Pharmacologic Treatment of Neonatal Pulmonary Hypertension

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I will be discussing the off-label use of inhaled nitric oxide, bosentan, sildenafil, milrinone, prostacyclin, norepinephrine.
Pulmonary Hypertension in Children

- Critical determinant of morbidity and mortality in many pediatric cardiac, lung and systemic diseases.
- Advances in basic pulmonary vascular biology have directly led to novel therapies.
- Survival and quality of life of children with pulmonary hypertension has improved over last decade.
- However, pulmonary hypertension and vascular disease continues to contribute to poor survival in diverse settings.
Physiologic Mechanisms of PAH

**Endothelin-1**
- Preproendothelin
- Proendothelin
- Endothelin-1
- Endothelin-receptor A
- Endothelin-receptor B
- Endothelin-receptor antagonists
- Vasoconstriction and proliferation

**Nitric Oxide**
- Arginine
- Nitric oxide (NO)
- cGMP
- Phosphodiesterase type 5
- Vasodilatation and antiproliferation
- Exogenous nitric oxide
- Prostacyclin derivatives

**Prostacyclin (PGL₂)**
- Arachidonic acid
- Prostaglandin I₂
- Prostacyclin (PGI₂)
- cAMP
- Vasodilatation and antiproliferation

PH-Specific Drug Therapy

• NO-cGMP Agents:
  - Inhaled NO
  - PDE5 Inhibitors
    - Sildenafil (Revatio; PO, IV)
    - Tadalafil (PO)

• Endothelin Receptor Antagonists
  - Bosentan (Tracleer; PO)
  - Ambrisentan (PO)

• Prostacyclin Analogues
  - Epoprostenol (Flolan; iv)
  - Treprostinil (Remodulin; SQ, iv, inhaled)
  - Iloprost (inhaled)
Survival in Children with Severe PAH Prior to Approved Treatments for Adult PAH

1, 3 and 5 year survival: ~40-65%, ~45% and ~30%, respectively

Survival

Years

(Robyn Barst, 2012)
1, 3 and 5 year survival: ~85-95%, ~70-95% and ~50-95%, respectively vs prior to therapies: ~40-65%, ~45% and ~30%, respectively (Robyn Barst, 2012)
Pediatric PAH ≠ Adult PAH

• Intrinsically linked to developmental biology of the cardiopulmonary system;
• Timing of vascular injury during susceptible periods of adaptation and development (e.g., hyperoxia, hypoxia, inflammation, infection, hemodynamics, drugs);
• Role of vascular disease beyond PH alone (e.g., distal lung growth as in BPD, CDH, lung hypoplasia);
• Differences in genetics, vascular function and structure, responsiveness to therapeutic strategies;
• Additional importance of “preventive” strategies as well as “reverse remodeling.”
Pharmacologic Treatment of Neonatal Pulmonary Hypertension

Diseases Associated with Severe PH in Newborns:

- PPHN
- Congenital Diaphragmatic Hernia
- Bronchopulmonary Dysplasia (BPD)

Current therapeutic strategies:

- NO-cGMP Signaling (iNO, PDE5 inhibitors)
- Endothelin Receptor Antagonists (ERA)
- Prostacyclin Analogues
  - Epoprostenol (Flolan)
  - Treprostinil (Remodulin)
Hypoxemic Respiratory Failure in the Term Newborn

Idiopathic PPHN

Meconium Aspiration

Pneumonia

Congenital Diaphragmatic Hernia
Role of NO in the Perinatal Lung

**Endogenous NO at Birth**

**Inhaled NO**

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**Figure A**

- **PA Pressure (mm Hg)**
  - **LNA-TREATED**
  - **CONTROL**
- **LNA INFUSION**

**Figure B**

- **LPA Flow (ml/min)**

**Figure**

- **Pulmonary artery pressure**
- **Aortic pressure**
- **AoP**
- **PAP**
- **NO 20 ppm**
- **Ventilation, FIO $\geq 0.10$**
Inhaled NO Improves Oxygenation in Severe PPHN

(Kinsella JP et al, Lancet, 1992)
Inhaled NO Reduces the Need for ECMO Therapy in Term Newborns with PPHN

(N = 58 patients)                              (N = 235 patients)                               (N = 248 patients)
Elements of Pulmonary Hypertension

Lung Disease
• Hyperinflation
• Atelectasis
• Hypoxemia
• Hypercarbia

Heart Disease
• RV Dysfunction
• Impaired LV Contractility
• LV Diastolic Dysfunction

Pulmonary Vascular Disease
• High tone and reactivity
• Hypertensive arterial remodeling
• Decreased vascular growth

High Pulmonary Artery Pressure
Pulmonary Vasodilator Therapies

- Inhaled NO (5 – 20 ppm)
- Sildenafil (Revatio), PDE5 inhibitor
  - NG: 0.5 mg/kg test dose, then 1-2 mg/kg q 6 hrs.
  - iv: 0.4 mg/kg over 3 hours, then 1.6 mg/kg/day
- Milrinone, PDE3 inhibitor *
  - iv: 0.3 – 0.7 ugm/kg/min
- Bosentan (Tracleer), Endothelin Receptor Antagonist
  - NG: 1-2 mg/kg twice daily
- Epoprostenol or Treprostinil (Pgl₂ analogues; continuous infusion, inhalation or SQ)
NO-cGMP Signaling: Therapeutic Targets for Severe PPHN

Endothelial cell

Endothelial cell

NO synthase

L-citrulline

L-arginine

L-arginine

NO

NO

sGC

sGC

GTP

GTP

cGMP

cGMP

5’-GMP

5’-GMP

PDE5

PDE5

Sildenafil

Sildenafil

Smooth Muscle cell

Smooth Muscle cell

Vasodilation

Vasodilation

Inhaled NO

Inhaled NO

sGC Activators and Stimulators

sGC Activators and Stimulators

0₂
Sildenafil Causes Pulmonary Vasodilation and Enhances the Effects of Inhaled NO

* P<0.01 versus baseline; # P<0.01 versus inhaled NO

Oral Sildenafil Therapy for PPHN

(Baquero H et al. Pediatrics 2006)
Intravenous Sildenafil Improves Oxygenation in Human PPHN

Dose: 0.4 mg/kg over 3 hours, then 1.6 mg/kg/day

(Steinhorn RH et al. J Pediatrics, 2009)
Aerosolized Epoprostenol in PPHN

*B 4 pts went to ECMO post EPO
2 pts on ECMO prior to EPO
2/11 with ECHO improvement

* may lose “micro-selective” effects at high doses, worsening V/Q;
- well-absorbed by bronchial vessels, risk of systemic hypotension

(Brown AT et al. Pulmonary Circulation, 2012)
Milrinone Therapy for PPHN

Dose: 50 ug/kg bolus over 1 hour
Infusion: 0.4 - 1.0 ug/kg/min infusion

(Porta and Steinhorn)

(McNamara PJ et al. Pediatr Crit Care Med. 2013)
Milrinone Therapy for PPHN

**Physiologic Effects:**
- *Pulmonary Vascular*
  - augments Pgl2 and iNO dilation
- *Cardiac*
  - enhances contractility
- *Systemic Vascular*
  - lowers resistance, LV afterload

**Potential Adverse Effects:**
- ↓ systemic arterial (diastolic) pressure
  - ↓ myocardial perfusion
    - ↓ myocardial O₂ delivery
      - ↓ RV or LV function
Norepinephrine Therapy for PPHN

* Increased SAP may enhance RV and LV perfusion

Increased Plasma ET-1 Levels in PPHN

(OI = 14 ± 2

49 ± 6)

(Rosenberg A et al, J Pediatr, 1993)
Bosentan Therapy for PPHN

(N = 24, Bosentan; 23, Placebo)

Dose: Bosentan 1 mg/kg BID

(Mohamed, Ismail J Perinatol. 2012)
Matching Therapy to Physiology

- Diagnose and treat primary disorder
- Optimize lung recruitment
- Improve cardiac performance and hemodynamics:
  - Poor RV function, decreased pulmonary blood flow, decreased left sided filling, poor systemic output
  - Cardiotonic therapy: dobutamine, dopamine, epinephrine, AVP
  - LV output can improve with decreased PVR (inhaled NO)
  - LV dysfunction- role for afterload reduction (eg, milrinone)
  - Maintaining ductal patency (PGE₁ infusion)
- Close monitoring- labile disease, changes with time often related to changes in physiology
- Serial echocardiograms
Pulmonary Hypertension in Congenital Diaphragmatic Hernia

Relationship of Pulmonary Hypertension to Survival in CDH

(Dillon et al, 2004)
Impaired Lung Vascular Growth in CDH

(Keller R, 2007)
Successful iNO Treatment of a Newborn With Congenital Diaphragmatic Hernia

(Kinsella J et al, J Pediatr 1993)
Stages of Pulmonary Vascular Disease in CDH

• **Early** (hours to weeks)- severe PPHN, but with variable contribution of lung disease and LV abnormalities (size, function);

• **Late** (weeks to months)- PH remains high, often near systemic levels, which can persist despite weaning from mechanical ventilation;

• **Chronic** (months to years)- significant PH despite stable respiratory course.
Prolonged Nasal NO Therapy for Late Pulmonary Hypertension in Congenital Diaphragmatic Hernia

Table II. Ventilator settings and blood gas tensions in patients with CDH treated with endotracheal iNO (2 to 5 ppm) before extubation and treatment with nasal cannula iNO

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ON iNO</th>
<th>Off iNO</th>
</tr>
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<tbody>
<tr>
<td>Age (d)</td>
<td>26 ± 3</td>
<td></td>
</tr>
<tr>
<td>Fio₂</td>
<td>0.34 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>Ventilator rate (bpm)</td>
<td>12 ± 2</td>
<td></td>
</tr>
<tr>
<td>Peak inspiratory pressure (cm/H₂O)</td>
<td>23 ± 1</td>
<td></td>
</tr>
<tr>
<td>PEEP (cm/H₂O)</td>
<td>4.9 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Mean airway pressure</td>
<td>7.1 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>PH</td>
<td>7.38 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>Paco₂ (mm Hg)</td>
<td>43 ± 2</td>
<td></td>
</tr>
<tr>
<td>Pao₂ (mm Hg)</td>
<td>62 ± 5</td>
<td></td>
</tr>
<tr>
<td>Oxygenation index</td>
<td>4 ± 1</td>
<td></td>
</tr>
</tbody>
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(Kinsella et al, 2003)
Pulmonary Hypertension Drugs: Chronic Lung Disease

- Inhaled NO (5 - 20 ppm)
- Sildenafil (0.5 -2 mg/kg/dose q 8 hours)
- Bosentan (1/4 tab daily initially, then BID)
- Prostacyclin analogues:
  - Epoprostenol (Flolan; iv)
  - Treprostinil (Remodulin; iv, SQ, inhaled)
  - Inhaled Iloprost
The Pulmonary Circulation in BPD
Reduced Lung Surface Area in Infants with Chronic Lung Disease

(Balinotti et al, AJRCCM, 2010)
Pulmonary Vascular Disease in BPD

Abnormal Growth
- Impaired Angiogenesis
- Intrapulmonary Shunt Vessels
- Decreased Alveolarization

Abnormal Function
- High tone
- Abnormal Reactivity

Abnormal Structure
- SMC hyperplasia
- Adventitial thickening
- Intimal occlusion (rare)

Decreased Lung Surface Area and Gas Exchange
- Prolonged oxygen therapy
- Altered distribution of blood flow with infection, stress
- Exercise intolerance
- Pulmonary Hypertension
Lack of Decline in RIMP in Preterm Infants who Develop BPD

Diagnosis of Pulmonary Hypertension Increases Risk of Late Morbidities Independent of BPD Severity

(* p < 0.05 PH vs Other Groups)

(Peter Mourani)
Late Pulmonary Hypertension is Associated with High Mortality in BPD

(Khemani et al, Pediatrics, 2007)
Whom to Screen?

- Extreme prematurity (< 26 weeks)
- IUGR or pre-eclampsia
- Prolonged ventilator course
- Inability to wean $\text{FiO}_2$, lack of overall improvement with time, poor growth, recurrent “spells”
- Severity of BPD
- Or, all infants with BPD near term corrected age, even if clinically stable?
Pulmonary Hypertension and BPD: Association with Disease Severity

Relationship of Pulmonary Hypertension and Severity of BPD at 36 Weeks PCA

(13% of study population with PH)

(PM Mourani et al, unpublished data)
Utility of Echocardiograms in Assessments of Pulmonary Hypertension in BPD

(Mourani PM et al, Pediatrics, 2008)
Utility of ECHO for the Evaluation of Pulmonary Hypertension in BPD

- TRJV could be quantified in only 61% of studies in at risk BPD infants;
- Estimates of sPAP correctly diagnosed the presence or absence of PH as determined by cardiac catheterization in 79% of studies
  - Correctly determined severity of PH in 47% of cases;
- 58% of children without a measureable TRJV were found to have PH by cardiac catheterization;
- Qualitative measures of PH had worse predictive value for subsequent diagnosis of PH during catheterization.

Mourani PM et al J. Pediatrics 2008
Lung Pathophysiology of BPD

**Central Airways:**
- Tracheomalacia
- Subglottic stenosis, cyst
- Granulomas
- Bronchomalacia
- Bronchial stenosis

**Small Airways:**
- Structural remodeling
  - Mucus gland hyperplasia
  - Epithelial injury, edema
  - Smooth muscle hyperplasia
- Bronchoconstriction
- Hyper-reactivity

**Distal Airspace and Vasculature:**
- Decreased alveolarization, vascular growth
- Abnormal vascular remodeling, tone and reactivity
- Impaired lymphatic function, structure
Diagnostic Approach to Infants with Pulmonary Hypertension in BPD

- **Evaluation of Underlying Lung Disease:**
  - Prolonged monitoring of $O_2$ (awake, asleep, feeds)
  - $\text{PaCO}_2$ – contribution to PH or marker of disease severity, need for chronic (effective) ventilation?
  - Chronic aspiration (barium swallow, swallowing study, pH probe, impedance study)
  - Sleep study
  - Structural airway disease: flexible bronchoscoppy
  - Reactive airways disease
  - Chest CT Scan

- **Cardiac Catheterization**
Increased Hypoxic Pulmonary Vasoconstriction in BPD

(Abman et al, 1985)
Pulmonary Vascular Effects of Inhaled NO and Oxygen in Older Children with BPD

(Mourani et al, 2004)
Role of Cardiac Catheterization

- Assess severity of pulmonary hypertension
- Anatomic heart disease/shunt lesions (esp. assessment of atrial septal defects)
- Structural vascular abnormalities (eg, arterial stenosis, pulmonary vein stenosis, hemangiomatosis, others)
- Assess cardiac function (LV dysfunction)
- Catheter-based interventions (collaterals, stenosis, shunt)
- Acute vasoreactivity/hypoxia testing for selection of chronic therapy
Pulmonary Vein Stenosis in BPD

High Mortality in PVS

(Drossner et al, 2008)
Severe Pulmonary Hypertension in a Preterm Infant with BPD and PVS

Pulmonary Artery Remodeling

Pulmonary Vein Remodeling
Left Ventricular Diastolic Dysfunction in BPD
Increased Systemic to Pulmonary Collaterals in BPD
"It's the only treatment option he has under his current health plan."
Chronic Sildenafil Therapy for Late Pulmonary Hypertension in CLD

(Mourani P, J Peds, 2009)
Clinical Response to Prolonged Sildenafil Therapy in BPD

Percent of Patients Showing Hemodynamic Improvement by Echo

Censored Observations

(Mourani, J Pediatr, 2009)
Revatio shown to be fatal in kids
Off-label use in children not recommended
Conclusions

• Pulmonary hypertension can be identified early in preterm newborns and is associated with:
  - an increased risk for developing BPD
  - higher mortality and late morbidity.

• Evaluation requires an aggressive diagnostic and therapeutic approach to lung disease.

• Cardiac catheterization plays an important role in the diagnosis and treatment of PH in BPD.

• Chronic PH drug therapy should only follow treatment of underlying lung disease.
Pediatric Heart Lung Center

Clinical Team

Lab Group