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Neonatal abstinence syndrome in methadone exposed infants: Role of genetic variability

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Advantages: Methadone (MD):
- Currently the only FDA/TGA “approved” opioid substitution therapy during pregnancy.
- Disadvantages: Neonatal Abstinence Syndrome (NAS).

Limitation: Small sample size to date.

Premature (n (%))
- Drug transporters (ABCB1)
- Metabolising enzymes (CYP2D6)
- Immune response (IL-1β)
- Glial activation
- proinflammatory cytokines interleukin-1 beta (IL-1β), creates proinflammatory environment → neuronal excitability to ↑ opioid reward and dependence.

This study of possible impact of Genetic variability on NAS incidence and severity.

By assessing genetic variability in mothers and infants, the association between genetic variability and NAS could be used as a predictive tool:
- Management of the infant by potentially morphine administered to control NAS.

Aim

Investigate the impact of IL-1β -31 and OPRM1 A118G genetic variability on NAS incidence (treatment required) & severity (dose of morphine).

Morphine Treatment

IL-1β -31 Infant genotype (morphine (mg), median (range))

<table>
<thead>
<tr>
<th>Genotype</th>
<th>WT (n=21)</th>
<th>&gt; 1 Var (n=5)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>0.15 (0.1-0.4)</td>
<td>0.2 (0.14-0.3)</td>
<td>0.3 (0.17-0.66)</td>
<td>0.28 (0.23-0.68)</td>
<td>33.8 (14.3-79.3)</td>
<td>34.8 (26.7-91.8)</td>
<td></td>
</tr>
</tbody>
</table>

Initially morphine (p=0.06)

Max morphine (p=0.94)

Total morphine (p=0.67)

OPRM1 A118G Infant genotype (morphine (mg), median (range))

<table>
<thead>
<tr>
<th>Genotype</th>
<th>WT (n=24)</th>
<th>&gt; 1 Var (n=2)</th>
<th>WT (n=24)</th>
<th>&gt; 1 Var (n=2)</th>
<th>WT (n=23)</th>
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</thead>
<tbody>
<tr>
<td>0.17 (0.1-0.4)</td>
<td>0.22 (0.13-0.3)</td>
<td>0.29 (0.17-0.68)</td>
<td>0.24 (0.18-0.3)</td>
<td>34.8 (14.3-91.8)</td>
<td>25.4 (19.4-31.5)</td>
<td></td>
</tr>
</tbody>
</table>

Initially morphine (p=0.73)

Max morphine (p=0.39)

Total morphine (p=0.38)

Nature vs Nurture

Genotyping for OPRM1 and IL-1B

Infant characteristics

Maternal methadone dose at delivery: mg (median (range))

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</tbody>
</table>

Gestational age: weeks (median (range))

<table>
<thead>
<tr>
<th>Premature (n (%))</th>
<th>Gender male (n (%))</th>
<th>Birth weight: g (median (range))</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 (35-41)</td>
<td>2 (8)</td>
<td>2963 (2157-3883)</td>
</tr>
</tbody>
</table>

Low birth weight (n (%))

<table>
<thead>
<tr>
<th>Exposure to (n (%)):</th>
<th>Benzdiazepines</th>
<th>Nicotine</th>
<th>Adjunctive phenobarb (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 (42)</td>
<td>15 (63)</td>
<td>6 (23)</td>
<td></td>
</tr>
</tbody>
</table>

71 methadone exposed infants; 46 with NAS; 26 with genetic & morphine treatment data.

No difference in IL-1B or OPRM1 genotypes between Infants with & without NAS, OR (p):

IL-1B: 1.9 (0.21) OPRM1:0.23 (0.24)

Conclusion

- Despite impact of IL-1B and OPRM1 genetic variability on opioid response in adults, this was not observed in infants.
- Limitation: Small sample size to date.
- This study of possible impact of IL-1B and OPRM1 genetic variability on NAS is ongoing, and could lead to tools to predict NAS incidence & severity.

References