Patent Ductus Arteriosus in the Newborn: Management from a Pharmacy Perspective

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Objectives

- Describe the role of the ductus arteriosus antenatally and postnatally
- Understand the choice of treatment options for a hemodynamically significant PDA
- Develop a pharmacy care plan for a neonate with a medically or surgically managed PDA
**Acronyms**

- LV=left ventricle
- RV=right ventricle
- LA=left artery
- RA=right artery
- CO=cardiac output
- PVR=pulmonary vascular resistance
- VLBW=very low birth weight
- CHD=congenital heart disease
- L-R=left to right
- CLD=chronic lung disease
- RDS=respiratory distress syndrome
- ARF=acute renal failure
- NEC=necrotizing enterocolitis
- IVH=intraventricular hemorrhage
- PA=pulmonary artery
Fetal Circulation
Fetal Circulation

- RV=2/3 of CO through ductus arteriosus (DA)
- Patent Foramen Ovale (PFO)

At birth

- PVR decreases and get 10x increase in pulmonary blood flow
- Increased LA pressure gets closure of PFO
Fetal Circulation: DA
Physiology of closure

- 2 stages
  1. Functional closure
     - smooth muscle contraction in 72 hours (full term infants)
  2. Anatomical closure
     - Remodeling from pulmonary end due to hypoxia and cell death
     - Opposed by PGE$_2$ and NO
Patent Ductus Arteriosus (PDA)

- Failure of spontaneous closure 24-48h after birth
- Common issue
  - Preterm infants
    - 40-55% of babies <29 weeks
  - VLBW infants (<800g)
Significant PDA

- Complications
  - L-R transductal shunt
    - Pulmonary overcirculation
    - Hypoperfusion
    - Pulmonary edema
  - LV failure
    - Decreased CO (oliguria, hypotension, acidosis)
  - CLD
    - (from increased/prolonged ventilator requirements)
  - End Organ Damage (decreased systemic perfusion)
    - ARF, NEC, IVH
Significant PDA

- Signs and Symptoms
  - Systodiastolic murmur
  - Hyperactive precordium
  - Bounding pulses
  - Delayed hypotension
  - Oxygenation failure

- Diagnosis
  - ECHO
Significant PDA
Significant PDA

- **Role postnatally: Cyanotic CHD**
  - Pulmonary Artery/Pulmonary Ventricle Stenosis
  - Tetrology of Fallot
  - Transposition of the Great Arteries
  - Coarctation of the Aorta

- MUST be ruled out before artificial closure of PDA
Significant PDA

- Cyanotic CHD: Role of the PDA
- Supply systemic circulation with some oxygenated blood (i.e. bypass aorta)
- Maintain patency:
  - Alprostadil Infusion
    - Dose: 0.05-0.1mcg/kg/min continuous infusion
  - Interim management until corrective surgery
Management: Risk vs. Benefit

- Prophylactic medical treatment
  - Questionable during 1st 24 hours of life
  - Decreases significant PDAs, BUT 40% of infants are treated unnecessarily
  - Risk of undiagnosed cyanotic CHD
  - Even VLBW infant’s PDA may close spontaneously in 1st week of life
Management: Risk vs. Benefit

Goals
- Reduce pulmonary overcirculation and/or LV failure
- Improve systemic and/or end-organ perfusion

Risks/benefits assessed by neonatologists and surgeons and discussed with parents

Ligation typically follows failure of indomethacin, or if contraindications exist to treatment
Medical vs. Surgical Management

Search strategy:
- Embase, Medline
- Search Terms
  - Infant, premature
  - Patent ductus arteriosus
  - Ligation
  - Anti-inflammatory agents, non-steroidal
Medical vs. Surgical Management

- **Early surgery preferable**
  - Low morbidity, almost certain success\(^1,2\)
  - Lower incidence of NEC\(^3\)
  - Decreased incidence and severity of CLD\(^4\)

- **Meta-analysis\(^5\)**
  - Inconclusive if medical or surgical management preferable

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Medical Management
Twin B.C. – Medical Management

- GA: 30 weeks, BW: 1.355kg
- Mother: 22yo, G1P0, GBS unknown
- Admission weight: 1.09kg, day 1 of life
- Issues:
  - Premature
  - RDS – Surfactant x 1 dose, CPAP
  - Hypotension – dopamine (10mcg/kg/hr) x 2 days
  - Suspected sepsis – ampicillin + gentamicin x 48hours (cultures negative)
  - Apnea of prematurity – caffeine 3mg/kg/dose IV Daily
Twin B.C. – Medical Management

- Day 3 of life
  - PDA seen on ECHO
  - Indomethacin 0.2mg/kg/dose IV Q12H x 3 doses
  - TFI=140mL/kg/day (non-restricted)
    - TPN, Lipids
    - D10W/NS 0.2
Twin B.C. – Medical Management

- Monitoring:
  - U/O = 2.2cc/kg/hr, SCr=60, Urea = 4.2
  - Na = 143, K = 4.4
  - HR=140-160, BP=43/25
  - PLTs=215
  - No murmur heard after 2 doses
Prostaglandin Inhibitors

- MOA
  - Decreased the activity of cyclooxygenase, inhibiting prostaglandin synthesis

- DOC
  - Literature comparing ibuprofen and indomethacin
  - Ibuprofen as effective, evidence for less adverse effects (resulting in higher u/o, lower SCr values, less decrease in organ blood flow)
  - Risk of kernicterus exists with ibuprofen

- Duration of therapy
  - Some evidence suggests that prolonged therapy with indomethacin at a lower dose may decrease renal effects and IVH
  - Evidence that short course therapy may optimize efficacy, provided appropriate monitoring performed and contraindications considered
Prostaglandin Inhibitors

- **Indomethacin**
  - **Dosing**
    - 0.2mg/kg/dose IV Q12H x 3 doses
    - May try multiple courses
  - **Adverse Effects**
    - Impaired renal function
    - Compromised cerebral/mesenteric blood flow
  - **Monitoring Parameters**
    - BUN, SCr, U/O, K, Na, glucose, platelet count, hemoglobin, signs of bleeding, IVH, signs of NEC
Fluid Restriction

- Conflicting evidence
  - Evidence that restriction might prevent the DA from becoming clinically significant
  - in VLBW, studies have shown no effect on patient outcomes

- Current recommendation is NOT to restrict fluid
  - Reduce LV stroke volume and CO
  - Increases risk of indomethacin related nephrotoxicity
Ventilation

- **Goal**
  - Minimize pulmonary over-circulation

- **Maintain**
  - $pCO2 = 45-55\text{mmHg}$
  - $pH = 7.25-7.35$
  - Oxygen saturations = 88-93%

- **Increasing PEEP**
  - Reduces LV after-load, improving CO
Feeding

- Risk of Necrotizing Enterocolitis (NEC)
  - Decreased systemic perfusion
  - NSAID effects on intestinal perfusion
- Conservative approach
- Consider holding feeds
Surgical Management
Surgical Management

- **Procedure**
  - Lateral subcostal approach
  - Video-assisted thoracoscopic ligation

- **Ligation is not performed during first week of life due to risk of cerebral hemorrhage**
  - Sudden cerebral reperfusion of neonatal blood vessels can cause rupture
Baby J.K. – Surgical Management

- GA: 23 6/7 weeks, BW: 0.63kg
- Mother: 30yo, G2P0A1, hypothyroid, GBS unknown
- Admission weight 0.88kg, day 26 of life

Issues:
- Premature, VLBW
- RDS/CLD
- Grade III IVH
- *E. coli* sepsis
- PDA
  - Day 4 of life on ECHO in peripheral hospital
  - Received indomethacin x 2 courses (unresolved)
  - Ligated @ HSC day 23 of life
Post-Ligation Complications

- Post ligation cardiac syndrome
  - BW< 1000g
  - Low apgar scores at birth
  - Cortisol level < 250mmol/L
  - Requirement for cardiotropic support pre-ligation
Post-ligation Complications

- Immediate systolic and diastolic hypertension
- Cerebral ischemia-reperfusion hemorrhage
- Air-leak syndromes
- Pulmonary edema
- Hypotension
  - (requiring vasopressor support)
- Laryngeal nerve palsy
- Ligation of the left PA or aorta
## Baby J.K. – Complications

<table>
<thead>
<tr>
<th>Time Post-Ligation</th>
<th>Complication(s)</th>
<th>Treatment/Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediately Post-ligation</td>
<td>Hemodynamic instability</td>
<td>Dobutamine (20mcg/kg/min)</td>
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<tr>
<td>12 hours post-</td>
<td>Pericardial effusion, L pleural effusion</td>
<td>Chest tube drainage, ventilation</td>
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<tr>
<td>8 days post-</td>
<td>Persistent chylothorax, coagulopathy</td>
<td>NPO, restart on portagen, FFP/vitamin K</td>
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<tr>
<td>14 days post-</td>
<td>R/O sepsis, excessive chylothorax losses (30mL/kg/hr)</td>
<td>Vancomycin + Tobramycin, thoracic duct ligation</td>
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<tr>
<td>17 days post-</td>
<td>Persistent chylothorax s/p thoracic duct ligation</td>
<td>Octreotide (4mcg/kg/hr)</td>
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</table>
Baby J.K. – Current Medications

- **Cardiotropic Support**
  - Dobutamine (18mcg/kg/min)
  - Hydrocortisone 0.6mg IV Q6H (2mg/kg/dose)

- **Edema**
  - Furosemide (0.05mcg/kg/hour)

- **Chylothorax**
  - Octreotide (7mcg/kg/hour)
  - Sodium Bicarbonate (HELD)

- **Pain**
  - Fentanyl (1.2mcg/kg/hour)
  - Morphine (27mcg/kg/hour)
  - Midazolam (10mcg/kg/min)

- **Coagulopathy**
  - Vitamin K 0.1mg daily x 6 days
  - FFP Q48H
Baby J.K. - Monitoring Parameters

- Hemodynamics
  - HR, BP, ventilation, pH
- Electrolytes
  - Na, K, Cl, Glucose
- Renal function
- Hematology
  - WBC, Bands/Polymorphs, bilirubin
- Coagulation
  - INR/PTT
- Pain control
- Ins & Outs
  - Chest tube drainage
    - mL/kg/hr, protein, bicarbonate, electrolyte content, cultures
- Cultures
Baby J.K. – Follow-Up

- Medical team recommended withdrawal of care to parents
- Parents intend to pursue further surgical management options
**PDA: Take Home Messages**

- Role for pharmacists in both medical and surgical management of significant PDAs
- For medical management, can assess risk/benefits for neonates and identify contraindications
- Post-surgical ligation, complications should be managed with ongoing evaluation
- Appropriate monitoring is crucial for identification and prioritization of DRPs
References


References

