiate exposure reduces brain growth

Neonate Opiate Pharmacology

- Twelve newborn infants were given morphine intravenously for postoperative analgesia.
- Dose 0.006 to 0.04 mg/kg/hr
- Elimination half-life of morphine was significantly longer than in older children and adults
- Morphine concentrations in neonates receiving 0.02 mg/kg/hr for 24 hours were three times higher than in older children receiving the same schedule.
- Because of the apparently greater sensitivity to morphine and the lower elimination rate in newborn infants, the infused dose should not exceed 0.015 mg/kg/hr.
Opiate Induced Hyperalgesia vs Tolerance

- **NMDA Receptor**
  - → hyperalgesia
  - → neuronal irritation

- **Opiate Receptor**
  - → pain relief
  - → sedation

MULTIMODAL ANALGESIA
Multimodal Analgesia

- More than one medication or intervention
- Different mechanisms of action augment effect
- Improve or maintain analgesia
- Decreases side effects

Acetaminophen and Opiate Sparing

- Full-term infants randomized to acetaminophen + morphine required significantly less opiate post-op\(^1\)
  - 121 ug/kg vs 357 ug/kg, 66% reduction

- Preterm infants <32 weeks who received around-the-clock IV acetaminophen required significantly less cumulative morphine for similar pain scores\(^2\)
  - 0.17 mg/kg vs 0.37 mg/kg

1 Ceelie et al, JAMA, 2013
Local Analgesics – wound catheter

- Karolinska University Hospital

Bartocci et al, World Congress of Pediatric Pain, 2006
PhD Thesis Marie Anell Olofsson

Caudal Analgesia

- Prospective, randomized controlled study at a single center
- 60 patients, aged 1 day to 6 months, 2-5 kg
- Caudal vs IV opiates and tylenol were used for major thoracic and abdominal surgery
- FLACC was assessed for postoperative pain management


1) Less inhaled anesthetic required during operation

2) Better pain scores in 48 hrs post-op

Alternative Analgesics and Sedatives

Clonidine

- Neonatal PK well described\(^1\)
- 112 newborns aged 1-28 days treated with clonidine infusion required less fentanyl and midazolam consumption while mechanically ventilated\(^2\)
  - Fentanyl consumption (clonidine: 2.1 ± 1.8 μg/kg/hr, placebo: 3.2 ± 3.1 μg/kg/hr; \(p = 0.032\))
  - Midazolam consumption (clonidine: 113.0 ± 100.1 μg/kg/hr, placebo: 180.2 ± 204.0 μg/kg/hr; \(p = 0.030\)).

\(^1\) Xie et al, J Clin Pharm, 2011
\(^2\) Hunseler et al, PCCM, 2014

Alternative Analgesics and Sedatives

Dexmedetomidine

- Neonatal PK recently described\(^1,2\)
- Neonatal studies show augmented sedation\(^3\), potentially earlier extubation times and shorter time to reach full feeds\(^4\)
- Much stronger central alpha-2 agonist, only studied for 1-3 day exposure
  - short and long term safety is a concern
  - 2017 – 2 case reports of neonatal death in post-op cardiac infants after cardiovascular collapse (also receiving anti-arrythmics)

\(^1\) Greenberg et al, J Clin Pharm, 2017
\(^2\) Su et al, Anesth Analg, 2016
\(^3\) Whalen et al, PCCM, 2014
\(^4\) O’Mara et al, J Ped Pharm Ther, 2012
Intense Focus on Non-Pharmacologic Measures

<table>
<thead>
<tr>
<th>Non-Pharmacological Treatment</th>
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<tbody>
<tr>
<td>Environmental interventions</td>
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<tr>
<td>Swaddling, positioning and touch</td>
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<td>Non-nutritive suckling</td>
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<td>Sweet solutions: Sucrose, Glucose</td>
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<td>Multisensory stimulation</td>
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<td>Skin to skin contact</td>
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<tr>
<td>Breastfeeding analgesia</td>
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<td>Breast milk</td>
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<td>Music</td>
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Potential Novel Approaches in the NICU
Opiate Pharmacogenetics

Genetic variation in
- drug metabolizing enzymes
- drug transporters (gut and hepatic)
- drug receptors
have all been implicated in varying response to opiate medications in other patient populations.

These genetic variations are common and can cause marked differences in need for different opiate doses.

Genetic Modifiers of Opiate Response in Preterm Infants

Genetic Predisposition to Poor Opioid Response in Preterm Infants: Impact of KCNJ6 and COMT Polymorphisms on Pain Relief After Endotracheal Intubation

Laure Elens, MSc, PhD.*† Elisabeth Norman, MD,† Maja Matic, PharmD,* Anders Rune, MD,‡ Vineta Feltman, MD,† and Ron H. N. van Schai克, PharmD, PhD*

![Image of tables and graphs]

FIGURE 3. Cumulative proportions of patients achieving a pain-free state (ALP<Neo score = 1) after intubation according to COMT c.472G>A (*rs6680, Val158Met) genotype in (A) the entire population (n = 29), (B) the morphine group (n = 13), and (C) the remifentanil group (n = 16). Crosses denote censored patients (nonresponders). No 5 patients had a first ALP<Neo score = 1 and were not included in the survival analysis.
Opiate Pharmacogenetics in Preterm Infants

64 preterm infants on placebo infusions

Question: Do certain genetic variants correlate with need for rescue morphine or amount of rescue morphine?

OPRM1 – mu opioid receptor (drug target)

COMT – catecholamine-O methyltransferase (metabolizes endogenous endorphins)

Iatrogenic Opiate Withdrawal

Matic et al, Pharmacogenomics, 2014
Increasing Incidence

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<tr>
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<tbody>
<tr>
<td>Total Number Inaryl</td>
<td>71</td>
<td>54</td>
<td>28</td>
<td></td>
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<tr>
<td>Positive Diagnosis, N (%)</td>
<td>7 (10)</td>
<td>3 (6)</td>
<td>10 (36)</td>
<td>0.423</td>
</tr>
<tr>
<td>Omen (N=25 infants)</td>
<td>7 (28)</td>
<td>3 (12)</td>
<td>5 (20)</td>
<td></td>
</tr>
<tr>
<td>PAIN IN (N)</td>
<td>0 (0)</td>
<td>2 (8)</td>
<td>9 (32)</td>
<td></td>
</tr>
<tr>
<td>HLH (N)</td>
<td>1 (4)</td>
<td>4 (16)</td>
<td>6 (23)</td>
<td></td>
</tr>
<tr>
<td>Gastrostomy Ongulation (N)</td>
<td>1 (3)</td>
<td>0</td>
<td>4 (14)</td>
<td></td>
</tr>
<tr>
<td>CDI</td>
<td>2 (9)</td>
<td>0 (0)</td>
<td>3 (11)</td>
<td></td>
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<tr>
<td>Overall Weight, Median (SD)</td>
<td>2801 (1003,1011)</td>
<td>2485 (740,1045)</td>
<td>2975 (1998,1280)</td>
<td>0.554</td>
</tr>
<tr>
<td>Infant Stay, days (N)</td>
<td>36 (18,35)</td>
<td>20.8 (10,15)</td>
<td>18.9 (10,8)</td>
<td>0.142</td>
</tr>
<tr>
<td>Thromboembolism, Median (SD)</td>
<td>35 (31,47)</td>
<td>65.5 (30.8,20)</td>
<td>11.9 (29.4)</td>
<td>0.504</td>
</tr>
<tr>
<td>Days on Anticoagulant, Median (SD)</td>
<td>3.6 (2.6,6)</td>
<td>33.5 (20.5,30)</td>
<td>11.4 (29.4)</td>
<td>0.142</td>
</tr>
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<td>Days before Discharge, Median (SD)</td>
<td>1 (3)</td>
<td>2 (15)</td>
<td>9 (27)</td>
<td>0.218</td>
</tr>
<tr>
<td>Days prior to Hospital Discharge, Median (SD)</td>
<td>1 (3)</td>
<td>1</td>
<td>1</td>
<td>0.387</td>
</tr>
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*Infant stay does not include days spent at neonatal facilities.

Iatrogenic Opiate Withdrawal: 9%, 35%, 50%

Lewis et al., JOM, 2015
Novel Ways to Minimize Opiate Exposure

 Interruption of Sedation

 Risk-stratified Opiate Weaning Protocol

Final Thoughts

• Pain & sedation drugs are beneficial, but we are increasingly aware of risk
• Multi-modal analgesia is an important tool in minimizing exposure to any given drug class
• Titrating opiate analgesia frequently and carefully
  – more labor intensive than the common practice of oversedating infants who require opioid analgesia for painful conditions
  – affects rates of respiratory depression, hypotension, and opioid tolerance observed in many centers
• Developmental pharmacology and pharmacogenetics are important factors in personalizing drug therapy in the NICU
Thank you!

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