

Bloodstream infections among patients treated with intravenous epoprostenol and intravenous treprostinil for pulmonary arterial hypertension, United States 2004-2006

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Investigation

- In Fall 2006, DHQP notified of possible increase in gram-negative bloodstream infection (BSI) in patients on IV treprostinil
- We wanted to:
 - Determine rates of BSI for both IV prostanooids
 - Overall
 - Gram-negative



Methods

- Largest IV treprostinil prescribing centers were asked for infection rate information (both drugs)
 - If unable to provide this, asked for the number of BSI on IV treprostinil in 2006
- UT provided denominator (medicine days) for Jan 1 to Oct.1, 2006



Case Definition

- Bloodstream Infection (BSI) – microbiology records or a clinician note indicating a positive blood culture in someone receiving IV prostanoid
- Study time period January 2004-2006
- Incidence density was calculated per 1000 medicine days



Methods -- Laboratory

Providers were asked to send patient isolates and used IV treprostinil vials from patients with BSI to CDC or State labs in an attempt to culture pathogens



Organism types

- 144 BSIs identified
 - Treprostnil 57
 - Epoprostenol 87
- 26 different organisms
 - 12 gram-positive
 - 12 gram-negative
 - 2 AFB



Organisms

- Epoprostenol
 - 14 types
 - 9 gram-positive
 - 4 gram-negative
 - 1 AFB
 - 3 most common
 - *Staphylococcus* (coagulase – negative) (28)
 - Micrococcus (18)
 - *Staphylococcus aureus* (12)



Organisms

- Treprostinil
 - 18 types
 - 7 gram-positive
 - 10 gram-negative
 - 1 AFB
 - 3 most common
 - *Pseudomonas* (11)
 - *Enterobacter* (9)
 - *Staphylococcus* (coagulase – negative) (8)



Results – Incidence Density

- In response to our request:
 - 2 centers provided infection numbers for 2006 (numerator only)
 - 3 centers provided their BSI rates
 - 2 centers agreed to have CDC investigators review charts on site to determine BSI rates



Results – Crude Incidence Rates (overall)

Bloodstream infections

	Treprostinil Medicine days	Epoprostenol Medicine days	Treprostinil Rate per 1000 medicine days	Epoprostenol Rate per 1000 medicine days	IRR (95% CI)
Total	51,183	201,158	1.11	0.43	2.57 (1.81-3.64)
Historical data)* (epoprostenol)		335,285		0.15	

*Oudiz RJ et al. Micrococcus-associated central venous catheter infection in patients with pulmonary arterial hypertension. Chest 2004;126:90-4.

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Results – Crude Incidence Rates (gram-negative)

Gram-negative bloodstream infections

	Treprostinil	Epoprostenol	Treprostinil	Epoprostenol	IRR (95% CI)
	Medicine days		Rate per 1000 medicine days		
Total	55,343	201,158	0.76	0.06	12.77 (6.55–26.80)
Historical data * (epoprostenol)		335,285		0.01	

*Oudiz RJ et al. Micrococcus-associated central venous catheter infection in patients with pulmonary arterial hypertension. Chest 2004;126:90-4.

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Center Level

- Range for crude rates (per 1000 medicine days)
 - BSI
 - Treprostinil = 0.28 – 2.10
 - Epoprostenol = 0.23 – 1.02
 - Gram-negative BSI
 - Treprostinil = 0.28 – 1.11
 - Epoprostenol = 0.03 – 0.25



Center Level

- All 5 centers with data for both medications had higher crude rates for gram-negative infections in those on IV treprostinil
 - IRR range (1.19-29.90)
- Four of 5 had higher crude rates for overall BSI in those on IV treprostinil
 - IRR range (0.59-3.90)



Results – Stratified Incidence Density (2 centers)

- Results stratified by :
 - Age (younger than 18 y.o. vs. 18 y.o. or older)
 - Treatment time (less than 2 years vs. 2 years or more)
 - Data collection method (this was at 7 centers)
 - Home health (largest vs. 2 smallest)
 - Co-administration of immune suppressing medications
- For each, overall BSI and gram-negative BSI rates remained higher for treprostiniil



Results – Laboratory

- 10 vials were obtained from patients with BSI
- 2 cultured by State of NY, 1 by NYC public health laboratory, and the rest were sent to DHQP lab in Atlanta
- None grew any bacteria



Limitations

- Retrospective analysis, not designed or powered to look at specific risk factors
- Data from only 7 centers (5 for both medications)
- Time from which data collected varied between centers
- Sample of centers providing data was not random
- Denominator smaller for treprostinil
- Microbiologic definition used for BSI



Possible Mechanisms

- Infection Control Issues
 - Multi-use vial and vial adaptor
 - Uniformity of practice (e.g., dressing/tubing change)
 - Refresher sessions for patients
- Immune modulation issues
 - Possible decrease in T-cell function and/or modulation of immune system products
- Differences with detaching line



Communication of findings

- Findings being shared with practitioners so they can review the information first hand.
- Findings have been shared with:
 - United Therapeutics
 - The Food and Drug Administration



Prevention

- Clinicians should help patients make an informed decision of relative risks and benefits of each IV prostanoid
- Uniform, best practices for the care and maintenance of central venous lines and the outpatient use of IV prostanoids.
- Educational materials for patients on best practices for IV therapy.



Summary

- IV treprostinil was associated with a higher rate of BSI, particularly gram negative BSI, than IV epoprostenol
- Reason for this higher rate unknown
 - Infection control vs. immune modulation
- Further studies needed to
 - Confirm or refute these findings
 - Determine risk factors and best prevention strategies

