The Patent Ductus Arteriosus (PDA) and the Preterm Baby

Tanya Hatfield, RNC-NIC, MSN
Neonatal Outreach Educator
Objectives

- Describe normal cardiac physiology and development
- Understand the unique physiologic needs of the preterm infant with a PDA
- Define the implications prematurity presents with the cardiac system
Normal Cardiovascular Function: Review

Normal Cardiovascular Function: Review

Right
Lungs
Pulmonary Artery (PA)

Left
Body
Systemic Aorta (Ao)
Fetal Circulation

(c) Scheme of fetal circulation
Fetal Circulation

- Gas exchange is liquid to liquid
- Organ of respiration is placenta
- High flow, low resistance
- Fetal lungs
  - Low flow, high resistance
- PA’s constricted
- High right heart and lung pressures
- Low left heart pressures
- Open fetal shunts
Review of Fetal Shunts

- Ductus arteriosus
- Foramen ovale
- Ductus venosus
The PDA and the Fetus

The ductus arteriosus serves to divert blood away from the fluid-filled lungs toward the descending aorta and placenta.
The PDA and the Fetus

- Has a high level of intrinsic tone
- Produces several vasodilators that oppose the ability of the intrinsic tone and oxygen to constrict the vessel
Vasodilators Present in Ductus Arteriosus

- $\text{PGE}_2$
  - Most potent prostaglandin produced by the ductus
- $\text{PGI}_2$
- Nitric Oxide
Did you know that NO and prostaglandin production occurs in the tunica intima?
Introducing the Vasa Vasorum -

- The vasa vasorum is a network of small blood vessels that supply the walls of larger blood vessels
Vasa Vasorum Preterm vs Term
Ductal Constriction and the Full-Term Infant

- ↑ Arterial PaO₂
- ↓ Blood pressure within the ductal lumen
- ↓ Circulating PGE₂
- ↓ Number of PGE₂ receptors in the ductal wall
In the Full Term Neonate…

▪ Marked reduction in vasa vasorum flow

▪ Loss of flow leads to a threefold increase in diffusion distance for oxygen across the ductus wall

▪ Profound ductal wall hypoxia occurs before luminal flow has been eliminated
In the Full Term Neonate...

- Profound ductal wall hypoxia
  - Inhibits local production of PGE$_2$ and NO
  - Produces smooth muscle apoptosis
  - Induces local production of growth factors
    - TGF-β Transforming growth factor-β
    - VEGF vascular endothelial growth factor
In the Preterm Neonate…

▪ Ductus frequently remains open for many days after birth

▪ Even with constriction the premature ductus frequently fails to develop profound hypoxemia
  • Vessel does not undergo anatomic remodeling
    – Susceptible to vessel reopening
Ductal Constriction and the Preterm Infant

- Intrinsic tone of the extremely immature ductus is <70% compared to term infant
- ↑ Sensitivity to the vasodilating effects of PGE$_2$ and NO
In the Preterm Neonate...

A PDA is normal on DOL 3 and may remain open through the first week of life in 50% of preterm infants
In the Preterm Neonate...

- The presence of a hemodynamically significant PDA with a large left-to-right shunt is a common cause of morbidity in the extremely premature neonate
## Incidence of PDA by Postnatal Age

<table>
<thead>
<tr>
<th>Gest (wk)</th>
<th>Healthy</th>
<th>RDS</th>
<th>Healthy</th>
<th>RDS</th>
<th>Healthy</th>
<th>RDS</th>
<th>Healthy</th>
<th>RDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40</td>
<td>55</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>38-40</td>
<td>85</td>
<td>50</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34-37</td>
<td>96</td>
<td>42</td>
<td>12</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-33</td>
<td>87</td>
<td>31</td>
<td>56</td>
<td>13</td>
<td>25</td>
<td>0</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>≤29</td>
<td>80</td>
<td>40</td>
<td>84</td>
<td>20</td>
<td>77</td>
<td>7</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>
A Hemodynamically Significant PDA May Increase the Risk of...

- Intraventricular hemorrhage
- Pulmonary edema/hemorrhage
- Necrotizing enterocolitis
- BPD/ventilator dependence
- Retinopathy of prematurity
- Surgical intervention
- Death
Pathophysiology of a PDA…

▪ Term infants-
  • Left ventricular distension may produce a higher ventricular end-diastolic pressure at smaller ventricular volumes

▪ Preterm infants
  • Ventricles are less distensible than term and generate less force per gram of myocardium
  • The relative lack of ventricular distensibility is more a function of the tissue rather than poor muscle function
Dependent on:
- Magnitude of left-to-right shunting
- Cardiac and pulmonary responses to shunting
- How do term and preterm infants differ in presence of PDA?
True or False???

Preterm infants can triple their cardiac output better than a marathon runner?
Redistribution of Systemic Blood Flow

Even with a small PDA blood is shunted away from the:

• Skin
• Bone
• Muscle
• GI tract
• Kidneys
Shunting May Cause…

- Decreased perfusion
  - Due to a drop in diastolic pressures
- Decreased blood flow to organs
- Localized vasoconstriction… why?
- Organs may experience significant hypoperfusion before there are any signs of left ventricular compromise
How Does a PDA Present?

Actual Monitor of Preemie with Significant PDA
PDA Presentation

- Usually asymptomatic when ductus is small
- Bounding pulses
- Palmar pulses
- Active precordium
- Wide swings in oxygen saturation
- Murmur
- Widening pulse pressure (>20mm Hg)
- Low diastolic pressure
### Hemodynamically Significant PDA

**Patent Ductus Arteriosus in Premature Neonates**

(Mezu-Ndubuisi et al, 2012)

#### Cardiovascular Distress Score (CVD) in Premature Infants with PDA [38]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Heart murmur</td>
<td>None</td>
</tr>
<tr>
<td>Peripheral pulse</td>
<td>Normal</td>
</tr>
<tr>
<td>Precordial pulsation</td>
<td>None</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>&lt;0.60</td>
</tr>
</tbody>
</table>
PDA Presentation

- ↑ Vascular markings on CXR
- ↑ Heart size is a late sign
- Apnea or worsening respiratory status
- Prolonged capillary fill time from ↓ systemic output
Diagnostics for Diagnosis of PDA

- Chest x-ray
- Echocardiogram
- BNP
Chest X-ray of CHF

- The increase in left ventricular pressure increases pulmonary venous pressure, causing pulmonary congestion
- Cardiomegaly is a late sign
Echocardiographic Findings

Echocardiography is the best way to determine:

- Presence of PDA
- Size of PDA
- Hemodynamic significance
- Degree and direction of shunting
Laboratory Findings with PDA

▪ B-Type Natriuretic Peptide (BNP) is released from the heart in response to increased wall tension.

▪ Can be useful to help evaluate the left to right shunting through the ductus.

▪ Normal Value
  • Normal <25
  • >100 indicates significant left to right shunt
PDA: Treatment Modalities

- Conservative measures are employed initially:
  - Fluid Restriction
  - Diuretics (lasix)
  - Positive end-expiratory pressure: useful in reducing left-to-right shunt via PDA
Fluid restriction

- Restricted fluid administration reduces the risk of PDA and NEC and demonstrates trends towards reducing the risk of BPD, IVH, and death (Cochrane Database, 2010)

- Total fluids on admission will be 80mL/kg/day
  - Slow increases

- Be cautious of flushes

- Document, document, document
PDA Treatment Modalities

- Pharmacologic
  - Indomethacin (Indocin)
  - Neoprofin (Ibuprofen)
  - Acetaminophen (Paracetamol)
Indomethacin: Clinical Pharmacology

- Indomethacin, an indole derivative, is one of the most potent inhibitors of the cyclo-oxygenase pathway.
- Inhibits the action of prostaglandin synthetase, and thus inhibits the synthesis of the prostaglandin E series.
- Indomethacin is a potent vasoconstrictor and ↓ cerebral, gastrointestinal, and renal blood flow.
Indomethacin: Clinical Pharmacology

- Elimination half-life is approximately 30 hours (range 15-50 hours)
- Individual differences in rate of distribution, drug metabolism, rate of renal and biliary excretion, and re-entry of drug into the circulation by enterohepatic recirculation all contribute to the variability in plasma clearance.
Indomethacin IV Administration

Special Considerations:
Rapid infusions of intravenous indomethacin have been associated with significant reductions in cerebral blood flow.
UCSF Indomethacin Therapy: Intravenous Administration

- Administer by syringe infusion pump over 30 minutes
- Flush what is left in the tubing with 1 ml NS over 30 minutes
- Administer into dedicated peripheral IV
Indomethacin Therapy

- **Notify provider for...**
  - Creatinine >2mg/dL
  - UO <1mL/kg/hr
  - Abdominal distension
  - Platelets <100k
  - Bilious gastric residual
  - Hemoccult positive stool
UCSF Indomethacin Protocol:

- Prior to administering indomethacin, a BUN, BNP, creatinine, and platelets must be checked.
- Careful monitoring of gastrointestinal and renal status is required during a course of therapy.
Indomethacin Side Effects

- Hypertension
- Edema
- Hyperkalemia
- Dilutional hyponatremia
- Hypoglycemia
- GI bleeding
Possible Adverse Effects

- Renal impairment
- Gastrointestinal dysfunction
  - (Abdominal distension, gastrointestinal bleeding, necrotizing enterocolitis, gastric perforation, gastric ulceration).
- Platelet dysfunction and bleeding tendency.
Contraindications to Indomethacin

- Suspected CHD
- Known GI or renal anomaly
- Poor renal function
- Bleeding disorders or thrombocytopenia
- Necrotizing enterocolitis
- Sepsis
Ibuprofen Therapy: Cochrane 2015

▪ Effective in closing a PDA

▪ As effective as indomethacin in closing a PDA and reduces the risk of NEC and transient renal insufficiency

▪ Given the reduction in NEC noted in this update, ibuprofen currently appears to be the drug of choice

▪ Studies are needed to evaluate the effect of ibuprofen compared to indomethacin treatment on longer term outcomes in infants with PDA
Ibuprofen Side Effects

- Inhibits platelet aggregation, so signs of bleeding should be monitored.
- Ibuprofen solution may be irritating to the tissue; therefore, it should be administered carefully to avoid IV extravasation.
- Ibuprofen is known to displace bilirubin from albumin binding sites, and should be used with caution in patients with an elevated total bilirubin.
Ibuprofen Contraindications

- Proven or suspected infection that is untreated
- Congenital heart disease
- Active bleeding, especially ICH or GI
- Thrombocytopenia, coagulation defects
- Suspected NEC
- Significant impairment of renal function
Ibuprofen – Adverse events

- Bleeding
- Skin lesion/irritation
- Hypoglycemia
- Hypocalcemia
- Adrenal insufficiency
- Respiratory failure
- IVH and renal insufficiency have also been reported
Acetaminophen Therapy

- NSAIDs come with many risks
- Acetaminophen is an alternative for hemodynamically significant PDA
- IV or Oral
- No need to stop feeds
**Pharmacy Tip of the Week**
UCSF Medical Center & Benioff Children's Hospital

**Prophylactic PDA Regimens**

***INDOMETHACIN***

<table>
<thead>
<tr>
<th>Baby Age</th>
<th>Start Time from Birth</th>
<th>Doses</th>
<th>Additional doses required</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 24(^{w}) wks Gestation</td>
<td>Within 24 hours</td>
<td>0 hr 0.1 mg/kg</td>
<td>24 hr 0.1 mg/kg 48 hr 0.1 mg/kg</td>
</tr>
<tr>
<td>≤ 25 (^{w}) wks Gestation + Intubated &gt; 24 h after birth</td>
<td>After 24 hours and before 5th day</td>
<td>0 hr 0.2 mg/kg</td>
<td>24 hr 0.1 mg/kg 48 hr 0.1 mg/kg</td>
</tr>
</tbody>
</table>

Additional doses required:
- Yes, if after the 3rd dose, echo shows open ductus
  - Dose: 0.2 mg/kg at 72 and 96 hr

*Note: MD/NP are required to assess contraindications and place a nursing communication order that the medication is safe to administer.
When requesting medications, nurses are encouraged to notify pharmacy via Inbasket Message that medication appropriateness has been assessed

*Indomethacin is not compatible with TPN, lipids, or most other medications*

**Contraindications to Indomethacin**
Hydrocortisone administration within 24 hours, GI anomalies, concern for necrotizing enterocolitis or intestinal perforation, renal abnormalities, platelets < 50,000

---

**INTRAVENOUS ACETAMINOPHEN**

<table>
<thead>
<tr>
<th>Baby Age</th>
<th>Start Time from Birth</th>
<th>Doses</th>
<th>Key Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 3/7 - 27 6/7 wks Gestation + Intubated &gt; 24 hours after birth</td>
<td>After 24 hours and before 5th day</td>
<td>1 loading dose: 15 mg/kg &amp; 19 Maintenance doses: 12.5 mg/kg Q6H</td>
<td><em>Must check trough levels</em> Trough Level: 15 – 20 mg/l. Dose Adjustments: see protocol</td>
</tr>
</tbody>
</table>

Check acetaminophen trough level, just before the third maintenance dose (including whenever there is a change in dose)

References: Lexicomp

Kelsey Jape, PharmD, Sarah Scarpace Lucas, Pharm.D. Department of Pharmaceutical Services PDA = patent ductus arteriosus August 21st, 2017
Early Treatment Versus Delayed Conservative Treatment of the Patent Ductus Arteriosus (PDA:TOLERATE)

- Goal of the trial is to compare 2 treatment approaches
  - Early treatment
  - Conservative approach
- Hypothesis is the treatment of a moderate PDA will decrease need for respiratory support, diuretics, gavage feeding, ligation, and further intervention

https://clinicaltrials.gov/ct2/show/NCT01958320
PDA – Surgical Repair

- Ligation and division through a left posteriolateral thoracotomy without cardiopulmonary bypass
- The vessel is isolated and ligated with a clip or band.
PDA Ligation Complications

▪ Mortality less than 1%
▪ Complications are rare but may include:
  • Injury to the recurrent laryngeal nerve
  • Injury to left phrenic nerve
  • Injury to thoracic duct
  • Ligation of PA
  • Infection
  • Bleeding
PDA Ligation

The aorta and pulmonary trunk are separated

The open ends are closed
References


