Towards more effective assessment, communication, and treatment of neonatal withdrawal symptoms

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Workshop aims
- Provide an overview of the state of research and clinical practice on neonatal withdrawal
- Present new findings relevant to clinical practice
  - Improving the sensitivity and specificity of assessment
  - Assessment in particular patient groups
  - Treatment strategies in different settings
- Stimulate discussion of challenges, barriers and opportunities for optimal prevention and management

Opioids and benzodiazepines
- Relieve pain and anxiety
- Blunt physiological stress responses
- High hedonic value
- Adverse effects
  - Risk of tolerance
  - Increasing need for larger doses
  - Risk of physical dependence
  - Continued use to prevent withdrawal symptoms
  - Risk of addiction
  - Drug craving

Withdrawal (Abstinence) syndrome
- CNS hyperirritability/ANS dysregulation
  - Sneezing, yawning, sweating, tachycardia, mydriasis
  - Abnormal motor movements: tremors, hypertonicity, hyper-reflexivity, repetitive movements
- Gastrointestinal dysfunction
  - Diarrhoea, nausea, vomiting
- Respiratory distress
  - Tachypnoea
- Benzodiazepine vs opioid withdrawal
  - Usually no GI dysfunction
  - Abnormal movements more pronounced

Mechanisms
- Still not well understood...
  - Receptor down-regulation is not the main mechanism
- Other hypotheses
  - Desensitization due to receptor decoupling
  - Receptor internalization
  - Increased alternative coupling to stimulatory G-proteins
- Functional antagonism of opioid effects
  - Mediated by activation of NMDA receptors
  - Up-regulation of adenylyl cyclase and nitric oxide synthase
- Drugs blocking these mechanisms may prevent ??
  - Alpha2-adrenoreceptor agonists (clonidine)
  - NMDA antagonists (ketamine or dextromethorphan)
  - Opioid rotation and multimodal analgesia

Raith & Hochhaus, 2004
**Iatrogenic withdrawal syndrome**

- Precipitated by medical use of opioids and benzodiazepines for analgesia and sedation
  - Differs from ‘addiction’
  - Increases morbidity and prolongs hospital stay
- Prevalence unknown
- Surveys suggest it is problematic
- Risk increases with increased exposure
  - > 5 day = 50%
  - > 8 to 9 days = 90%
- Risk varies by drug and mode of delivery
  - Fentanyl > morphine
  - Cumulative fentanyl dose > .42 to 1.6 mg/kg
  - Cumulative midazolam dose > 60 mg/kg
  - Continuous infusion > intermittent bolus

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**Opioid withdrawal in infants following ECMO**

<table>
<thead>
<tr>
<th></th>
<th>Fentanyl (n=23)</th>
<th>Morphine (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of ECMO</td>
<td>5.40 ± 2.20</td>
<td>4.30 ± 1.20</td>
</tr>
<tr>
<td>Treated for Withdrawal*</td>
<td>13 (57%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Post-ECMO opioid therapy</td>
<td>20.70 ± 12.00</td>
<td>13.50 ± 8.80</td>
</tr>
<tr>
<td>Post-ECMO LOS*</td>
<td>31.10 ± 14.00</td>
<td>21.50 ± 7.00</td>
</tr>
</tbody>
</table>

*P = .01

Franck et al., Am J Crit Care, 1998

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**Withdrawal (Abstinence) syndrome**

- Range of severity
  - Mild to severe
  - Not related to blood levels
  - Seizures can occur in severe untreated cases
- Supportive care
  - Dark, quiet environment
  - Positioning
  - Symptom management
- Pharmacologic therapy
  - Increasing or reintroducing the opioid and/or benzodiazepine
  - Conversion to long-acting oral agents (methadone, lorazepam)
  - Introducing another sedative, hypnotic or alpha-2 adrenergic agonist (clonidine, dexmedetomidine)

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**Where are we now?**

- Lack of consensus on how to assess and treat
  - AAP 1998 guidelines not in use by more than half of units (Sarker & Donn, 2006)
  - Cochrane review 2006
  - Contributing to inadequate analgesia and sedation management and discontinuation

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**Withdrawal symptom assessment**

- 1970s: a few studies conducted in infants with prenatal opioid exposure
  - Heroin
  - Methadone
  - Finnegan scale, 1975
  - Lipsitz, 1975
  - Green & Suffet, 1981

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**In utero exposure to cocaine**

- Cocaine alone: 28.2%
  - Jittery, tremors
  - Irritability
- Opioids alone: 44.8%
  - Jittery, tremors
  - Irritability
  - High pitched cry
- Opioids + Cocaine: 62%
  - Jittery, tremors
  - Irritability
  - High pitched cry
  - Excessive suck
- Smoking increases likelihood of symptoms
  - ½ pack: OR 1.27
  - >1/2 pack: OR 1.4

Bada et al., 2002, n=11,811

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In utero exposure to SSRIs

- Jitteriness, poor tone, resp. distress, weak cry
- Sleepiness and irritability during feeding, resp. distress
- Myoclonus, restlessness, tremor, shivering, hyper-reflexia, uncoordination, rigidity
- Tremulousness, increased motor activity, decreased or heightened arousal
- Resp. distress, hypotonia
- Seizures

Sanz et al., 2005; Ruchkin & Martin, Compilation of study findings, 2005

Withdrawal symptom assessment in neonatal intensive care

- Mid-1980s: Adaptations of Finnegan scale for NICU use
  - Children’s Hospital Oakland OWS

Withdrawal symptom assessment in paediatric intensive care

- Only 9 prospective published studies
  - Katz et al., 1994; French & Nocera, 1994; Franck et al., 1998; Bicudo et al., 1999; Lugo et al., 2003; Dominguez et al., 2003; Franck et al., 2004; Ducharme et al., 2005; Berens et al., 2006

Confounders

Variability between studies makes it difficult to draw inferences
- Subjectivity and lack of IRR
- Bias from serial measurement
- Defining “resting” state
- Lack of ‘gold standard’ for comparison
- Lack of blinding
- Influence of other factors
- Polypharmacy
- Effect of research on treatment

Iatrogenic withdrawal assessment in cardiac PICU

- Prospective repeated measures study
  - Describe occurrence of withdrawal symptoms with use of a standardised slow tapering protocol
  - To test predictive validity of an opioid and benzodiazepine withdrawal assessment tool (OBWS)
- Sample
  - 15 children (6 weeks – 28 months), 693 assessments
  - Complex congenital heart disease and/or respiratory failure
  - Opioids and benzodiazepines for minimum of 4 days

Franck et al., 2004

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Withdrawal present (%)</th>
<th>Withdrawal absent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crying/spittery &gt; 75% of interval</td>
<td>11.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Crying/spittery 20-75% of interval</td>
<td>33.8</td>
<td>11.8</td>
</tr>
<tr>
<td>Sleep &lt; 20% of interval</td>
<td>53.7</td>
<td>10.7</td>
</tr>
<tr>
<td>Hyperactive Moro reflex</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Pupil &gt; 6mm</td>
<td>36.4</td>
<td>17.5</td>
</tr>
<tr>
<td>Tremors</td>
<td>20.7</td>
<td>17.0</td>
</tr>
<tr>
<td>Movement disorder</td>
<td>15.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Temperature &gt; 37.2</td>
<td>81.5</td>
<td>87.9</td>
</tr>
<tr>
<td>Respiratory rate high for age</td>
<td>7.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Frequent suctioning required</td>
<td>28.5</td>
<td>25.6</td>
</tr>
<tr>
<td>Sweating</td>
<td>10.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>5.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Sweating</td>
<td>2.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>7.9</td>
<td>3.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>42.4</td>
<td>20.2</td>
</tr>
</tbody>
</table>

OBWS

Franck et al., 2004
Iatrogenic withdrawal assessment in cardiac PICU

- Correlation with nurses' judgment
  - $r = .66$
- Specificity (true negatives)
  - 87% (13% false positives)
- Sensitivity (true positives)
  - 50% (missed 50% of cases)
- Compliance and usability
  - 70% staff trained in use of OBWS; 80% IRR
  - 85% compliance with daily assessment
  - 55% compliance with 4-hourly assessment
  - Preference for shorter tool, yes/no items, longer interval

Franck et al, 2004

Conclusions

- Significant withdrawal symptoms occur in critically ill children even with the use of a standardised assessment tool and tapering management protocol
- The predictive validity and utility of the OBWS needs further improvement
- Problems with compliance with clinical withdrawal prevention and management guidelines confound validation

Franck et al, 2004

A new approach

- Neonatal Withdrawal Inventory (NWI)
  - Zahorodny et al, 1998
  - Newborns with prenatal opioid exposure
  - 7 signs representing CNS, autonomic, GI, behavioural features of withdrawal
  - Observation pre-, during, post handling
  - IRR .89 to .98
  - 100% correct identification of 12 symptomatic and 13 control infants
  - 100% specificity and 100% sensitivity

Withdrawal Assessment Tool (WAT)

- Twice daily scoring
  - Pre-, during, post stimulation
  - Standardised routine progressive stimuli used to elicit response
- 3 symptoms assessed from previous 12 hour record
- 3 symptoms assessed pre-stimulus
  - Validated behavioural state assessment
- 4 symptoms assessed during stimulus
- Post-stimulus recovery time to previous state

Franck, Unpublished

WAT validation

- Nested within RCT of a PICU sedation protocol
  - Curley et al (NIH[5R21HD045020-02])
- Outcomes: LOS, Duration of ventilation, Withdrawal
- Sample: Mechanically ventilation, ARF
  - 2 USA PICUs
- Modified crossover design

Preliminary psychometric properties of the WAT

- N=245, 1180 observations
- Strong correlation between WAT scores and nurses’ clinical judgment of withdrawal symptoms
  - $r = 0.80$, ICC = .80
- Sensitivity = .884
- Specificity = .885
- WAT scores correlated with
  - Days weaning
  - Days on opioids and benzodiazepines before weaning
  - Days on opioids and benzodiazepines after weaning

Franck, Curley, Harris et al, unpublished
Parents’ role

- Breast milk/breast feeding to decrease symptoms (Abdel-Latif et al., 2006)
- Symptom monitoring
- Non-pharmacologic comfort
- Advocacy

Questions for discussion

- What are the most important indicators of withdrawal assessment in infants receiving long-term analgesia and sedation?
- Is the evidence sufficient to propose that all tapering and discontinuation of long term opioids and/or benzodiazepines be based on standardised assessment?
- What are the biggest challenges in changing intensive care unit practices in relation to analgesia and sedation?
- Should there be greater involvement of parents in symptom recognition and treatment?

References


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