Inhaled Prostacyclin (PGI2 / Epoprostenol) - Full Clinical Guideline

Reference No: CG-T/2014/211

Rationale:

- Prostacyclin (PGI_2) is a potent vasodilator that when given via inhalation is relatively selective for the pulmonary vasculature.
- The available evidence is inadequate to demonstrate a survival benefit. However, favourable effects on pulmonary haemodynamics and V/Q matching have been demonstrated in ARDS, acute RV failure and pulmonary hypertension.
- The available evidence suggests that inhaled PGI_2 is non-inferior to inhaled nitric oxide in reducing pulmonary vascular resistance, pulmonary arterial pressure, and improving V/Q matching.
- Inhaled PGI_2 demonstrates an acceptable safety profile and cost.

Indication (use should be discussed with the ICU Consultant prior to commencing PGI_2):

- ARDS with refractory hypoxaemia, secondary to infection with SARS-CoV-2

Dosing:

- The dose-response relationship is not clearly defined and displays high inter-individual variability. Therefore dosing should be commenced at the upper end of the dosing range and titrated to effect (i.e. improvement in cardiac output, pulmonary vascular resistance, or V/Q matching).
- Dosages in the published literature tend to fall in the range of 10-50 nanograms/Kg/min, based on ideal body weight (IBW).
- IBW is calculated as follows:
    - Males: Height (cm) - 100
    - Females: Height (cm) - 105
- An initial dose of 30 nanograms/Kg/min based on IBW is recommended
- An effect should be seen within 15 minutes of commencement. If there is no clinical effect at 15 minutes, the drug should be discontinued.
- In responders, the dose should be titrated to effect, up to a maximum of 50 nanograms/Kg/min based on IBW.
- Treatment in responders should not be stopped suddenly in order to avoid rebound pulmonary hypertension. Reduce the dose in 10 nanograms/Kg/min intervals every two hours until stopped.
- At a concentration of 20,000 nanograms/mL , the table below gives the required flow rate (mL/h) to provide the desired dose according to the patient's height:
    - The maximum stated flow rate for the Aerogen® Solo is 12mL/h. Rates above this value may lead to accumulation of drug in the reservoir. Values above this rate are capped at 12mL.
        - 12 mL/h maximum is based on the manufacturer's stated minimum nebulisation rate of 0.2 mL/min. There may be variations in this rate between individual nebuliser devices and for different drugs – in some literature the mean minimum nebulisation rate for epoprostenol when tested was ≈20mL/h. Thus, in very tall patients who are responding to treatment, an increase in the flow rate to >12mL/h can be trialled, but the reservoir should be monitored in case of accumulation.

Epoprostenol Concentration: 20,000 nanograms/mL (0.5mg vial in 25mL solvent)						
Height (cm)		**Dose (nanograms/Kg/min)**				
Male	**Female**	**≈10**	**≈20**	**≈30**	**≈40**	**≈50**
<150	<155	1.4	2.7	4.1	5.4	6.8
150-159	155-164	1.5	3.3	5.0	6.6	8.3
160-169	165-174	1.8	3.9	5.9	7.8	9.8
170-179	175-184	2.1	4.5	6.8	9.0	11.3
180-189	185-194	2.4	5.1	7.7	10.2	12.0*
>190	>195	2.7	5.7	8.6	11.4	12.0*
		Values above give the required flow rate (mL/h). Values followed by * have been capped at this rate.				

Preparation:

NB: the Flolan® product is supplied with a 50mL solvent vial. This solvent is made up of glycine, sodium chloride, sodium hydroxide and water for injection. As such, this solvent should *not* be substituted for an alternative diluent (NaCl 0.9% / WFI) as they are *not* identical.

1. Using a BD syringe, draw up 10mL of the provided solvent and use this to reconstitute the vial containing the Flolan® (epoprostenol) powder, then shake gently until the powder is dissolved.
2. Draw up the resulting solution into a 50mL BD syringe.
3. Make up to 25mL using the remaining solvent, then mix thoroughly. This solution has a concentration of 20,000 nanograms/mL.
4. Transfer this solution from the BD syringe into the blue 'Aerogen® Solo Continuous Nebulisation Syringe'.

Circuit Setup:

- 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 flow rates <10 mL/h and every 4 hours at higher rates.
- The Aerogen® Solo device should be placed in the inspiratory limb of the ventilator circuit immediately proximal to the humidification reservoir (see photo below).

- Attach the Aerogen® syringe to the tubing set provided ('Aerogen Solo Continuous Nebulisation Tube Set'), then prime the line (max. 3.65mL), before unplugging the silicone plug on the Aerogen® Solo nebuliser and screwing the line into the top of the nebuliser.
- Set the Aerogen® syringe into a suitable syringe driver, check the prescribed rate and commence delivery.
- Turn on the power to the Aerogen® controller and ensure the nebuliser cable is firmly connected to both the controller and nebuliser devices.

- Press and hold the blue power on/off button on the controller for 3 seconds to start continuous mode. The green continuous mode indicator light will be on.
- Once on, continue to monitor the nebulisation chamber:
    - Ensure fluid is dripping into the chamber:
        - It may appear to run dry, especially at low flow rates (<3mL/h) where the fluid will be nebulised more rapidly than it is delivered. Aerosol should be visible with regular intermittent pauses.
    - Ensure the chamber is not full (6mL volume) – if this occurs, check:
        - Nebuliser is correctly set up and functioning (cables, connection, power)
        - Flow rate is ≤12 mL/h
- Expiratory gas should be scavenged using techniques appropriate to the ventilator
- If the syringe needs to be replaced during use (even when empty), turn off the syringe pump and disconnect the nebuliser end of the tube set first. Failure to do this may result in primed medication in the tube flowing into the nebuliser reservoir.

Considerations:

- Check nebuliser function if there is unexpected hypoxia or pulmonary hypertension
- The nebuliser will need to be reset after transient power loss
- The Aerogen® Solo and nebulisation set should be replaced after a maximum of 7 days of continuous use
- Flolan® is stable in solution for up to 72h at up to 25°C. It is light sensitive, so should be protected from light.
- Flolan® solution is alkaline (pH: 12) and can result in coughing and bronchospasm. Tracheitis is rare.
- Tachyphylaxis has not been reported
- PGI_2 inhibits platelet function *in vitro*, and increased bleeding is common with systemic administration. However, this is not significant with inhaled administration.
- If there is need for pulmonary vasodilator therapy beyond a week consider oral sildenafil or intermittent nebulised iloprost.

Useful References:

Aerogen® Solo instruction manual: available at: https://u5i6p3z8.stackpathcdn.com/wp-content/uploads/2019/11/30-354-Rev-T-Aerogen-Solo-System-UK_WEB.pdf

Documentation Control

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