Intravenous Epoprostenol – Adult – Inpatient Clinical Practice Guideline

Table of Contents

EXECUTIVE SUMMARY ........................................................................................................... 2
DEFINITIONS ............................................................................................................................ 2
SCOPE ...................................................................................................................................... 4
METHODOLOGY ...................................................................................................................... 4
INTRODUCTION ....................................................................................................................... 5
RECOMMENDATIONS .............................................................................................................. 6
UW HEALTH IMPLEMENTATION ............................................................................................. 8
REFERENCES .......................................................................................................................... 9

Note: Active Table of Contents -- Click to follow link

CPG Contact for Changes: 
Name: Philip Trapskin, PharmD, BCPS  
Phone Number: 608-263-1328  
Email Address: ptrapskin@uwhealth.org 

CPG Contact for Content: 
Name: Cindy Gaston, PharmD, BCPS  
Phone Number: 608-265-8161  
Email Address: cgaston@uwhealth.org

Guideline Author: Matt Willenborg, PharmD, BCPS

Coordinating Team Members: 
C. Gaston, PharmD, BCPS

Review Individuals/Bodies: 
J. Runo, MD; D. Dalsing, MSN, RN; Anna Krupp, MSN, RN, CCRN; M. Pietruszka, PharmD, BCPS, AAHIVP, CNSC

Committee Approvals/Dates: 
Original approval date: October 2006  
Pharmacy & Therapeutics Committee: September 2015

Release Date: September 2015

Next Review Date: September 2018
Executive Summary
Guideline Overview
Intravenous (IV) epoprostenol is a high risk medication administered by continuous infusion for the treatment of idiopathic or heritable pulmonary arterial hypertension and pulmonary arterial hypertension associated with scleroderma spectrum of diseases. The purpose of this guideline is to provide recommendations for the proper utilization and monitoring of intravenous epoprostenol. This document provides guidance for drug-specific procedures related to inpatient handling and administration of intravenous epoprostenol and provides considerations related to admission and discharge procedures for patients receiving intravenous epoprostenol.

Definitions
1. Pulmonary arterial hypertension (PAH) is defined by a mean pulmonary artery pressure >25 mm Hg; pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure ≤ 15 mm Hg; and pulmonary vascular resistance > 3 Wood units.\(^1,2\)
2. Six minute walk distance (6MWD) is a quantitative value of the total distance a patient is able to walk in a six minute period. This test is used to evaluate changes in exercise capacity.
3. World Health Organization Functional Class (WHO FC) is a means of classifying disease severity in PAH developed by the World Health Organization and modified after the New York Heart Association functional classification according to level of function and associated symptoms. Increasing WHO FC reflects more severe symptoms and greater restriction in activity.

Key Practice Recommendations
1. For treatment naive PAH patients with WHO FC III symptoms who have evidence of rapid progression of their disease, or other markers of a poor clinical prognosis, consider initial treatment with a parenteral prostanoid. More specifically in these patients: we suggest continuous IV epoprostenol to improve functional class, improve 6MWD, and improve cardiopulmonary hemodynamics. (Class I Level C)

2. For PAH patients in WHO FC III who have evidence of progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents, consider the addition of a parenteral or inhaled prostanoid. More specifically in these patients: we suggest IV epoprostenol to improve WHO FC, improve 6MWD, and improve cardiopulmonary hemodynamics. (Class I Level C)

3. For treatment naive PAH patients in WHO FC IV, consider initiation of monotherapy with a parenteral prostanoid agent. More specifically in these patients: we suggest continuous IV epoprostenol to improve WHO FC improve 6MWD, and improve cardiopulmonary hemodynamics. (Class I, Level C)

4. In PAH patients initiating therapy with IV epoprostenol, we recommend against the routine simultaneous initiation of bosentan. (Class III, Level C)

5. In patients with congestive heart failure due to severe left ventricular systolic dysfunction (NHYA Class III/IV) the use of IV epoprostenol is not recommended due to lack of benefit. (Class III, Level C)
Companion Documents
1. Inhaled Epoprostenol in Adult and Pediatric Patients Clinical Practice Guideline
2. Intravenous Administration of Formulary Medications – Adult Clinical Practice Guideline

Pertinent UW Health Policies & Procedures
1. Nursing Policy 10.21 IV Epoprostenol Administration (Adult and Pediatric)
2. Epoprostenol Pharmacy Operating Procedure
3. Administrative Policy 8.17 Administration of Medications

Patient Resources
1. Health Facts for You - Pulmonary Hypertension Medications – prostacyclin analogs
2. Health Facts for You – Pulmonary Hypertension
Scope
Intravenous epoprostenol dosing and management for patients with WHO FC III-IV pulmonary arterial hypertension newly initiated on intravenous epoprostenol during hospitalization and patients whose existing intravenous epoprostenol therapy is being continued during their hospital stay.

Intended Users:
This document is intended to be used by physicians, advanced practice providers, registered nurses, and pharmacists involved with the care of patients receiving intravenous epoprostenol therapy.

Target Population:
Patients with WHO FC III-IV pulmonary arterial hypertension who are being newly initiated on intravenous epoprostenol during hospitalization and patients whose existing epoprostenol therapy is being continued during their hospital stay.

Interventions and Practices Considered:
This document focuses on the proper initiation and titration of intravenous epoprostenol in the hospital based on goal therapeutic parameters and titration-limiting side effects. This guideline also contains information related to transitioning a patient from their outpatient intravenous epoprostenol supply to inpatient epoprostenol.

Major Outcomes Considered:
Patients receiving IV epoprostenol therapy should experience significant improvement in clinical symptoms of pulmonary arterial hypertension measured by improvement in WHO FC, improvement in exercise capacity measured with a 6MWD, and improvement of cardiopulmonary hemodynamics. Specific hemodynamic effects include increased cardiac index and stroke volume; and decreased pulmonary vascular resistance, total pulmonary resistance, mean systemic arterial pressure, and pulmonary artery pressure.3

Methodology
A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology (Figure 1) has been used to assess the Quality and Strength of the Evidence in this Clinical Practice Guideline.4

A literature search was performed using the PUBMED database with search terms “epoprostenol”, “intravenous epoprostenol”, “pulmonary arterial hypertension”. Articles were included if they provided information on initiation of epoprostenol therapy, epoprostenol dosing, administration and monitoring, and discharge considerations.
**Introduction**

Pulmonary arterial hypertension (PAH) is a progressive syndrome in which fibrotic and proliferative changes in pulmonary arteries lead to increased pulmonary vascular resistance, right heart failure, and eventual death.\(^5\) The incidence of PAH is 5-52 cases per million people.\(^5\) Patients left untreated have an estimated mean survival of 2.8 years from diagnosis. With treatment, current survival for patients with PAH is 85%, 68%, 57%, and 49% at 1, 3, 5, and 7 years from diagnosis, respectively.\(^9,10\)

Epoprostenol, a potent vasodilator and platelet inhibitor, is used to treat symptoms, improve hemodynamics, and improve exercise capacity in patients with WHO FC III-IV PAH.\(^11,12\) Epoprostenol has also been shown to improve survival in patients with severe idiopathic PAH.\(^12-14\)
The in-vivo half-life of IV epoprostenol is estimated to be 3-5 minutes. Epoprostenol should be administered intravenously via a continuous infusion through a dedicated central venous catheter. Any interruption of the infusion can lead to life-threatening hemodynamic compromise from rebound pulmonary arterial hypertension. To prevent interruptions, epoprostenol is administered via computerized ambulatory drug delivery (CADD) pumps on an outpatient basis which allow drug to be run for twenty-four hours without refilling the drug reservoir. Inpatient use of epoprostenol at the University of Wisconsin Hospital involves the use of standard hospital infusion pumps. Most complications with intravenous epoprostenol administration result from delivery system malfunctions.

These recommendations aim to assist in converting patients from their home infusion pumps to hospital supplies without interruption of the infusion. The guidelines also serve to aid in initiating and maintaining therapy in epoprostenol naive patients.

**Recommendations**

1. Qualifying for initiation of intravenous epoprostenol
   1.1. For treatment naive PAH patients with WHO FC III symptoms who have evidence of rapid progression of their disease, or other markers of a poor clinical prognosis, consider initial treatment with epoprostenol. (Class I, Level B)
   1.2. For PAH patients in WHO FC III who have evidence of progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents, consider the addition of IV epoprostenol. (Class I, Level B)
   For treatment naive PAH patients in WHO FC IV, consider initiation of monotherapy with a parenteral prostanoïd agent. More specifically in these patients: we suggest continuous IV epoprostenol to improve WHO FC improve 6MWD, and improve cardiopulmonary hemodynamics. (Class I, Level B)
   1.2.1. A referral form for Veletri® is available at [http://www.accredo.com/sitecore/media/Accredo/Referral%20Form%20PDFs/Veletri.pdf](http://www.accredo.com/sitecore/media/Accredo/Referral%20Form%20PDFs/Veletri.pdf)
   1.2.2. The Advanced Pulmonary attending physician is responsible for submitting the referral prior to initiation of therapy. (Class I, Level C)
   1.2.3. Complete insurance screening prior to admission to the hospital for initiation of therapy. (Class I, Level C)
   1.2.4. Intravenous epoprostenol should not be used in the case of denial by Accredo Therapeutics after receiving the completed Pulmonary Arterial Hypertension Referral form for home epoprostenol therapy. (Class III, Level C)

2. In PAH patients initiating therapy with IV epoprostenol, routine simultaneous initiation of bosentan is not recommended. (Class III, Level C)

3. In patients with congestive heart failure due to severe left ventricular systolic dysfunction (NHYA Class III/IV) the use of IV epoprostenol is not recommended due to lack of benefit. (Class III, Level C)

4. Continuation of outpatient IV epoprostenol therapy
   4.1. Patients admitted to UW Hospital on chronic epoprostenol IV therapy should continue treatment with epoprostenol upon arrival to the inpatient care unit without interruption of the medication. (Class 1, Level C)
   4.1.1. Due to the short half-life of IV epoprostenol (3-5 minutes), any interruption of continuous epoprostenol therapy can result in rapid onset of PAH symptoms causing dyspnea, decreased exercise tolerance, and right heart failure.
4.1.2. Patients should be transitioned from the patient’s outpatient IV epoprostenol (Flolan® or Veletri®) via outpatient infusion pumps to UWHC epoprostenol (Veletri®) and infused using Alaris pumps. (Class I, Level C)

4.2. Hemodynamically stable patients may be treated outside of an intensive care in a patient care area with staff trained to manage IV epoprostenol (e.g., D6/5 IMC). This includes both stable dose and titration of dose (both increase and decrease) on D65 IMC. (Class IIb, Level C)

4.3. Patients receiving IV epoprostenol should be followed by the Advanced Pulmonary Service while hospitalized. The admitting service is responsible for notifying the Advanced Pulmonary Service of the patient’s admission and inpatient location. (Class I, Level C)

5. Dosing and titration of IV epoprostenol
5.1. A reasonable starting dose for patients newly initiated on IV epoprostenol is 1-2 ng/kg/min. (Class I, Level B)

5.2. Titrate the dose as ordered by the Advanced Pulmonary Service prescriber until a therapeutic dose is reached or until dose-limiting side effects occur (Table 2). (Class I, Level C)
5.2.1. If side effects occur, the Advanced Pulmonary Service prescribing clinician should be contacted. (Class I, Level C)
5.2.2. Increase the IV epoprostenol dose if PAH symptoms persist. Increase the infusion by 1-2 ng/kg/min at intervals sufficient to allow assessment of clinical response; these intervals should be no shorter than 15 minutes. (Class I, Level B)

Table 2: Common side effects of epoprostenol initiation and dose escalation (without regard to concomitant therapies)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>58</td>
</tr>
<tr>
<td>Headache</td>
<td>49</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>32</td>
</tr>
<tr>
<td>Hypotension</td>
<td>16</td>
</tr>
<tr>
<td>Anxiety, nervousness, agitation</td>
<td>11</td>
</tr>
<tr>
<td>Chest pain</td>
<td>11</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnea, back pain</td>
<td>2</td>
</tr>
<tr>
<td>Sweating, dyspepsia, hypesthesia/paresthesia, tachycardia</td>
<td>1</td>
</tr>
</tbody>
</table>

5.3. When continuing home epoprostenol therapy as an inpatient, the patient’s epoprostenol specific dosing weight should be used for dosing IV epoprostenol regardless of actual body weight. All titration must be dosed based on epoprostenol specific dose weight. (Class I, Level C)

6. Patients on IV epoprostenol should be closely monitored
6.1. Continuous evaluation of pulmonary function, including oxygen saturation and increased dyspnea. (Class I, Level C)
6.2. All patients on epoprostenol should have blood pressure, heart rate, and oxygen saturation recorded at least every 4 hours. (Class I, Level C)

6.3. Additional hemodynamic monitoring may be required for unstable patients and patients that are actively being titrated on epoprostenol (e.g., cardiac index, peripheral vascular resistance, total pulmonary resistance, mean pulmonary arterial pressure and stroke volume). (Class I, Level C)

6.3.1. Continuous monitoring for changes in non-respiratory PAH symptoms including chest pain, fatigue, syncope and peripheral edema. (Class I, Level C)

6.3.2. Continuous monitoring for dose-limiting side effects including hypotension, flushing, headache, nausea/vomiting and diarrhea. (Class I, Level C)

6.3.3. Systemic inflammatory response monitoring for catheter related infection.

6.4. Patients on IV epoprostenol therapy should be closely monitored for side effects. Patients most frequently experience side effects with initiation and escalation of epoprostenol dose. The most frequent side effects in this case are flushing, headache, nausea/vomiting and hypotension (Table 2). The most frequent side effects for patients on chronic therapy include jaw pain, flushing, headache, myalgias and diarrhea. Both IV epoprostenol preparations (Veletri® and Flolan®) have similar adverse effect profiles.23,24 (Class I, Level C)

UW Health Implementation

Potential Benefits/harms:
- Adoption of a standardized guideline for intravenous epoprostenol infusion optimizes patient safety and transitions of care.
- Intravenous epoprostenol therapy provides improved patient survival, diminishes symptoms of pulmonary arterial hypertension and improves patient quality of life for patients with WHO Class III-IV pulmonary arterial hypertension.
- Abrupt discontinuation of epoprostenol therapy may result in worsening of pulmonary arterial hypertension symptoms and could lead to significant hemodynamic compromise and death.
- Intravenous line or catheter infections are possible with intravenous epoprostenol infusion. Sepsis was reported at a rate of 0.3 infections per patient per year in patients receiving intravenous epoprostenol.16
- Improper transitions from a patient's home infusion pump to inpatient infusion pumps may lead to bolus administration of epoprostenol.
- Transitioning from outpatient epoprostenol therapy to inpatient epoprostenol therapy may require a change of epoprostenol concentration. Improper conversion could lead to overdosage or underdosage.

Qualifying Statements
The recommendations for selecting patients to be started on intravenous epoprostenol in the document represent current guideline recommendations. This guideline should be used in conjunction with the Epoprostenol Pharmacy Operating Procedure and Nursing Policy 10.21 IV Epoprostenol Administration (Adult and Pediatric). When evidence is absent or insufficient to provide evidence-based guideline recommendation statements, the best expert consensus statements were included.

Implementation Plan/Tools
1. Guideline will be housed on U-Connect in a dedicated folder for CPGs.
2. Links to this guideline will be updated and/or added in appropriate Health Link or equivalent tools, including:

3. Ordering IV epoprostenol in Health Link

3.1. Enter order for IV epoprostenol 500 mcg/100 mL for epoprostenol naïve patients and patients on chronic therapy with a low infusion rate.

3.2. A higher concentration 1500 mcg/100 mL can be considered for patients receiving chronic outpatient therapy at a high infusion rate.

3.3. The dose of IV epoprostenol must be ordered in ng/kg/min.

3.4. Dosing of IV epoprostenol is based on the patient’s drug-specific weight and must be documented in the administration instruction order.

3.5. The pharmacist will initially order two bags of IV epoprostenol. One for administration and a back-up bag to be kept in the refrigerator.

3.5.1. An additional bag of IV epoprostenol will be maintained in the refrigerator on the patient care area at all times. Refrigerated bags of epoprostenol (Veletri®) can be stored for up to 7 days and administered over 24 to 48 hours depending on the epoprostenol concentration.

3.5.2. Nursing staff will order additional epoprostenol bags in Health Link. The nurses will order a bag to ensure the next scheduled bag is prepared and on the unit approximately two hours prior to the anticipated hang time.

Disclaimer

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

References


