Inhaled Epoprostenol

Purpose
The purpose of this guideline is to achieve the following:
- Establish the safe and effective use of inhaled epoprostenol (PGI2, Flolan) for neonates and pediatrics.
- Serve as an educational tool to provide the appropriate indications for administration, management and monitoring of inhaled epoprostenol for physicians, pharmacists, nurses and respiratory care practitioners.

Description
Epoprostenol is a synthetic prostacyclin that mimics the actions of natural prostacyclins. Prostacyclin is a substance produced by vascular endothelium that stimulates adenyl cyclase in vascular smooth muscle cells resulting in vasodilatation, antiplatelet aggregation and cytoprotective effects. Epoprostenol is FDA approved for the treatment of primary pulmonary hypertension by intravenous infusion, but its use is limited by adverse effects including systemic hypotension and worsening of intrapulmonary shunt. When administered by IV infusion, epoprostenol is a potent vasodilator of all vascular beds. Epoprostenol administered by inhaled aerosol selectively dilates the pulmonary vascular bed. Hence it reduces pulmonary hypertension and improves oxygenation by matching perfusion and ventilation of lung units.

Epoprostenol must be reconstituted. The reconstituted solution has a very alkaline PH (10.2-10.8) No safety data are available for neonates related to the safety of administering the alkaline diluents utilized with prostacyclin aerosol.

The desired therapeutic effects of aerosolized epoprostenol are:
- In oxygenation by improving ventilation to perfusion matching as a result of redistribution of pulmonary blood flow to ventilated areas of the lung.
- A reduction in pulmonary artery pressure, pulmonary vascular resistance and right ventricular afterload.

Indications
Inhaled prostacyclin therapy is indicated with:
- Documented PPHTN on echocardiogram without structural disease and/or pre and postductal oxygen saturation gradient difference of 10%.
- Oxygen index (Paw x FIO2 x 100/PAO2) approaching or >25 on
optimal ventilator settings.
- Clinical evidence of hypoxic respiratory failure.
- Patients with respiratory failure per physician’s discretions.

Inhaled prostacyclin may be used in conjunction with or in place of Nitric Oxide.

**Contraindications**

Inhaled prostacyclins should not be used in the treatment of patients known to be dependent on right to left shunting of blood.

**Complications**

Potential complications include but are not limited to the following:
- Rebound hypoxemia and pulmonary hypertension from abrupt withdrawal.
- Systemic hypotension
- Bleeding (decrease in platelet aggregation)
- Tracheitis has been reported in animal studies due to the high alkalinity of the solution.

Any complications should be reported to the ICU faculty.

**Accountability**

Respiratory Care services with the assistance of nursing are responsible for the setup and administration of aerosolized epoprostenol via the Aeroneb Solo System and Medfusion 4000 Syringe pump. Infusion pump flow rate is adjusted to deliver prostacyclin solution that will result in a desired aerosolized dose per kilogram per minute.

A double check will be performed and documented at the initiation of therapy and with each change in syringe. The double check will be completed between two of the following Respiratory Care Practitioner, Nurse or Nurse Practitioner.

**Procedure**

**Guidelines for Initiating Therapy**

1. Epoprostenol for inhalation use is restricted to neonatology and PICU attending.

2. This modality may only be administered in a critical care setting. These areas include ISCU and PICU.

3. Prior to prostacyclin administration the following clinical/physiological conditions should be assessed.
   a. Minimize asynchronous or ineffective ventilation.
b. Restore blood volume if indicated based on history, hemorrhage, ante partum hemorrhage, HR, etc.

c. Initiate inotrope therapy if blood pressure is not at or above the 50th percentile. Consider administration of Milrinone.

d. Assess echo for anatomy, contractility and ductal shunting.

4. Blood pressure should be assessed prior to starting the medication. The patient’s blood pressure should be taken every 15 minutes for the first hour after starting the medication. Blood pressure should be reassessed after every dose change.

5. Patients that show ≥ 20% increase in PaO2 or other physiological metrics defined by the responsible physician will be considered responders to treatment. Patient response should be apparent within 10 minutes of initiating treatment.

6. The need to continue therapy should be reassessed every 24 hours and updated in physician’s notes.

7. The NNP, PA or Neonatology fellow’s order for aerosolized epoprostenol must be approved by Neonatology or PICU attending.

8. Flolan will be weight adjusted every Monday.

**Physician Order Set**

**Continuous Nebulized Epoprostenol (Flolan®, Prostacyclin)**

A. Pharmacy Orders

- Epoprostenol 50 ml X 3 syringes
  - 3 mcg/ml
  - 15 mcg/ml
  - 30 mcg/ml

- Dispense in 60 ml blue AeroNeb syringes with blue AeroNeb tubing sets attached and primed

- Refrigerate syringes until immediately before use; protect from light

B. Medication Administration

- Epoprostenol to be administered using Medfusion Syringe Pump

- Initial dose ________ MCG/kg/min via AeroNeb Solo Nebulizer
(Initial starting dose: 0.05 MCG/kg/min; range: 0.01 – 0.1 MCG/kg/min)

- Titration increment: 0.01 MCG/kg/min every ______ (30 minutes)
- Change medication syringes and tubing every 8 hours

C. Medication Administration & Storage Considerations

- Room temperature expiration is 8 hours strictly; may be stored up to 48 hours under refrigeration
- Use AeroNeb syringes and tubing sets ONLY to avoid inadvertent IV administration
- Confirm all tubing set connections between syringe and nebulizer with every syringe and tubing set change
- DOUBLE-CHECK Medfusion Pump settings with a second provider at the start of therapy and with each syringe and tubing change.

Pharmacy Order Verification

Before an order can be verified in EPIC the verifying Pharmacist will confirm that the patient is located in an ICU setting. If the patient is not located in an approved setting the pharmacist will contact the physician and inform them that the patient cannot receive inhaled epoprostenol in the non-permitted patient care area.

All orders for inhaled epoprostenol will require **DUAL VERIFICATION** in EPIC when approving the orders (Dual verification requires two pharmacists to verify the order before it is released)

Medication Preparation and Dispensing

Pharmacy will reconstitute epoprostenol with sterile diluents to approved pediatric concentrations based on patient’s weight.

Pharmacy will prepare and dispense ONLY epoprostenol in ready to infuse 60ml blue Aeroneb syringes. The tubing will be supplied by pharmacy and sent up with the syringe but not attached to it.

At the time of dispensing the Aeroneb syringes of epoprostenol must be labeled with the patient specific EPIC label, a High Alert label, the Inhalation Only Label, The Return Unused Syringe to Pharmacy Label and an expiration date (Expiration dating is 24 hours only)
Concentration dispensed will be determined by the following table:

<table>
<thead>
<tr>
<th>Wt range (kg)</th>
<th>Standard Concentration (mcg/ml)</th>
<th>Starting dose mcg/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 3</td>
<td>3</td>
<td>0.05</td>
</tr>
<tr>
<td>3.1 - 6</td>
<td>15</td>
<td>0.05</td>
</tr>
<tr>
<td>≥6</td>
<td>30</td>
<td>0.05</td>
</tr>
</tbody>
</table>

- Pharmacy will dispense three syringes per 24 hours.
- All syringes will be refrigerated in the medication fridge.
- Refrigerated stability will be 48 hours; however the medication will be replaced every 24 hours.
- Refrigerate syringes until immediately before use; protect from light.

**Medication Administration**

Administer according to procedure guideline and drip sheet.

**Changing/Weaning the dose**

- A physicians order is required to change the dose.
- Do **NOT** change the dose by more than 0.01 mcg/kg/min every 30 minutes.
- To wean decrease the dose by 0.01mcg/kg/min at a time.
- Monitor the patient for rebound hypoxemia and pulmonary hypertension.

**Charting**

The epoprostenol dose should be charted in EMR, MAR and on the drip sheet. Charting will occur every hour and upon any dose change or change out of syringe. Any adverse reactions should also be charted.
References

Established by San Francisco General Hospital, UCSF
Policy based on the following references

- Siobal MS, Hess DR. Are inhaled vasodilators useful in acute lung


• Siobal MS, Kallet RH, Pittet JF, Warnecke EL, Kraemer RW, Venkayya RV, Tang JF. Description and evaluation of a delivery system for aerosolized prostacyclin. Respir Care.

• Kelly L, Porta NFM, et el, Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. J. Pediatrics 2002, Dec. 830-832

• Bindl L, Fahnenstich H, Aerosolized prostacyclin for pulmonary hypertension in neonates Archives of Disease in Childhood 1994; 71: F214-F216
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