Acetaminophen for PDA Closure - Is this the magic bullet?

Ann Ebert, PharmD
Perinatal Clinical Pharmacy Specialist
UnityPoint Health – Meriter Hospital
2017 WAPC Annual Conference
Kalahari Resort – Wisconsin Dells

Disclosures
- The presenter has no actual or potential conflicts of interest to disclose in relationship to this presentation
- The presenter will be discussing off-label use of medications in this presentation

Overview
- PDA statistics
- Current treatment options
- Mechanism of action of acetaminophen
- Evidence
- Costs
- Conclusions

PDA – Statistics
- Incidence
  - 8 in 1000 preterm neonates
  - 2 in 1000 term neonates
- 65% of infants < 28 weeks gestation
- Spontaneous closure in preterm infants
  - ~57-58%
- Response to NSAIDS (indomethacin and ibuprofen)
  - ~70-85%

PDA – standard treatment
- Indomethacin – q12-24 hr dosing

<table>
<thead>
<tr>
<th>Days</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNA</td>
<td>0.1 mg/kg x 3 doses</td>
</tr>
<tr>
<td>2-7 days</td>
<td>0.2 mg/kg x 3 doses</td>
</tr>
<tr>
<td>&gt; 7 days</td>
<td>0.2 mg/kg x 1 doses, then 0.25 mg/kg x 2 doses</td>
</tr>
</tbody>
</table>

- Ibuprofen – q24 hr dosing

<table>
<thead>
<tr>
<th>Days</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNA</td>
<td>10 mg/kg x 1 dose</td>
</tr>
<tr>
<td>2 days</td>
<td>5 mg/kg x 2 doses</td>
</tr>
</tbody>
</table>

Standard Treatment - Adverse Effects
- Peripheral vasoconstriction
  - Reduction in renal blood flow
  - Reduction in cerebral blood flow
- Gastrointestinal
  - Perforation
  - NEC
- Inhibition of platelet aggregation
  - Bleeding
- Hyperbilirubinemia (ibuprofen)
Acetaminophen/Paracetamol (apap)

- Widely used over the counter medication
- Commonly used for analgesia
- Usual dosing:
  - Preterm infants <32 weeks PMA:
    - 20 to 25 mg/kg orally; then 12 to 15 mg/kg/dose q12h
  - Preterm infants ≥32 weeks PMA:
    - 20 to 25 mg/kg orally; then 12 to 15 mg/kg/dose q8h
  - Term infants:
    - 20 to 25 mg/kg orally; then 12 to 15 mg/kg/dose q8h
  - Target serum concentration 9-11 mg/L
  - Without the side effect profile notable for the standard PDA medications

Serendipity

- Observation:
  - Acetaminophen administered to a 26 week infant at 2.5 weeks of age (for other reason, 7 day course)
- Intervention: (n=5)
  - 15 mg/kg q6h PO x 48-72 hr

<table>
<thead>
<tr>
<th>Age at apap administration (d)</th>
<th>BPD</th>
<th>Diameter ratio</th>
<th>Pretermics - Dipiridamol</th>
<th>Permanent closure - Dipiridamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>Yes</td>
<td>n/a</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Yes</td>
<td>n/a</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>Yes</td>
<td>0.75</td>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Yes</td>
<td>1.25</td>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>Yes</td>
<td>n/a</td>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

Randomized, controlled trials

- Target serum concentration 9-11 mg/L

Early acetaminophen to accelerate closure of the PDA

- RCT, blinded (N = 48)
- 1st outcome: closure or decreased size of PDA
- Exclusion:
  - Septic shock, major malformation, chromosomal anomaly
- Randomized to:
  - IV acetaminophen vs placebo
  - LD of 20 mg/kg, then 7.5 mg/kg q6h x 4 days
- ECHO before med administration and daily
- 2nd outcomes:
  - Permanent closure, LA/Ao ratio, ductus therapies, SE’s of apap, short and long term morbidity and mortality

- Insert graphic
Early closure with apap - results

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen (n=42)</th>
<th>Placebo (n=43)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA, weeks, mean (SD)</td>
<td>28.4 (2.36)</td>
<td>28.3 (2.06)</td>
<td>NS</td>
</tr>
<tr>
<td>BW, kg, mean (SD)</td>
<td>1.13 (0.42)</td>
<td>1.13 (0.54)</td>
<td>NS</td>
</tr>
<tr>
<td>Persistent PDA mean (%)</td>
<td>7 (17)</td>
<td>2 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>PDA closure, h Median</td>
<td>41 (39, 55)</td>
<td>78 (59, 115)</td>
<td>NS</td>
</tr>
<tr>
<td>GA &gt;27 weeks (no ap)</td>
<td>80 (100)</td>
<td>94 (100)</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Increased closure rate in boys
- No adverse effects detected
- Serum concentrations were in range reported for analgesia

Härken et al. Pediatr 2010, 17(3) 67

Side Effects - Acetaminophen

- Liver injury
  - Overall good tolerance
- No change in liver enzymes during or after treatment
- Case reports – generally high total doses
- Asthma/ atopy
  - Epidemiologic data suggest a link to apap

Summary

Potential Benefits
- Reduced risk of:
  - Renal dysfunction
  - GI adverse effects
  - Platelet dysfunction
- Efficacy
  - Appears equally effective as NSAIDs

Unanswered questions
- Efficacy
  - Serum concentration – effect profile
- Limited data – small numbers of infants treated
- Safety
  - PDA dosing regimen higher than analgesic
  - Short term safety – hepatic
  - Long term safety
  - Atopy, asthma

References


Costs

<table>
<thead>
<tr>
<th></th>
<th>Indomethacin</th>
<th>Ibuprofen</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>$475.20 (1 mg)</td>
<td>$487.20 (20 mg/2 ml)</td>
<td>$313.60 (100 mg)</td>
</tr>
<tr>
<td>PO</td>
<td>NA</td>
<td>$437.40 (1 mg/mL)</td>
<td>$437.40 (1 mg/mL)</td>
</tr>
<tr>
<td>Cost per dose (1 kg)</td>
<td>$487.20</td>
<td>$487.20</td>
<td>$487.20</td>
</tr>
<tr>
<td>Daily cost</td>
<td>$487.20 x 2 days = $974.40</td>
<td>$487.20 x 3 days = $1461.60</td>
<td>$487.20 x 4 days = $1950.40</td>
</tr>
</tbody>
</table>

Conclusions

- Continue to use NSAIDs for primary treatment
- Consider use of acetaminophen for:
  - Infants with contraindication to NSAID therapy
  - Failed treatment with NSAID
- Less costly
- IV and PO can be used, but oral more cost-effective
- Monitor for possible effects on hepatic function long term outcomes

References