MATERNAL AND FETAL METHADONE EXPOSURE:
Associations with neonatal abstinence syndrome (NAS)

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The opiate epidemic and increasing NAS

Methadone and buprenorphine are recommended as long-term treatment for opioid use disorder in pregnancy.

METHADONE:

- Opioid analgesic (morphine analog) with long half-life (~22 hours - adults)
- Racemic mixture of R-Methadone and S-Methadone (R is more potent than S)
- Metabolized by CYP450 enzymes to R- and S-EDDP (CYP3A4, CYP2B6, aromatase, and CYP2C19).

Drug withdrawal syndrome that occurs primarily among opioid-exposed infants shortly after birth.

Up to 97% of newborns exposed to methadone in utero will require pharmacologic treatment (unable to predict NAS severity).

WITHDRAWAL SYMPTOMS (most commonly occur 48–72 hours after birth):

- Extreme irritability
- Increased muscle tone
- Difficulty sleeping
- Poor feeding
- Diarrhea
- Temperature instability
- Seizures (severe cases)

OBJECTIVE

Determine whether increased neonatal methadone exposure increases the severity of neonatal abstinence syndrome (NAS)
Measure R- and S-methadone and R- and S-EDDP: **HPLC-MS/MS** (API 4000, Applied Biosystems)

**NAS protocol**
- At our institution, Finnegan score is used to monitor NAS severity (e.g.: continuous high pitched cry, hours slept, tremors, convulsions, fever, respiratory rate, poor feeding, gastrointestinal disturbance)
- After 3 consecutive scores >8 or a single score >=12, treatment is initiated with morphine (Phenobarb may also be added for refractory NAS)
## Subject Demographics and Results

<table>
<thead>
<tr>
<th></th>
<th>NAS (N = 16)</th>
<th>no NAS (N = 4)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>110 (60 - 170)</td>
<td>131 (95 - 180)</td>
<td>0.2011</td>
</tr>
<tr>
<td><strong>Maternal age (years)</strong></td>
<td>28 (23 - 42)</td>
<td>35 (24 - 35)</td>
<td>0.2547</td>
</tr>
<tr>
<td><strong>Ethnicity (NH/L/H/L)</strong></td>
<td>15 / 1</td>
<td>4 / 0</td>
<td>1.0000</td>
</tr>
<tr>
<td></td>
<td>(94% / 6%)</td>
<td>(100% / 0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Race (White/Black/Unknown)</strong></td>
<td>15 / 0 / 1</td>
<td>2 / 2 / 0</td>
<td>0.1883</td>
</tr>
<tr>
<td></td>
<td>(95% / 0% / 6%)</td>
<td>(50% / 50% / 0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>164 (152 - 175)</td>
<td>160 (152 - 173)</td>
<td>0.4757</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>86 (56 - 114)</td>
<td>79 (58 - 90)</td>
<td>0.5080</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>31 (22 - 43)</td>
<td>29 (23 - 35)</td>
<td>0.6033</td>
</tr>
<tr>
<td><strong>Gestational age at delivery (weeks)</strong></td>
<td>38 (35 - 41)</td>
<td>39 (37 - 40)</td>
<td>0.8128</td>
</tr>
<tr>
<td><strong>Birth Weight (kg)</strong></td>
<td>3 (2.3 - 3.7)</td>
<td>2.6 (2.4 - 2.9)</td>
<td>0.2019</td>
</tr>
<tr>
<td><strong>Sex of Infant (Female / Male)</strong></td>
<td>8 / 8</td>
<td>2 / 2</td>
<td>1.0000</td>
</tr>
<tr>
<td></td>
<td>(50% / 50%)</td>
<td>(50% / 50%)</td>
<td></td>
</tr>
<tr>
<td><strong>Breastfeeding (Yes / No)</strong></td>
<td>6 / 10</td>
<td>3 / 1</td>
<td>0.2848</td>
</tr>
<tr>
<td></td>
<td>(38% / 63%)</td>
<td>(75% / 25%)</td>
<td></td>
</tr>
<tr>
<td><strong>1 minute APGAR score</strong></td>
<td>9 (1 - 9)</td>
<td>9 (7 - 9)</td>
<td>0.3202</td>
</tr>
<tr>
<td><strong>Peak Finnegan Score</strong></td>
<td>13 (10 - 20)</td>
<td>9 (7 - 10)</td>
<td><strong>0.0034</strong> *</td>
</tr>
<tr>
<td><strong>Number of days in hospital</strong></td>
<td>29 (19 - 55)</td>
<td>6 (5 - 6)</td>
<td><strong>0.0029</strong> *</td>
</tr>
<tr>
<td><strong>Peak morphine dose (mg/day/kg)</strong></td>
<td>0.05 (0.02 - 0.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total cumulative morphine dose (mg/kg)</strong></td>
<td>5.64 (1.02 - 17.53)</td>
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<td></td>
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</tbody>
</table>
Correlations between plasma and DBS concentrations

**R-Methadone**
- **Infant**
  - $p = 7.80 \times 10^{-07}$
  - $r_p = 0.93$
- **Maternal**
  - $p = 8.64 \times 10^{-10}$
  - $r_p = 0.84$

**S-Methadone**
- **Infant**
  - $p = 2.92 \times 10^{-05}$
  - $r_p = 0.8826$
- **Maternal**
  - $p = 2.33 \times 10^{-11}$
  - $r_p = 0.87$

**R-EDDP**
- **Infant**
  - $p = 0.0253$
  - $r_p = 0.59$
- **Maternal**
  - $p = 3.65 \times 10^{-05}$
  - $r_p = 0.65$

**S-EDDP**
- **Infant**
  - $p = 1.259 \times 10^{-05}$
  - $r_p = 0.4289$
- **Maternal**
  - $p = 1.32 \times 10^{-05}$
  - $r_p = 0.68$
Delivery concentrations are correlated with maternal methadone dose

\[ r_p \sim 0.7 \]

\[ r_p \sim 0.6 \]
Delivery concentrations are correlated with peak morphine per kg

\[ r_p \approx 0.7 \]

\[ r_p \approx 0.6 \]
CONCLUSIONS

• DBS collection on Whatman 903 paper may be a potential substitute for plasma methadone quantification but not for its metabolites.

• This pilot data indicates that maternal methadone AUC and cord blood concentration at delivery may be potential markers for NAS severity as measured by Finnegan score.

• Additional studies, with more objective markers of NAS, are needed to further understand the association between maternal and infant exposure to methadone and NAS.
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