

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

- PGI₂ 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 PGI₂ was first described in 1978 in canine experiments
- In most patients, the IV doses of PGI₂ required to decrease PA pressures induce systemic hypotension

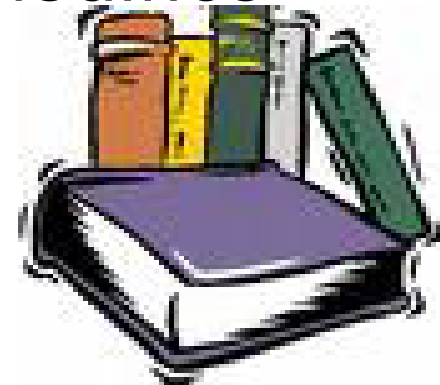


Inhaled Prostacyclin

- Welte and his colleagues (1993) reported that inhaled PGI₂ resulted in selective PA vasodilation in dogs
- Inhaled PGI₂ 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 PGI₂ by inhalation improves oxygenation and reduces PAP
- Decreases shunting while improving oxygenation
- Modulates vascular growth and modifies platelet function



Case Reports

- De Wet, et al. (2004) – prospective interventional study of 126 cardiothoracic surgical patients with pulmonary hypertension
- PGI₂ decreased mean PA pressures without altering mean arterial pressure
- There was a significant improvement in the PaO₂/FiO₂ ratio in patients with refractory hypoxemia



Case Reports



- Haché and her colleagues in Montreal (2001) performed a chart review of 27 patients who received inhaled PGI₂ over a one-year period
- Selective pulmonary vasodilation occurred in 78% of patients
- Improvement in PaO₂/FiO₂ ratio in 88%
- Concluded that inhaled PGI₂ can be useful in the treatment of patients with pulmonary hypertension & severe hypoxia

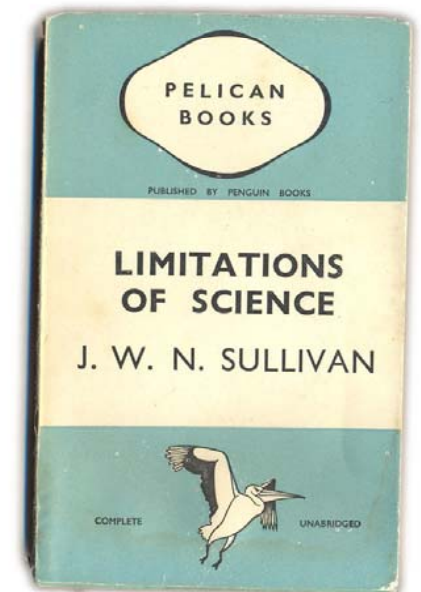
Evidence



- PGI₂ 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 PGI₂
- Incomplete data for some variables, such as PVR, wedge pressure, CVP





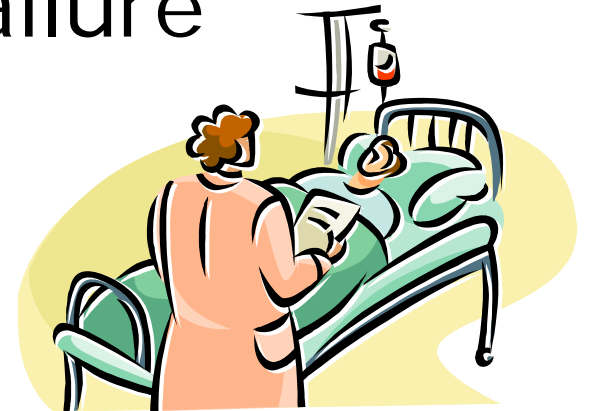
Inhaled Prostacyclin

- 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 PGI₂ during active pulmonary hemorrhage

Dose

- Aerosolized PGI₂ 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 PGI₂ 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

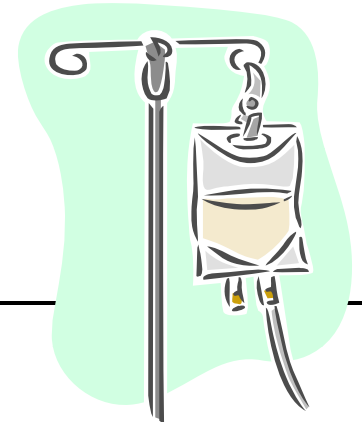
- Determine PBW (for adult patients)
- Reconstitute epoprostenol with glycine buffer diluent as per guidelines
- Determine infusion rates of PGI₂ & normal saline
- Fill nebulizer with 8 ml (1 hour supply)
- Power nebulizer with O₂ at 2 L/min

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



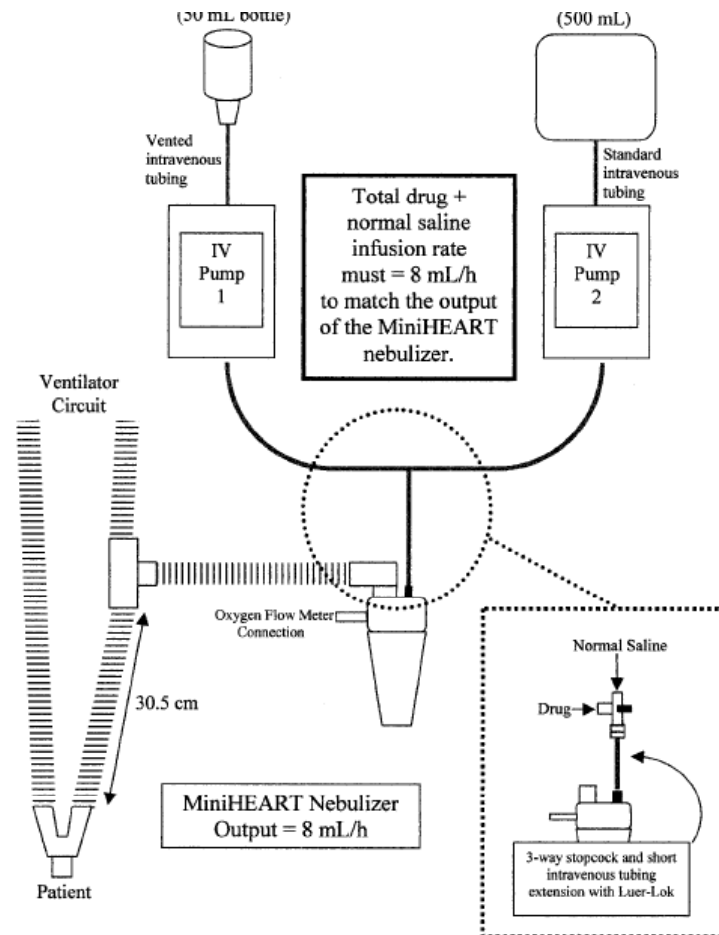
Weight (kg)	PGI ₂ Dose (ng/kg/min)	Flolan® Infusion Rate (mL) = [(body weight x PGI ₂ dose) x 60 min] / PGI ₂ concentration	NS Infusion Rate (mL) = neb output (mL/h) – PGI ₂ infusion rate	Flolan strength (mg)
4	10	0.24	7.76	0.5
8	10	0.48	7.52	0.5
20	30	1.2	6.8	1.5
70	50	7.0	1.0	1.5
100	30	6.0	2.0	1.5

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



Delivery System



Siobal, M. (2004). Aerosolized prostacyclins. *Respiratory Care* 49(6), 640-652

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 PGI₂ & 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 \$540
(average duration)
- Per year \$12,960
(2 pts/month)



Kingston General Hospital Experience

- To Pharmaceuticals & Therapeutics Committee in December 2005 (since delivery route not HPB approved)
- Implemented PGI₂ 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 PGI₂ use in newborn patient population

Summary

- Use of inhaled PGI₂ 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



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Questions?

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