AEROSOLIZED PROSTACYCLIN THERAPY

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Background Information

- Prostaglandin \( I_2 \) (PGI\(_2\)) is one of several naturally occurring prostacyclins produced in all vascular tissues, particularly in endothelial cells and smooth muscle cells.

- It leads to potent relaxation of smooth muscle cells induced by a receptor-mediated increase in intracellular adenosine 3′,5′ cyclic monophosphate (cAMP).
Effects of Prostaglandin

- $\text{PGI}_2$ produces vasodilation of the pulmonary & systemic vasculature in a dose-dependent manner
- In addition, prostaglandin has an inhibitory effect on platelet aggregation, thereby preventing adhesion of platelets to the vascular endothelium
- Finally, prostaglandin inhibits activation of leukocytes and monocytes during the inflammatory reaction
Intravenous Prostacyclin

- IV prostacyclin is effective in treating severe pulmonary hypertension
  - Use of IV PGI$_2$ was first described in 1978 in canine experiments
- In most patients, the IV doses of PGI$_2$ required to decrease PA pressures induce systemic hypotension
Welte and his colleagues (1993) reported that inhaled PGI$_2$ resulted in selective PA vasodilation in dogs. Inhaled PGI$_2$ reaches only well-ventilated areas of the lungs, causing greater vasodilation in these regions than the IV route does, while not causing systemic hypotension.
Research

- Case reports and descriptive and randomized trial research in the last 12 years suggest that administration of PGI$_2$ by inhalation improves oxygenation and reduces PAP.
- Decreases shunting while improving oxygenation.
- Modulates vascular growth and modifies platelet function.
Case Reports

- PGI$_2$ decreased mean PA pressures without altering mean arterial pressure
- There was a significant improvement in the PaO$_2$/FiO$_2$ ratio in patients with refractory hypoxemia
Haché and her colleagues in Montreal (2001) performed a chart review of 27 patients who received inhaled PGI$_2$ over a one-year period. Selective pulmonary vasodilation occurred in 78% of patients. Improvement in PaO$_2$/FiO$_2$ ratio in 88%. Concluded that inhaled PGI$_2$ can be useful in the treatment of patients with pulmonary hypertension & severe hypoxia.
Evidence

- PGI$_2$ has been shown to be safe and effective in:
  - Reducing pulmonary vascular resistance in heart transplant patients
  - Decreasing PAP in primary & secondary pulmonary hypertension
  - Improving oxygenation in patients suffering from hypoxemia

- Benefit of inhaled vasodilators is well documented in the literature
Limitations of Studies

- Many studies had a small number of patients
- No control or placebo groups
- Not all results are attributable to inhaled PGI$_2$
- Incomplete data for some variables, such as PVR, wedge pressure, CVP
Inhaled Prostacyclin

- Epoprostenol (Flolan®)
- Easy to administer
- Requires no special monitoring equipment
- Can be safely administered via face mask or endotracheal tube
- Easy to use on transport
Indications

Adult or pediatric patients with:

- Pulmonary hypertension
- Right ventricular failure
- ARDS
- Hypoxemic respiratory failure
Effects of Prostacyclin

- Pulmonary vasodilation
- Reduced PA pressure
- Improved right heart function
- Improved $V_A/Q$ mismatch
- Improved oxygenation
Common Adverse Effects

- Flushing
- Headache
- Nausea & vomiting
- Hypotension
- Anxiety
- Chest pain
- Dizziness
Adverse Effects

- Systemic hypotension & bleeding
  - Not reported in dose range of 5 to 50 ng/kg/min

- Avoid aerosolized PGI$_2$ during active pulmonary hemorrhage
Dose

- Aerosolized PGI$_2$ is initiated at doses of 5 to 50 ng/kg/min
- 0.5 mg strength for patients < 10 kg
- 1.5 mg strength for patients > 10 kg
- Pediatric – use actual body weight
- Adult – use predicted body weight
Discontinuation

- Wean slowly to reduce potential for rebound
- Abrupt withdrawal can cause rebound pulmonary vasoconstriction, acute $V_A/Q$ mismatch, hypoxemia, pulmonary hypertension, & right ventricular failure within 20 to 25 minutes
Toxicity

- No known toxic effects or toxic metabolites
- Reconstituted PGI$_2$ solution has a very alkaline pH (10.2-10.8) that may act as an irritant when inhaled
- Caution in patients with reactive airways disease
Procedure

- Determine PBW (for adult patients)
- Reconstitute epoprostenol with glycine buffer diluent as per guidelines
- Determine infusion rates of PGI$_2$ & normal saline
- Fill nebulizer with 8 ml (1 hour supply)
- Power nebulizer with O$_2$ at 2 L/min
Predicted Body Weights

- Male $50 + 2.3 \times (\text{height (in)} - 60)$
  Male $50 + 0.91 \times (\text{height (cm)} - 152.4)$

- Female $45.5 + 2.3 \times (\text{height (in)} - 60)$
  Female $45.5 + 0.91 \times (\text{height (cm)} - 152.4)$
## Infusion Rates

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>PGI₂ Dose (ng/kg/min)</th>
<th>Flolan® Infusion Rate (mL) = [(body weight x PGI₂ dose) x 60 min] / PGI₂ concentration</th>
<th>NS Infusion Rate (mL) = neb output (mL/h) – PGI₂ infusion rate</th>
<th>Flolan strength (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>10</td>
<td>0.24</td>
<td>7.76</td>
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<tr>
<td>8</td>
<td>10</td>
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<td>7.52</td>
<td>0.5</td>
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<td>30</td>
<td>1.2</td>
<td>6.8</td>
<td>1.5</td>
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<td>70</td>
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<tr>
<td>100</td>
<td>30</td>
<td>6.0</td>
<td>2.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Photosensitivity

- Prior to use, reconstituted solution must be protected from light & must be refrigerated if not used immediately.
- When reconstituted PGI₂ is stable for 8 hrs at room temp or 24 hrs with refrigeration.
- Must discard after 24 hrs.
- Change reconstituted solution & IV tubing Q24H.
- Change gel pack Q4H.
Ventilator Care

- Expired minute volume, ventilation pressures, patient-initiated triggering, FiO$_2$, & heated humidifier settings may vary due to nebulizer flow into circuit
- Glycine buffer makes aerosol sticky
- Change expiratory filters Q4H or sooner to prevent sticking of expiratory valve and auto PEEP
Manual Ventilation

- Flolan nebulizer can be added to manual resuscitator set up
- Ensure adequate functioning of expiratory valve on manual resuscitator
- Change manual resuscitator after use
Transport

- Determine volume of PGI$_2$ & volume of normal saline to obtain ordered dose
- Add to nebulizer to a total of 8 ml
- Nebulizer output is 8 ml/hour
- For inter-hospital or intra-hospital transports
Cost

- Cost $45/vial
- Per 24 hour $180
- Per 72 hour (average duration) $540
- Per year (2 pts/month) $12,960
Kingston General Hospital Experience

- To Pharmaceuticals & Therapeutics Committee in December 2005 (since delivery route not HPB approved)
- Implemented PGI$_2$ guidelines for adult patients in April 2006 in surgical suites, ICU, & cardiac surgical unit
- Revised guidelines in March 2008 to include pediatric patients
- Currently reviewing case reports of PGI$_2$ use in newborn patient population
Summary

- Use of inhaled PGI$_2$ is a promising therapy for the treatment of pulmonary hypertension & hypoxia of various origins
- Further studies are required to determine dose-responsiveness, optimal condition of utilization, and impact on survival
- The pursuit of its use requires the collaborative effort of respiratory therapists, nurses, physicians, and pharmacists


References


Questions?

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