Options in Action: A Case-Based Approach to Pulmonary Hypertension

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Conflict of Interest

- No conflicts of interest to disclose

Objectives

- Describe key elements to ensure safe and effective use of injectable agents to manage pulmonary hypertension
- List steps involved in transitioning a patient from hospital to home

Additional Goals

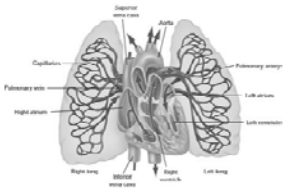
- Review differences between injectable prostacyclin therapies
- Recognize potential complications associated with preparation and administration

DW: Presents to Hospital

- **Chief Complaint**: Shortness of breath and lower extremity edema x 2 days
- **History of Present Illness**: DW is a 51 year old F with a past medical history significant for idiopathic pulmonary hypertension with symptoms of right heart failure. She presents to the ED with shortness of breath with minimal exertion and also notes lower extremity edema. She denies fever or other infectious symptoms.
- **Past Medical History:**
  Idiopathic pulmonary hypertension
  Diabetes mellitus
- **Medications:**
  –Metformin 1000mg BID
  –Sildenafil 20 mg q8h
  –Digoxin 125mcg daily
  –Furosemide 40mg daily

Pulmonary Hypertension

- Pulmonary hypertension is a syndrome resulting in increased blood pressure in the pulmonary arteries which eventually leads to right sided heart failure
- Hemodynamic definition: Mean pulmonary artery pressure >25mmHg with pulmonary capillary wedge pressure ≤15mmHg



http://www.hwcrc.org/Health/Disease/circulatory%20system.htm

WHO Classification

I. *Primary* Pulmonary Arterial Hypertension
- Idiopathic, familial, connective tissue disorders, HIV, portal hypertension, toxins, etc

II. Associated with left heart disease

III. Associated with lung disease
- COPD, interstitial lung disease, etc

IV. Chronic thrombotic or embolic disease

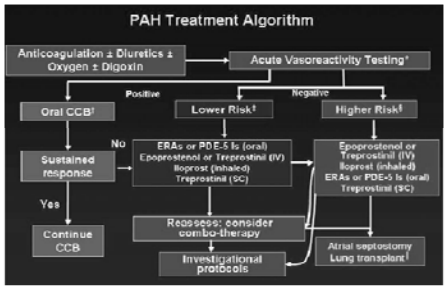
V. Miscellaneous
- Sarcoidosis, compression of pulmonary vessels, etc

Pulmonary Hypertension

- Approximately 15% mortality within 1 yr on modern therapy[1]
- Predictors of a poor prognosis:
  - Advanced functional class (NYHA Functional classes)
  - Measured by 6-minute walk test (<300m)
  - Significant right ventricular dysfunction or evidence of RV failure
  - Elevated brain natriuretic peptide (BNP)
  - Underlying diagnosis of scleroderma spectrum of diseases
- Hemodynamic measurements
  - High right atrial pressure >20mmHg
  - Low cardiac index <2 L/min/m^2

JACC 2009;53:1573–619

Treatment Algorithm



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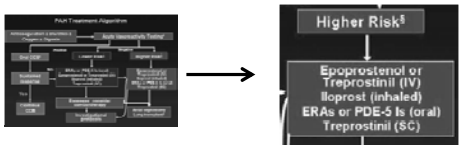
DW: Symptoms and Prognosis

- NYHA Functional Class –III (symptoms with minimal exertion)
- 6 minute walk test: 122meters (reduced, high risk)
- Right heart catheterization
  - Right atrial pressure ~30mmHg (elevated, high risk)
  - Cardiac Index ~1.8 (reduced, high risk)
  - Pulmonary capillary wedge pressure ~12mmHg (normal)
- Patient candidate for injectable Prostacyclin therapy



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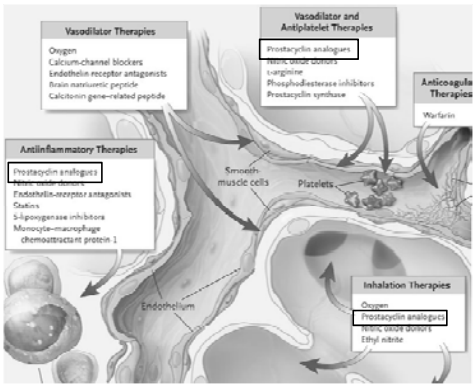


N Engl J Med 2004;351:1655-65.

Injectable Prostacyclin Therapy

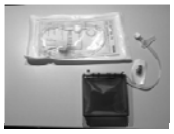
- Epoprostenol
  - Intravenous (generic, Flolan® or Veletri®)
- Treprostinil
  - Intravenous (Remodulin®)
  - Subcutaneous (Remodulin®)

Prior to Initiation

Requirements for Safe Use: Physicians

- Authorized Prescribers
  - Knowledge of disease state
  - Cost $100,000-$160,000/year
  - Appropriate selection of agent
  - Administration challenges
  - Insurance approval process and requirements
  - Knowledge of side effects, monitoring parameters
  - Complications:
    - Infected lines
    - Transitioning between agents
    - Abrupt discontinuation

Requirements for Safe Use: Technicians, Pharmacists, Nurses



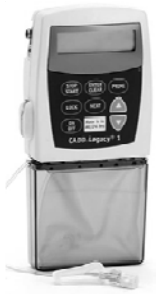
- Pharmacy technicians
  - Supply management
  - Preparation
- Pharmacists
  - Preparation, dispensing
  - Assist MDs, technicians, RNs in all responsibilities
- Nurses
  - Assist MDs in all responsibilities
  - Administration
  - Pump management, monitoring

Product Selection[3-5]

	Epoprostenol IV	Treprostinil IV	Treprostinil SQ
Half-life	6 mins	4 hours	4 hours
Side effects	ALL: Flushing, headache N/V/D, hypotension, dizziness, anxiety, arthralgia, jaw pain, rash , especially with titration		
Specific Side Effects	Infection risk		Infusion site pain
Stability	On ice: 24hrs Room Temp: 8hrs (Veletri 24h at RT)	48h, no ice	72h, no ice
Cassette or Syringe change	Q24h	Q48h	Q72h
Tubing change	Q72h	Q72h	Q72h
Dilution	Required	Required	None

Epoprostenol

- Inpatient therapy
  - Hospital Pumps
    - Drug good for 48hr (okay to make back up)
    - 40hr in fridge + 8hr **no ice needed**
  - CADD pumps
    - Drug good for 48hr (okay to make back up)
    - 24hr in fridge then 24hr **on ice**
- Home therapy
  - CADD pump



http://www.smiths-medical.com/

Treprostinil

- Intravenous

Cane Crono Five

Smiths Medical CADD-MS™ 3

CADD-Legacy® 1

- Subcutaneous

Smiths Medical CADD-MS™ 3

http://www.smiths-medical.com/
http://www.remodulin.com/hcp/iv-administration.aspx

DW: Initiation of Therapy

- Feb 24: Initiation of epoprostenol through PICC line
  - Dosing weight selected at 106kg
  - Started at 2ng/kg/min
  - Rush utilizes CADD pumps for all IV prostacyclin administration
- Pharmacist
  - Verified indication (weight, dose, concentration)
  - Planned titration
    - Increase 24h dose by 30-50%
  - Minimum flow rate for CADD ~40mL/24 (100mL cassette)
    - Specialty pharmacy recommendation to ensure accurate delivery of epoprostenol
  - Coordinate dispense times

Example Cassette Calculations

- Vial sizes: 0.5mg, 1.5mg (0.5mg=500,000ng)
- Cassette volume 100mL
- Pump programmed for mL/24h (round to nearest mL)
- 0.5mg/mL into 100mL cassette=5,000ng/mL

$$\frac{2\text{ng/kg/min} * 106\text{kg} * 60\text{ min} * 24\text{h}}{5000\text{ng/mL}} = 61\text{ mL/24h}$$

Enough for titration?

61mL x 1.5 = 92mL (50% extra allows for titration)

DW: Therapy Complications

- Feb 25: Insurance paperwork started
  - Requirements (Medicare guidelines)
  - First time prescriber, difficultly identifying required paperwork without specialty pharmacy guidance
- Mar 4: Patient develops E. Coli bacteremia, UTI
  - Antibiotics started, unable to culture PICC
  - Per ID service, bacteremia from UTI, unlikely line infection
  - Okay to use PICC until new line can be placed

DW: Therapy Complications

- Mar 7: ID service approves tunneled catheter
- Changing lines:
  - "Bolus" or "IVP" dose
    - Duration of drug to get through new lumen
    - 48mL/24hr, lumen =4 mL=1.6hr for drug to get to circulation
  - Lumen volume
    - Attach syringe to line and withdraw until blood returns
    - Bolus dose is 60-80% of lumen volume
    - 0.6 x 4mL = 2.4mL (same concentration)

DW: Complications Continue

- Mar 8: Informed coverage denied
  - Treprostinil preferred/approved

- Mar 9: Transition to IV Treprostinil

Transitioning to IV Treprostinil

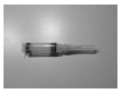
- Technique used (PICC line to tunneled catheter)
  - Bolus dose, lumen volume
  - Overlap epoprostenol and treprostinil x 15-30min
  - 1:1 conversion, typically higher treprostinil requirements
- Others (published reports)
  - IV Epoprostenol to IV Treprostinil
    - Rapid switch: change reservoir (same line used)[6]
    - ↓ epoprostenol and ↑ treprostinil over 24-48h (2 lines used)[7]
  - IV Epoprostenol to SQ Treprostinil
    - Over 14 days (2 lines used)[8]

SQ Treprostinil

- Pump programmed for **mL/hr**
- Rate must be in increments of 0.002mL/hr
- Vial sizes (multi-dose): 1mg/mL, 2.5mg/mL, 5mg/mL, 10mg/mL
- Concentration 1,000,000ng=1mg
- 2.5mg/mL into 3mL syringe

$$\frac{8\text{ng/kg/min} * 106\text{kg} * 60\text{ min}}{2{,}500{,}000\text{ng/mL}} = 0.02\text{mL/hr}$$

- 0.02mL x 72h=1.5mL in syringe



Administration/Nursing

- Trained nurses
  - Programming rates
  - Alarms
  - Priming lines
  - Monitoring
- Miscellaneous
  - Secondary means of IV access
  - **Do not interrupt infusion**
  - Do not FLUSH line, single lumen preferred
  - No other medications should be administered through the same line
  - Do not change dose based on daily weights

Specialty Pharmacy Training

- Training typically started prior to initiation
- Safety screen/cleanliness
  - Patients generally not send to SNF
- Mar 9 and 10: specialty pharmacy training

Home Training

- Training
  - Disease state
  - Mixing, documented mixing partner, aseptic technique, quiet area
  - Pump use, titrations, alarms
  - Drug and supply distribution
  - Extra supply
  - Signs and symptoms of too much/too little medication
    - When to call
- Specialty RN determines when safe to go home
- Mar 10: HOME!!

Home Therapy

- Example: SQ treprostinil titration protocol
- 63.6kg

Dose	ng/hr	Conc (mg/mL)	Rate	Syringe volume (mL)
15.5 ng/kg/min	59,148	2.5	0.024 mL/hr	1.8 mL
17 ng/kg/min	64,872	2.5	0.026 mL/hr	1.9 mL
18.5 ng/kg/min	70,596	2.5	0.028 mL/hr	2.1 mL
19.5 ng/kg/min	74,412	2.5	0.030 mL/hr	2.2 mL
21 ng/kg/min	80,136	2.5	0.032 mL/hr	2.4 mL
22 ng/kg/min	83,952	2.5	0.034 mL/hr	2.5 mL
23 ng/kg/min	87,768	5	0.018 mL/hr	1.3 mL
24 ng/kg/min	91,584	5	0.018 mL/hr	1.4 mL
26 ng/kg/min	99,216	5	0.020 mL/hr	1.5 mL

Questions?

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Assessment Question 1

Which of the following is NOT true regarding injectable epoprostenol?

A. Half life˜6mins

B. Can be administered SQ

C. Requires 24h cassette changes with the CADD pump.

Assessment Question 2

Which of the following should NOT change throughout a patient's course of therapy?

A. Dosing weight

B. Drug concentration

C. Dose

Assessment Question 3

Which of the folloiwng are potential complications of IV treprostinil use?

A. Infected lines

B. Calculation errors

C. Flushing the line it is infusing in

D. All of the above