Training for healthcare professionals in the safe handling of intravenous (IV) treprostinil and the prevention of catheter-related bloodstream infections (CRBI)

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Background

This healthcare professional training guide is a mandatory part of the approval of Treposuvi Solution For Infusion.

This document is part of the additional risk-minimisation measures implemented to reduce the risk of occurrence of catheter-related blood stream infections when Treposuvi Solution For Infusion is administered by intravenous continuous infusion via an external infusion pump and a central venous catheter (CVC).

The other risk minimisation measures include a patient brochure and a patient questionnaire. Copies of all these materials are available via the electronic Medicines Compendium (eMC) website.

Prescribers should also read the currently approved summary of product characteristics for this product via the electronic Medicines Compendium website:
https://www.medicines.org.uk/emc/

Main components of this training unit

- Background of the risk of CRBI
- Practical techniques to minimise CRBI and patient training
- The treprostinil license
- Detecting and reporting of suspected CRBI, dosage errors and pump/infusion tube malfunctions
- The transition from SC to IV Treprostinil
- Reporting of catheter related infections and review of completed patient questionnaires
- Summary
- Recommended readings

BI = bloodstream infection;
CRBI = catheter-related bloodstream infection;
CVC = central venous catheter

The risk of catheter-related bloodstream infections (CRBI)

CRBI and IV prostanoids: A retrospective study by the CDC

	Days of medication (total)	CRBI rate per 1,000 days of medication
IV epoprostenol	201,158	0.43
IV treprostinil	51,183	1.11
Total[1]	**252,341**	**0.57**

- Retrospective study of records from patients at seven large centres in the USA, who received IV prostanoids (epoprostenol or treprostinil) between 2003 and 2006
- Higher rate of CRBIs observed in IV treprostinil patients in comparison with epoprostenol patients

BI = bloodstream infection; CDC = Centers for Disease Control; CRBI = catheter-related bloodstream infection; IV = intravenous; MMWR = mortality and morbidity weekly report

1. Barst et al. MMWR Morb Mortal Wkly Rep. 2007;56:170-172;

The incidence of CRBI in connection

- In patients who regularly receive IV treatment via CVC, around five CRBI occur per 1,000 catheter days in the USA[1]
- This results in 80,000 CRBI yearly[2]

Rate of CRBI per 1,000 catheter days (Range)

Total IV treatment via CVC: Range 0.3 to 9.1 [3-5]

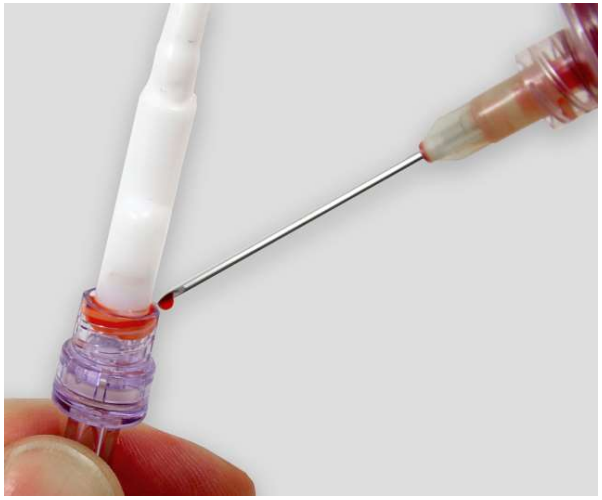
PAH IV treatment via CVC: Range 0.1 to 1.1 [6,7]

CRBI = catheter-related bloodstream infection; CVC = central venous catheter; IV = intravenous; PAH = pulmonary arterial hypertension

1. National Nosocomial Infections Surveillance System. *Am J Infect Control*. 2004;32:470-485; 2. O'Grady et al. *MMWR Recomm Rep*. 2002;51(RR-10):1-29;
3. van Hoff et al. *J Clin Oncol*. 1990;8:1255-1262; 4. Decker et al. *Pediatr Clin North Am*. 1988;35:579–612; 5. Moureau et al. *J Vasc Interv Radiol*. 2002;13:1009–1101; 6. Akagi et al. *Circ J*. 2007;71:559-564; 7. Barst et al. *MMWR Morb Mortal Wkly Rep*. 2007;56:170-172

Occurrence of pathogens in the central venous catheter

Dye follows the course of the thread[1]



Contamination occurs upon removal[2]

A connection covered with a plastic barrier (for example: GLAD Press'n Seal®)

GLAD Press'n Seal® is an example of a sealable plastic wrap, which can be used to protect the catheter hub connection from water contamination[2]

1. Ivy et al. Infect Control Hosp Epidemiol. 2009;30:823-829; 2. Doran. Health Matters; Herbst 2008. http://www.phassociation.org/Document.Doc?id=226. Accessed in May 2010

Society for pulmonary hypertension: Bloodstream infection guidelines and catheter care

Possible entry sites of bloodstream infections

- CVC entry site on the skin
- Catheter hub and tube connections
- Prostaglandin bottles and containers

CVC = central venous catheter

Society for pulmonary hypertension CRBI guidelines and catheter care

The guidelines for CRBI prevention of the Society for Pulmonary Hypertension should be followed [1]

- Protecting the catheter hub is crucial
- Avoiding contact with water is important
- Please take care of the type of dressing at the insertion site, and observe the site

BI = bloodstream infection; CRBI = catheter-related bloodstream infection; CVC = central venous catheter

1. Doran et al. Adv Pulm Hypertens. 2008;7:245-248

Practical techniques to minimise CRBI

Important patient training & general principles

- Patients must understand the risks associated with the treatment and be aware of the role they can play themselves in the minimisation of such risks. It is the duty of the responsible clinical team to train patients in the following areas:

  - **Hand hygiene** – the significance of good hand hygiene with relevant cleaning agents as well as easy and effective techniques when the catheter is inserted, replaced, accessed, repaired or when the catheter insertion site is examined and/or dressed
  - **Area preparation** – The need to always carefully prepare the environment at home before changing the container solution and the tube must be discussed.
  - **Maintenance and observation of** the insertion site of the catheter into the skin. A sterile gauze (replaced every two days) or sterile transparent semi-permeable dressing (replaced at least every seven days) should be used to cover the catheter insertion site through the skin. The dressing should be replaced whenever it becomes damp, loosened, or soiled or after examination of the site

Important patient training & general principles cont.

- **The importance of maintaining dry connection hubs:** The risk of contamination with water-borne Gram negative organisms is likely to be increased if a Luer lock inter-connection is wet at the time of exchanging either the infusion line or the closed hub. Therefore:
  - swimming and submersion of the infusion system at the site of connection with the catheter hub should be discouraged
  - at the time of replacing the closed-hub device, there should not be any water visible in the luer lock connection threads
  - the infusion line should only be disconnected from the closed hub device once every 24 hours at the time of replacement
- **Awareness of signs and symptoms** of suspected CRBI and the procedure for reporting them to healthcare specialists
- **Topical antibiotic ointments or creams** should not be applied as they may promote fungal infections and antimicrobial-resistant bacteria

0.2 micron inline filter

- Eliminates bacteria, fungi, moulds and foreign particles from the infusion tube
- During a study performed by the originator, the catheter tube was deliberately contaminated in order to assess the filter efficiency
- There were no signs of contamination in the fluid samples taken after the filter, which had been cultivated for disease pathogens

Closed hub system with split septum

- The catheter hub is the most common source of central venous catheter infections.[1,2]
- Closed hub systems became available at the end of the 1980s.
- A needle-free setup with a split septum is preferred over a mechanical valve device. If a mechanical valve device is used, it should have a flat, smooth surface for disinfection before use.[3]
- Closed hub devices provide direct access to the fluid route for medication delivery, but also are self-sealing in case of detachment. (Comment: Closed hub devices do not prevent backflow; a clamp on a Hickman line is therefore required before removing the infusion tube).

1. Sitges-Serra et al. JPEN J Parenter Enteral Nutr. 1984;8:668-672
2. Sitges-Serra et al. Surgery. 1985;97:355-357
3. Doran et al. Adv Pulm Hypertens. 2008;7:245-248

Closed hub systems with split septum decrease the risk of bloodstream infections

- Akagi et al. demonstrated the efficacy of closed hub systems[1]
- 20 PAH patients (24 cases) were evaluated:
  - Closed hub (n=13)
  - Unclosed hub (n=11)
- Catheter-related bloodstream infection:
  - Closed hub: 0.10 per 1,000 catheter days
  - Unclosed hub: 0.89 per 1,000 catheter days

BI = bloodstream infection; IV = intravenous;
PAH = pulmonary arterial hypertension

1. Akagi et al. Circ J. 2007;71:559-564

Hub protection in Children's Hospital Denver

- CRBI were evaluated in patients receiving IV prostanoid treatment before and after the introduction of the closed hub system
- The data collection comprised
  - Type of IV prostanoid (epoprostenol or treprostinil)
  - Type of bacterial infection (gram-positive/negative)
  - Specific pathogens
  - Number of CRBI/catheter days
  - Use of the closed hub system (yes or no)

CRBI = catheter-related bloodstream infection;
IV = intravenous

Ivy et al. Infect Control Hosp Epidemiol. 2009;30:823-829

Children's Hospital Denver
incidence of bloodstream infections before and after hub protection

Closed-Hub Systems with Protected Connections and the Reduction of Risk of Catheter related Bloodstream Infection in Pediatric Patients Receiving Intravenous Prostanoid Therapy for Pulmonary Hypertension (Ivy et al., 2009)

Fifty patients received intravenous prostanoid therapy for a total of 41,840 catheter days.

The rate of CRBI during the study period was 0.51 infections per 1,000 catheter-days for epoprostenol and 1.38 infections per 1,000 catheter-days for treprostinil, which differed significantly ($P < 0.01$).

CRBI caused by gram-negative pathogens occurred more frequently with treprostinil than with epoprostenol (0.91 infections per 1,000 catheter-days vs 0.08 infections per 1,000 catheter-days; $P < 0.01$).

Patients treated with treprostinil after the implemented changes had a significant decrease in CRBI rate (1.95 infections per 1,000 catheter-days vs 0.19 infections per 1,000 catheter-days; $P < 0.01$).

Ivy et al. Infect Control Hosp Epidemiol. 2009;30:823-829

Summary of Product Characteristics of Treprostinil

IV treprostinil Summary of Product Characteristics

- Treposuvi strengths 1, 2.5, 5, 10 mg/ml Solution For Infusion (PL 21344/0030 to 0033) are available in 10ml vials
- The Summary of Product Characteristics states “Due to the risks associated with chronic indwelling central venous catheters, …
  - subcutaneous infusion (undiluted) is the preferred mode of administration,
  - and continuous intravenous infusion should be reserved for patients stabilised with treprostinil subcutaneous infusion ...
  - ... and who become intolerant of the subcutaneous route...
  - ... and in whom the risks of an indwelling central venous catheter are considered acceptable.
  - The maximum duration of use of the diluted product should be no more than 24 hours

- The clinical team responsible for treatment must ensure that the patient is

IV treprostinil Summary of Product Characteristics

- To minimise the risk of catheter-related bloodstream infections, the following is recommended:
  - Use of a cuffed and tunnelled central venous catheter (CVC) with a minimum number of ports, inserted using sterile barrier techniques
  - The use of a 0.2 micron inline filter, to be positioned between the infusion tube and the catheter hub and replaced every 24 hours at the time of changing the infusion reservoir
  - The use of a closed-hub system (preferably a split septum rather than a mechanical valve device), ensures that the lumen of the catheter is sealed each time the infusion system is disconnected. This reduces the risk of microbial contamination of the lumen. The split-septum closed hub device should be replaced every 7 days
  - Ensure that Luer lock connections are kept dry when replacing the infusion tube or the closed hub
  - The maximum duration of use of the diluted product should be no more than 24 hours.

Detecting and reporting suspected CRBI, dosage errors and pump/infusion tube malfunctions, and Patient Questionnaires to gauge the level of understanding

Patient questionnaires

Each patient who undergoes treatment with IV treprostinil is to be offered a questionnaire by his or her healthcare specialist in order to enable AOP Orphan Ltd., to assess the effects and acceptance of measures for risk minimisation for patients.

Patients receive the questionnaire from their healthcare specialist to be completed within three to six months after the start of treatment.

Reason for completing questionnaire:

- To check patient knowledge after initial education
- To check patient knowledge after 3-6 months therapy
- To check patient knowledge after catheter-related blood stream infection (In which case report any suspected blood stream infections by e-mail to drugsafety@pharsafer.com)

Patient questionnaires

The questionnaire will

- … give patients time to consider their answers carefully – without interference e.g. from interviewer.
- … result in uniformity of information, since each patient receives the same set of questions. Answers are standardised through the use of primarily closed questions. This is helpful when interpreting data.
- … deal with a series of topics and issues in a relatively efficient way with the possibility of a high response rate.

Completed questionnaires are collected by the clinical team responsible and returned to AOP Orphan Ltd., within an appropriate time frame. The data is analysed and published by the department for medical affairs as well as AOP Orphan's pharmacovigilance department.

Reporting suspected CRBI, dosage errors and pump/infusion tube malfunctions

- Reporting of suspected adverse reactions after authorisation of a medicinal product is important. Please report any suspected adverse reactions with Treposuvi, particularly any suspected cases of catheter-associated bloodstream infections, bacteraemia and sepsis. Any dosage errors or pump/infusion tube malfunctions should also be reported.
- Reports of catheter-associated bloodstream infections should be reported using the Patient Questionnaire Form provided.

Adverse events should be reported to the MHRA via the yellow card scheme at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to AOP Orphan Pharmaceuticals on 0121 262 4119 or drugsafety@pharsafer.com.

Intravenous continuous infusion

- IV treprostinil is administered via intravenous continuous infusion through a central venous catheter using an infusion pump for an outpatient setting.
  - It can also be administered temporarily via a peripheral venous cannula, which is ideally inserted into a major vein.
  - The administration of the infusion via a peripheral vein over several hours can be accompanied by an elevated risk of thrombophlebitis.
- Pumps for subcutaneous administration should be avoided in favour of dedicated IV pumps.
  - Subcutaneous pumps generally have output of 0.1 to 0.2 ml/hour and deliver undiluted medication, which is transferred from the bottle directly to the injection container.
  - Concentrated medications are associated with an increased risk of an overdose if an unintentional bolus is given.
  - These pumps run at relatively slow infusion rates, which may be associated with an elevated risk of a catheter blockage.

Intravenous continuous infusion

- To avoid potential interruptions in the supply of medication, the patient must have access to a backup infusion pump and a backup infusion set in the event that the device malfunctions
- If problems arise, the patient must be informed of the following:
  - That they must check their pumps and infusion connections at the first signs of inexplicable shortness of breath or other deteriorations in their condition.
  - How to recognise signs of an overdose (hot flushes, headache, jaw pain, nausea, diarrhoea, weakness).
  - That they should urgently seek advice, which may require not using their infusion system temporarily until it can be inspected.
- All suspected dosage errors, overdoses, catheter blockages etc. should be monitored closely and reported using the standard “post marketing safety report” form for side effects, which can be obtained from AOP Orphan Ltd.

Selection of a suitable infusion pump

- A pump should be selected which has been specifically developed for use with intravenous infusions. In general, the infusion pump for an outpatient setting should have the following features:

  - Small and lightweight,
  - capable of adjusting infusion rates in increments of approximately 0.002 ml/h. Typical flow rates would be between 0.4 ml and 2 ml per hour,
  - fitted with occlusion (no delivery), low battery, programming error and motor malfunction alarms,
  - Accurate to within ±6% of the programmed delivery rate,
  - be positive pressure driven (continuous or pulsated).

  The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Example for an infusion pump

	CADD-Legacy™
Use	suitable for IV use
Container	50–100 ml Cartridge
Dimensions	41 x 97 x 112 mm
Weight (empty)	391 g

The treprostinil container must be replaced at least every 24 hours.

IV = intravenous; CADD-MS is a trademark and CADD-Legacy is a registered trademark of Smiths Medical System

Calculation of IV solutions

- Example calculation: A patient weighing 70 kg at a dose of 30 ng/kg/min using a 20-ml syringe container, a tube with a 2 ml filling volume, and with 2.5 mg/ml vials
- Initially, the concentration required in the syringe is calculated:

$$\frac{\text{(dose) 30 ng/kg/min x (weight) 70 kg x 0.00006*}}{\text{(infusion rate) 0.83 ml/hour **}} = 0.15 \text{ mg/ml}$$

- The volume of medication to be taken from the vial is then calculated:

$$\frac{\text{(diluted concentration) 0.15 mg/ml x (container \& filling volume) 22 ml}}{\text{(vial strength) 2.5 mg/ml}} = 1.3 \text{ ml}$$

- Saline solution is then added until the total volume is reached (1.3 ml treprostinil + 20.7 ml of saline) = 22 ml

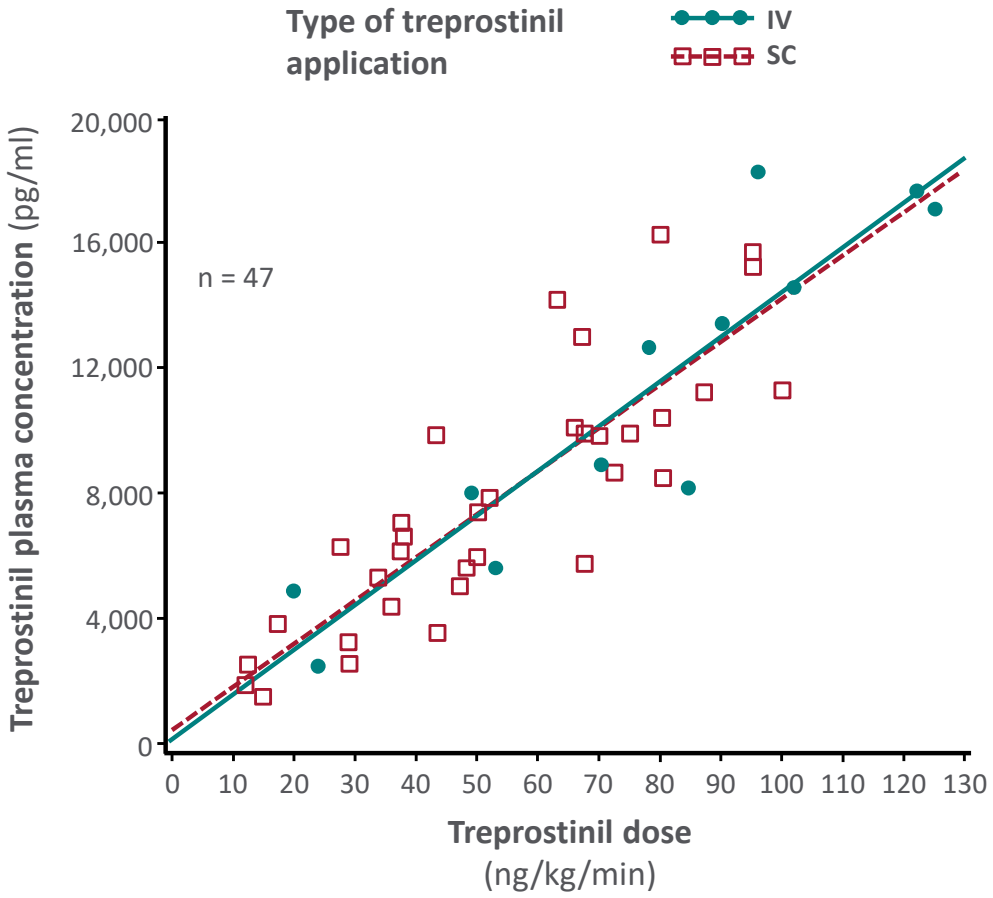
* The factor 0.00006 is used to convert ng/min into mg/hour

- ** using a 20 ml/day pump

The transition from SC to IV treprostinil

Bioequivalence of SC/IV treprostinil

- In patients with PAH, the increase in the dose of SC or IV treprostinil leads to a linear increase in plasma concentrations
- **Conclusion:** Treprostinil plasma concentrations follow a predictable relationship with the dose of treprostinil

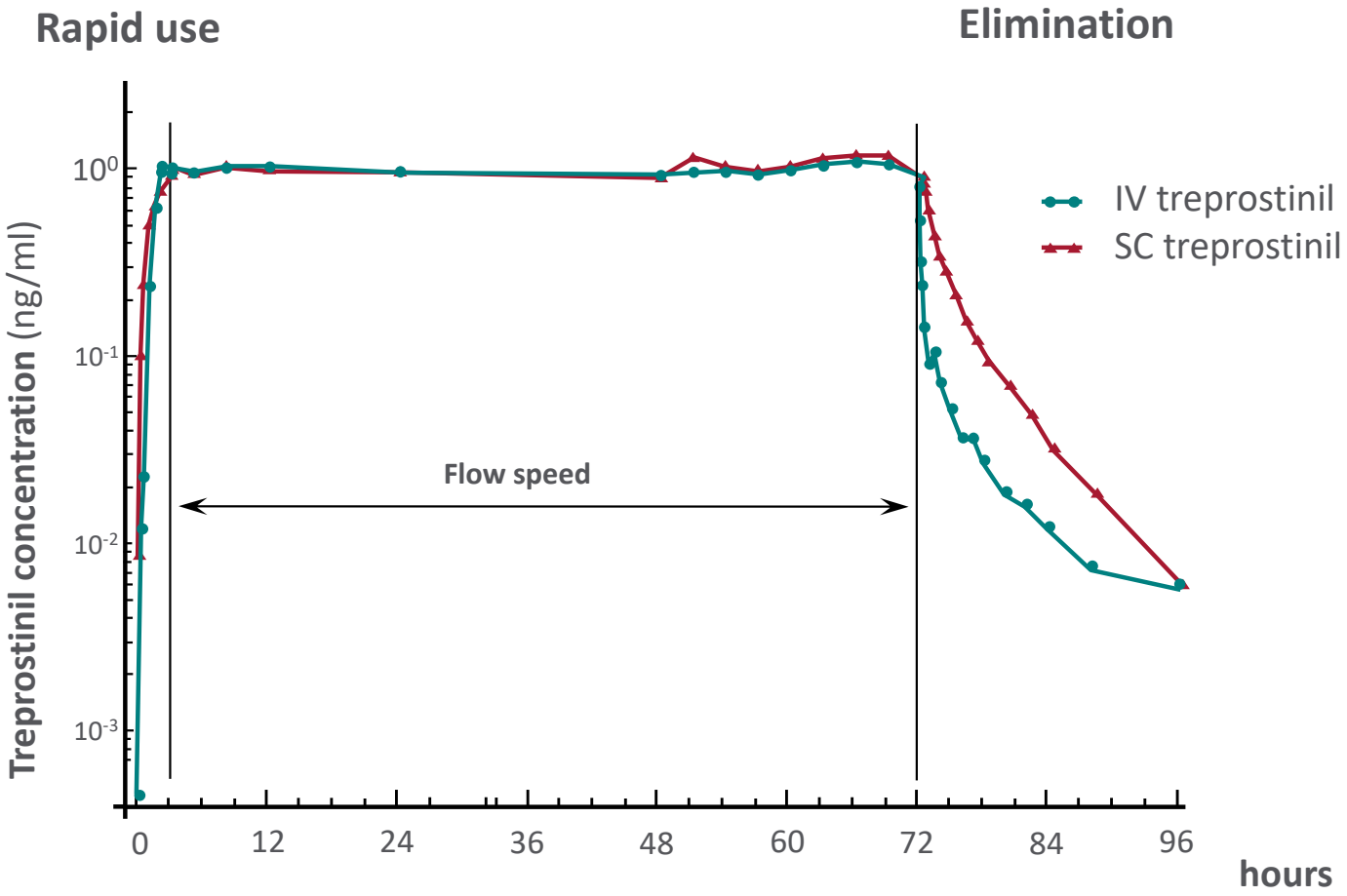


IV = intravenous; PAH = pulmonary arterial hypertension; PK = pharmacokinetics; SC = subcutaneous

McSwain et al. J Clin Pharmacol. 2008;48:19-25

Bioequivalence of SC/IV treprostinil

- Treprostinil plasma concentrations over 72 hours after SC or IV dose [1]



IV = intravenous; SC = subcutaneous

Laliberte et al. J Cardiovasc Pharmacol. 2004;44:209-214

The transition from SC to IV treprostinil

- If you are planning a transition from SC to IV infusion:

  - Select an outpatient pump with a higher flow rate than the SC micro infusion pumps for undiluted medication.
  - Be careful when recalculating concentrations and infusion rates for the diluted application system.
  - Make sure that the patient is well trained and knows how to use the new pump, the connection tubes and risk management strategies to prevent CRBI.
  - Always perform the transition under clinical observation.
  - Watch for signs of temporary overdose (headache, hot flushes etc.) and be prepared to stop the IV infusion for a short time if necessary, since there may be a short depot effect if the SC injection site continues to deliver any remaining medicine.

IV = intravenous; SC = subcutaneous

Summary: Catheter Related Bloodstream Infection (CRBI)

- CRBI are potentially severe complications in patients who require an IV infusion via a CVC.
- Compared with other chronic diseases, CRBI rates are very low in PAH,[1-5] but sufficient training and awareness are crucial.
- The available data suggest that the rates of CRBI with gram-negative organisms are slightly higher with IV treprostinil (than with IV epoprostenol), although there is a significant overlap.[5]
- The rates of CRBI can be reduced further by
  - CVC systems with a closed hub[4]
  - Avoidance of water contamination[6]
  - Thorough training and preparation of the patient, followed by continuous compliance with good hygiene standards and alertness of nursing staff and patients.

BI = bloodstream infection; CRBI = catheter-related bloodstream infection; CVC = central venous catheter; IV = intravenous; PAH = pulmonary arterial hypertension

1. van Hoff et al. J Clin Oncol. 1990;8:1255–1262; 2. Decker et al. Pediatr Clin North Am. 1988;35:579–612; 3. Moureau et al. J Vasc Interv Radiol. 2002;13:1009–1101;
4. Akagi et al. Circ J. 2007;71:559-564; 5. Barst et al. MMWR Morb Mortal Wkly Rep. 2007;56:170-172; 6. Doran et al. Adv Pulm Hypertens. 2008;7:245-248

Summary: Essential patient training

- Summary of essential patient training:
  - Hand hygiene and area preparation
  - Maintainance and monitoring of catheter insertion site and dressing
  - The risk of contamination with water-borne Gram negative organisms is likely to be increased if a Luer lock inter-connection is wet at the time of exchanging either the infusion line or the closed hub. Therefore ensure the patient understands:
    - The importance and use of inline filters and closed hub systems: the infusion line should only be disconnected from the closed hub device once every 24 hours at the time of replacement
    - The importance of maintaining dry connection hubs and the use of waterproof bandages or wrapping when bathing or showering: at the time of replacing the closed-hub device, there should not be any water visible in the Luer lock connection threads
  - The importance of avoiding swimming or other direct risks of water contact with the infusion connections or dressings
  - Knowledge of the signs of suspected CRBI and system-related medication side effects and prompt reporting of these to healthcare professionals.

Summary of training unit

- Background to the risk of CRBI
  - Retrospective study into CRBI by the Centers for Disease Control
  - Context of the incidence of all treatment-related bloodstream infections
  - Catheter care guidelines from the society for pulmonary hypertension
- Practical techniques to minimise CRBI
  - Important patient training & general principles
  - 0.2 micron inline filter
  - Connection with the closed hub with a split septum and waterproof dressing wrap
- Summary of Product Characteristics for Treprostinil solution for injection
- Detecting and reporting suspected CRBI, dosage errors and pump/infusion tube malfunctions
  - Patient questionnaires
  - Risk minimisation, follow-up
  - Administration via intravenous continuous infusion
  - Suitable infusion pumps for the IV administration
  - Calculation of infusion rate and concentration required
- Transition from SC to IV treprostinil
  - SC and IV bioequivalence
- Summary:
  - Summary: CRBI
  - Summary: Important patient training
- Recommended reading

Recommended reading

Doran A. K, Ivy D. D, Barst R.J, et al. “Guidelines for the prevention of central venous catheter-related blood stream infections with prostanoid therapy for pulmonary arterial hypertension” International Journal of Clinical Practice. 2008 62(s160): 5–9

Akagi S, Matsubara H, Ogawa A, et al. “Prevention of catheter-related infections using a closed hub system in patients with pulmonary arterial hypertension” Circ J. 2007 71(4):559-64

Ivy DD, Calderbank M, Wagner BD, et al. “Closed-hub systems with protected connections and the reduction of risk of catheter-related bloodstream infection in pediatric patients receiving intravenous prostanoid therapy for pulmonary hypertension” Infect Control Hosp Epidemiol. 2009 30(9):823-9

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