Inhaled Prostacyclin (Epoprostenol)

Rationale:
- Prostacyclin (PGI₂) is a potent vasodilator that when given via inhalation is relatively selective for the pulmonary vasculature
- Whilst there are no studies demonstrating survival benefit favourable effects on pulmonary haemodynamics and V/Q matching have been demonstrated in ARDS, acute RV failure and pulmonary hypertension
- Data suggest that inhaled PGI₂ is equally efficacious as inhaled nitric oxide in reducing pulmonary vascular resistance, pulmonary artery pressure and improving V/Q matching
- Inhaled PGI₂ demonstrates an acceptable safety profile and cost

Indications:
- ARDS with refractory hypoxaemia
- Acute RV dysfunction / pulmonary hypertension post cardiac surgery
- Severe pulmonary arterial hypertension (vaso-reactivity test or treatment in responders)
- Discussion with the ICU Consultant is required prior to commencing PGI₂

Guidelines:
- PGI₂ is administered via a closed ventilator circuit through either a well-fitting naso-oral mask (for vasoreactivity testing) or endo-tracheal tube
- The limit of the dose / response relationship is not clearly defined and varies between individuals, therefore with the exception of vasoreactivity testing, inhaled PGI₂ should be commenced at the upper end of the dosing range and titrated to effect (improvement in cardiac output / pulmonary vascular resistance or V/Q matching)
  - Dose is based upon ideal body weight calculated from height (see table below). An initial dose of 30 ng/kg/min is recommended
  - The half-life of epoprostenol is 3-6 minutes, hence effect should be seen within 15 minutes of commencement of drug. If there is no clinical effect the drug should be discontinued
  - In responders the dose should be titrated to effect.
  - Maximal recommended dose is 50ng/kg/min
- PGI₂ (Epoprostenol) is presented as 500ug vials. This should be diluted into 50 ml of diluent provided to give a concentration of 10ug/ml
- At a concentration of 10ug/ml nebulisation rate (ml/hr) can be derived from height (cm) as follows:

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>150 – 159</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>160 – 169</td>
<td>3.6</td>
<td>7</td>
</tr>
<tr>
<td>170-179</td>
<td>4.2</td>
<td>8.4</td>
</tr>
<tr>
<td>180-189</td>
<td>4.8</td>
<td>9.6</td>
</tr>
<tr>
<td>&gt;190</td>
<td>5.4</td>
<td>10.8</td>
</tr>
</tbody>
</table>

- It is recommended that prior to cessation of therapy PGI₂ is slowly down-titrated to a dose of ≤ 10ng/kg/min to avoid rebound pulmonary hypertension
Drug Preparation:
- Using a 50ml BD syringe draw up 10ml of the diluent provided in the Folan kit (the second bottle of diluent is not required)
- Inject the 10ml of diluent into the drug vial and shake gentle to dissolve the powder, then aspirate all the solution into the 50ml BD syringe
- Return the 10ml from the 50ml syringe into the remaining 40ml of diluent, mix then aspirate 50ml into the DB syringe. The solution will now contain 10ug/ml Folan
- Using a drawing-up needle decant the 50ml from the BD syringe into the blue “Aerogen - For Continuous Nebulization” syringe
- Attach the Aerogen nebulisation tubing to the Aerogen syringe, screw the distal end into the Aerogen nebuliser then prime the line so fluid is entering the nebulisation chamber

Circuit Set-up:
- A filter should be placed in the expiratory limb prior to the ventilator flow sensor
  - Filters will become saturated with glycine and can create significant expiratory resistance, therefore they should be changed every 8 hours at nebulisation rates below 10ml/hr and every 4 hours at higher rates
- The Aerogen nebuliser should be placed in the inspiratory limb of the ventilator circuit immediately proximal to the humidification reservoir

- In this orientation the maximal nebulisation rate of 0.9% saline is 24ml/hr. Do not exceed this rate – if a higher dose is required a more concentrated solution should be used (500ug epoprostenol in 25ml diluent at half the flow rate)
- Check the Aerogen syringe line is primed and set the Aerogen syringe in a suitable syringe driver, confirm prescribed rate and commence delivery
• Turn the power on to the Aerogen controller, ensure this is connected to the nebuliser then press the blue button for three seconds to select continuous mode
• Check the nebulisation chamber:
  ◦ Ensure fluid is dripping into the chamber
    – This may appear to run dry at low flow rates as fluid is nebulised more rapidly than it is delivered. Aerosol should be visible with regular intermittent pauses.
    – The half-life of PGI₂ is 3-6 minutes so the chamber appearing dry is not a problem as long as fluid is regularly entering the chamber from the syringe. At flow rates of 3ml/hr a drop should enter the nebuliser every minute. Do not run flow rates < 3 ml/minute
  ◦ Ensure the chamber is not full (6ml) – if this occurs check
    – Nebuliser function (cables, connection, power)
    – Drug infusion rate is < 24ml/hr - if needed use of a more concentrated solution
• Expiratory gas should be scavenged using techniques appropriate to the ventilator

Considerations:
• Check nebuliser function if there is unexpected hypoxia or pulmonary hypertension
• The nebuliser will need to be reset after transient power loss
• It is recommended by the manufacturer the nebuliser be replaced after three days of continuous use (or 7 days of intermittent use)
• Epoprostenol is stable in solution for 8 hours (or 48 if refrigerated), syringes should be reconstituted as required and changed 8 hourly
• Epoprostenol solution should be protected from light
• Reconstituted epoprostenol has a pH of 10.2-10.8 and can result in coughing and bronchospasm. Tracheitis is rare.
• Tachyphalaxis is not reported
• Although systemic PGI₂ inhibits platelets function in vitro this has not found to be significant in vivo with inhaled PGI₂
• If there is need for pulmonary vasodilator therapy beyond a week consider oral sildenafil or intermittent nebulised iloprost.