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Prostacyclin administration errors in pulmonary arterial hypertension patients admitted to hospitals in the United States: a national survey

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Abstract

BACKGROUND—Epoprostenol and treprostinil are intravenous prostacyclin medications used to treat pulmonary arterial hypertension (PAH). This survey explored hospital policies regarding prostacyclin infusions, and investigated the type and frequency of errors that occurred in the inpatient setting.

METHODS—Information on prostacyclin infusion policies and inpatient errors was obtained through detailed interviews with 18 PAH nurses, and through an electronic survey completed by 97 PAH clinicians.

RESULTS—The electronic survey respondents reported wide variability in prostacyclin infusion policies, including variability in the use of home vs hospital infusion pumps, and variability in the use and storage of back-up epoprostenol and treprostinil. Serious or potentially serious errors in medication administration were reported by 68% of survey respondents. The most common error types (reported by 25%), included: incorrect cassette placed in the pump; inaccurate pump programming; errant drug dosing; and inadvertent cessation of the pump. Nine errors, all at different centers, were believed to have contributed to patient death. In the separate interviews with the PAH nurses, 94% reported serious errors. These errors prompted many of the centers to implement policy changes in an attempt to reduce future errors, improve safety and optimize patient outcomes.

CONCLUSIONS—These findings suggest that prostacyclin infusion therapy is problematic and that an opportunity exists to improve safety. The development of standardized treatment guidelines should be considered.

Keywords

pulmonary hypertension; pulmonary arterial hypertension; prostacyclin; epoprostenol; treprostinil

Pulmonary arterial hypertension (PAH) is characterized by vasoconstriction and proliferation of the small pulmonary arteries. Intravenous epoprostenol (Flolan; GlaxoSmithKline and Teva) and treprostinil (Remodulin; United Therapeutics) are continuous intravenous medications used in the most advanced cases of PAH.¹ These medications, referred to here as “prostacyclins,” are administered by ambulatory infusion pumps attached to central venous catheters. Dosing is adjusted based on clinical response, side effects and symptoms. Dose changes are made in minute increments to avoid severe symptoms of toxicity, and sudden increases or decreases in the dose can be life-threatening.^{2,3}

When patients require hospital admission, preparation, administration and programming of their home infusion pump becomes the responsibility of the pharmacy and nursing staff. Inpatient management can be challenging for nurses, because even at large PAH centers there are typically only a few inpatients receiving intravenous prostacyclin at any given time. Many nurses have had limited exposure to both the medications and the ambulatory infusion pumps. We conducted this survey to determine the type and frequency of prostacyclin administration errors in the hospital setting and to explore hospital policies regarding prostacyclin infusions.

Methods

This project consisted of two separate queries. First, nurses and nurse practitioners at 18 large pulmonary hypertension (PH) centers were interviewed by telephone. The centers were chosen based on size, experience treating PH, involvement with the Pulmonary Hypertension Association (PHA) and geographic diversity. Information on inpatient prostacyclin administration policies and any adverse events was obtained. Following this, a large-scale electronic survey was sent to a convenience sample of all PAH centers in the USA whose physicians or nurses are members of the Pulmonary Hypertension Association (PHA). Pharmacists working for Accredo, a PAH specialty pharmacy, were also included in the electronic survey. Probable recipients included approximately 420 physicians who are members of the PHA emailing list, 140 nurse members of the PH Resource Network and another 600 pharmacists and nurses included from a large PH specialty pharmacy database. Institutional review board approval was obtained from the University of Texas Southwestern Medical Center at Dallas prior to launching the survey. The design and completion of the survey were accomplished using the internet survey tools available at [SurveyMonkey.com](https://www.surveymonkey.com).⁴ This electronic survey included nine questions, as shown in the Appendix, and included policy questions as well as questions on type, frequency and severity of errors. Participants had the option of leaving their medical center name and contact information, or completing the survey anonymously. The survey was opened during the month of February 2009.

Statistical analysis

The interview results for the 18 PH nurses are presented as descriptive, qualitative data. Frequency distributions for the responses to the nine electronic survey questions are reported. Chi-square or Fisher's exact tests (when expected cell values were <5) were performed to compare error rates and specific error types among centers with a policy of home infusion pump use as compared with hospital pump use. McNemar's test was performed to evaluate the storage of epoprostenol and treprostinil on nursing units. NCSS 2004 was used for the analysis. Where descriptive or qualitative information is presented, errors are not reported around each proportion. The maximum margin of error for the survey is 11%, based on between 87 and 97 responses to each individual question.

Results

Introduction and respondent characteristics

One nurse or nurse-practitioner from each of 18 pulmonary hypertension centers was approached by telephone, and all 18 agreed to be interviewed. Each of the centers included routinely utilized intravenous prostacyclins, and the nurses who were interviewed were directly involved in patient care; responses are detailed in what follows. Separately, a survey evaluating prostacyclin policies and errors across a larger and more diverse group of respondents was conducted. This survey was completed by 97 respondents from a recipient pool of up to 1,200 individuals (~8% response rate), and the respondents included 30 physicians, 18 nurse practitioners, 29 nurses, 19 pharmacists and 1 respiratory therapist.

Nursing telephone interviews

Errors and policies—Significant variability was reported in prostacyclin administration policies by the nurses and nurse-practitioners interviewed by phone. Eight of 18 respondents reported that either or both epoprostenol and treprostinil back-up cassettes or bags were kept on the nursing unit, whereas the remaining kept back-up cassettes or bags were in the pharmacy. Ten of 18 nurses reported that patients at their institution were usually or always transitioned to a hospital infusion pump, whereas 8 kept patients on their home infusion pumps.

Errors were also common, with 17 of 18 nurses reporting at least one serious error at their center, including 3 deaths. Serious errors occurred whether patients were kept on home infusion pumps or were transitioned to hospital pumps. Two error types were reported only with the use of home infusion-style pumps: failure to restart the infusion pump, and mix-up of medication cassettes. The medication cassette errors took place despite proper labeling, typically when a nurse removed a cassette from a storage location that was for the wrong patient. In 2 additional cases, an epoprostenol cassette was accidentally switched for treprostinil, or vice versa, with patients receiving the wrong medication. Symptoms resulting from both types of errors ranged from no symptoms to nausea, flushing, light-headedness, syncope and, in 1 case, death. The fatal event occurred when a patient on a moderate dose of epoprostenol received an epoprostenol cassette intended for another patient and was overdosed (4× concentration). The patient developed nausea and hypotension followed by pulseless electrical activity arrest.

Institutions that transitioned patients to hospital pumps also had serious errors. These included the wrong rate being programmed in the pump, errors in dose calculations, and episodes in which the dedicated prostacyclin line was flushed, leading to a bolus of prostacyclin. Two errors involved very high doses of prostacyclin administered over a short time period, with both cases leading to severe hypotension and cardiopulmonary arrest. In the first instance, a near-fatal hypotensive event occurred when a nurse flushed undiluted treprostinil through the in-dwelling line. In this case the patient was resuscitated with CPR. In the second case, a patient died after a nurse programmed a rate that was intended for a potassium drip. Epoprostenol ran at 100 ml/h, which was approximately 100 times the correct dose. This led to hypotension and death, despite attempts at resuscitation.

Finally, another serious error was related to a line flush in a patient being treated with a home miniaturized infusion pump (CADD MS3). This patient was admitted with an infection and required the placement of a peripherally inserted central catheter. His hospital pump that was delivering an antibiotic emitted a high-pressure alarm, and a covering nurse responded by flushing both ports of his catheter. This led to a bolus of about 1.5 ml of concentrated treprostinil (about 50-fold more concentrated than standard infusions), resulting in nausea, vomiting, hypotension and syncope. The patient recovered, but in a patient with more severe PAH this error could easily have been fatal.

Policy changes—Policy changes aimed at error reduction were also reviewed during the nursing interviews. Interestingly, several centers underwent root-cause analysis and independently reached similar conclusions regarding avoidance of certain types of errors. For instance, after repeated errors where 1 patient received a cassette or bag intended for another patient, several institutions removed back-up cassettes and bags from the nursing units. Instead, prostacyclin cassettes or bags are now brought to the nursing unit just prior to the time the cassette is due to be changed. In other cases there was more concern that epoprostenol remain immediately available because of its short half-life, and only treprostinil back-up cassettes and bags were removed from the nursing units. Additional strategies included: using different color cassettes for treprostinil vs epoprostenol; highlighting patient names on the cassettes; requiring a second nurse to sign off on the medication record prior to administration; and adding patient involvement by asking them to double check the name and dose printed on the cassette.

Assessing outcome results for these policy changes is difficult because many centers lack a method for systematically tracking prostacyclin infusion errors and because the centers that are *now* tracking errors often began tracking them after policy changes were made. Two centers did report that epoprostenol cassette mix-ups decreased noticeably from multiple episodes yearly prior to policy changes to *no* cassette mix-ups per year over the last 18 to 24 months, after several policy changes. This included one center where the main intervention was requiring two nurses to sign off electronically, with no override allowed, and another institution that went several steps further—in addition to removing the back-up cassettes and asking a second nurse to sign off on cassette changes, this institution now requires the pharmacist to hand-deliver the appropriate cassette to the specific nurse and all cassette changes occur at the same time each day.

Electronic survey

Policies—Ninety-seven respondents completed the electronic survey on prostacyclin administration policies and errors. The prostacyclin experience of their centers varied, but most centers (72%) cared for 10 or more prostacyclin patients (Figure 1). Institution name was provided by 52 respondents, including one duplicate center. Similar to the nursing interviews, policies on pump use and prostacyclin storage varied. More than half (59%) of the respondents kept patients on their own ambulatory infusion pumps, 12% transitioned patients to hospital CADD pumps, and the remaining 28% transitioned patients to regular hospital infusion pumps. Back-up epoprostenol cassettes were stored on nursing units at 65% of the respondent's hospitals, whereas only 28% kept back-up treprostinil on the unit ($p < 0.05$).

Errors—Serious or potentially serious errors were reported by 65 (68%) of the 95 respondents who completed the survey section on errors. Some of the errors resulted in minimal or no symptoms, but 28 (29%) reported errors that led to a serious adverse event, including 9 deaths (Figure 2). The most commonly reported error, described by 31 respondents, involved flushing the dedicated prostacyclin line. Other errors reported by multiple respondents included use of the wrong medication dose due to calculation or concentration error ($N = 29$), use of a prostacyclin cassette or bag that was intended for a different patient ($N = 25$), incorrect rate programmed into the infusion pump ($N = 24$), and pump inadvertently stopped for a period of time ($N = 24$). There were also 15 miscellaneous errors written in by respondents (Table 1). Three of the 15 written-in errors involved an inappropriate change in patient weight. Prostacyclin infusions are dosed in nanograms per kilogram per minute, but rarely, if ever, should the dosing weight be changed when a patient is admitted to the hospital. Overall error rates were similar regardless of whether home infusion pumps or hospital pumps were used for prostacyclin administration ($p > 0.05$).

Discussion

In this survey we found that practitioners at a majority of PH centers reported errors related to prostacyclin infusions, including some errors that led to serious and even fatal events. Four additional fatal events were subsequently brought to our attention in the months since the survey closed. Although response bias with the electronic survey could have artificially inflated the number of reported errors, reported error types and frequencies were similar (or higher) in the nursing interviews in which the response rate was 100%.

Our findings suggest that prostacyclin infusion errors are not uncommon, and carry considerable safety risk. We believe the errors occur for several reasons: the identical appearance of treprostinil and epoprostenol cassettes; the multitude of available concentrations; the inability to store the cassettes within automated medication dispensing systems; the lack of familiarity of some nursing staff with the infusion pumps; the complex weight-based dosing; and the lack of standardized guidelines. Further, the narrow therapeutic dosing range, combined with patients who often have tenuous hemodynamics, means that even modest dosing errors can, and do, lead to serious or fatal outcomes.

Potential hospital policy changes

Although many of the errors relate to a mistake on the part of a nurse or pharmacist, addressing human error alone is unlikely to result in lasting improvements. Instead, best practices should be identified and implemented across centers treating PAH patients. Many centers reported making changes in their prostacyclin administration policies, often after errors, and a summary of these policies is presented in Table 2. The similarities in certain policy improvements across multiple experienced centers adds strength to these recommendations, but evidence-based support is lacking. It is the belief of the present investigators that the most important policies involve limiting the number of epoprostenol and treprostinil back-up cassettes stored on the nursing units at any given time in order to limit the opportunity for a mix-up. Also, requiring a second RN signature, as is commonly done with blood products, seems to be a prudent and important safety measure. These recommendations are intended only to represent a potential starting point for conversations on prostacyclin safety. Further study will be needed to better define best practice guidelines.

Limitations

In the larger electronic survey, approximately 50% of the respondents completed the survey anonymously, making duplicate entries from each center a possibility. However, of the 52 respondents who did leave their center name, only one center was represented twice, suggesting that this was not common. Because each individual may have cared for different patients, we did not remove this known duplicate. We are also unable to report true error rates, as the number of inpatient prostacyclin exposure days for each respondent's center is unknown. Additional study to more quantitatively assess errors and to evaluate additional hospital or ICU days incurred as a result of errors should be considered.

Conclusion

Similar to our findings, other studies have found that the most common type of medical error is incorrect quantity of drug.⁴ In this survey we found that serious and even fatal errors with intravenous prostacyclins are not uncommon. We are particularly concerned about the serious adverse events involving mix-up of one patient's medication with another, which was responsible for 1 of the 9 deaths reported and 29 of the serious events reported. Recommendation 7.3 of the Institute of Medicine's (IOM) Executive Summary of To Err is Human (2000) advises the Food and Drug Administration to improve drug safety, both in the pre- and post-marketing arenas.^{5,6} These concerns along with the findings in this survey suggest that hospitals should consider standardized prostacyclin administration policies, including ongoing training of staff to decrease the likelihood of a serious event or death. Special consideration will be required for home miniaturized pumps. Because most centers will also have patients on subcutaneous treprostinil infusions, policies should be in place for these infusions as well, as was suggested by Roncesvalles et al.⁷ The use of prostacyclins for symptomatic PH has resulted in an improvement in quality of life. It appears that achieving safer administration of these compounds is now warranted.

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Disclosure statement

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Appendix: electronic survey

This brief, nine-question survey is being sent to physicians, nurses and pharmacists who are involved in the care of pulmonary arterial hypertension patients in the United States. Specifically, we are interested in gaining an understanding of the types of errors that occur when administering intravenous prostacyclins in the hospital setting. When the data collection is complete, we plan to provide this information back to the PH community in a way that will not associate errors with any center names. You may list your center name on the survey or complete the survey in an anonymous fashion by simply not entering your center name. This survey will not capture any personal or computer information (e.g., IP address) of the respondent. In this study, you, the survey respondent, are considered the research subject. A modified informed consent process was approved by the University of Texas Southwestern Medical Center Institutional Review Board. Under this process, your consent is assumed by your proceeding with the survey. If you do not wish to complete the survey you may exit now.

Sincerely,

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Questions

1. How many intravenous (IV) prostacyclin patients (Flolan®, Remodulin® or generic epoprostenol) do you treat in your center?
None (if none, please stop here)
1 to 9
10 to 40
41 to 80
81 or greater
Other (please specify)
2. Practitioner type:
Nurse
Advanced Practice Nurse
Pharmacist
Physician
Other (please specify)
3. When IV Flolan®, Remodulin® or generic epoprostenol sodium patients are admitted to your hospital/center, you:
Leave patients on their own pump
Transition patients to a hospital CADD pump
Transition patients to a regular hospital infusion pump
Don't know
Other (please specify)
4. Do you keep backup Flolan® or generic epoprostenol cassettes (or bags) on the nursing unit?
Yes
No
Don't know
Other (please specify)
5. Do you keep backup Remodulin® cassettes (or bags) on the nursing unit?
Yes
No
Don't know

- Other (please specify)
6. Has your hospital/center EVER experienced one or more potentially serious errors where a patient received an incorrect dose of generic epoprostenol, Flolan® or Remodulin®?
- No
- Yes, once
- Yes, 2–5 instances
- Yes, 6–10 instances
- Yes, >10 instances
7. As a follow-up to the previous question, if errors occurred, which types of errors occurred? (check all that are applicable)
- No errors
- Wrong dose; a patient received another patient's cassette or bag which was at a different concentration
- Wrong dose; a patient received wrong dose due to wrong rate programmed into the pump
- Wrong dose; a patient received wrong dose due to a calculation or concentration error
- Medication stopped; a patient's pump was inadvertently left off for a period of time
- Error due to infusing other drugs into the dedicated prostacyclin line
- Error due to flushing the prostacyclin line
8. If errors occurred with prostacyclin administration, did any of these result in significant clinical consequences?
- No, no errors
- No, patient(s) experienced no symptoms
- No, patient(s) had only mild or moderate symptoms
- Yes, patient(s) experienced severe symptoms
- Yes, patient death(s) [if you chose this, please answer Question 9 below]
9. Please list number of deaths related to prostacyclin errors.

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Figure 1.
Number of prostacyclin patients being treated at electronic survey respondent's center.

Figure 2.
Error severity, as reported in the electronic survey.

Table 1**Miscellaneous Write-In Errors**

Pump malfunction—medication ran out.
Two instances of where patients received approximately 0.5 ml “extra” of epoprostenol during a line change, causing flushing, hypotension and headache for about 30 minutes.
Patient off epoprostenol because of failure to consider line dead space when changing central line.
Dose infusing is correct but label on syringe was wrong.
Errors occurred during switch from home to hospital infusion pump, and another error in calculation led to a significantly increased dose.
Accidental disconnect once.
Error due to computer defaulting to admission weight vs dosing weight.
Wrong dose due to using admission weight vs drug initiation weight.
Patient was given expired cassette.
Purge syringe (to prime Hickman) was not pulled from mix.
Solution was full strength.
Nurse changed line over and left room, connection not tight and blood on floor.
Wrong dose due to patient’s dose weight changed in calculation resulting in too much or too little prostacyclin.
Failed IV access for a patient on epoprostenol with a 12-hour “line holiday” during treatment for sepsis.
Flushing episode occurred due to involvement of a non-PGI ₂ -specific certified nurse.
Infusing drugs in the dedicated prostacyclin line occurred in the OR by anesthesia.

Table 2**Potential Hospital Prostacyclin Infusion Policies****Potential pharmacy policies:**

- Double check all calculations for concentration and infusion rate.
- Contact the pulmonary hypertension clinic or the patient's specialty pharmacy upon admission to obtain the patient's dose, dosing weight, concentration and pump rate. Confirm with the patient that this is correct, and that the pump is actually going at this rate. If a titration schedule exists, obtain a copy and send it with the patient to the floor; post it in the room next to the patient's bed as well as in the medication record.
- Ensure pharmacy labels are easy to read including name, date, concentration and pump rate.
- Ensure that all information is clearly stated in the medication administration record, including the time for next cassette change and whether ice packs are required.
- If using cassettes, consider using a different color cassette, or a different color or type of label, for treprostinil vs epoprostenol.

Potential nursing policies:

- Place markers on the epoprostenol/treprostinil line near connection sites stating "do not flush" and "dedicated epoprostenol/treprostinil line."
- Institute a policy where two nurses sign off on the cassette or bag change, as well as any change in infusion rate.
- Do not keep back-up treprostinil cassettes or bags on the nursing unit unless they can be kept in a secure location, unique to the patient, such as a medication dispensing system. If treprostinil must be kept on the nursing unit and it does not fit in the medication dispensing system, do not store it in the refrigerator with epoprostenol as it does not require refrigeration and increases the opportunity for a mix-up.
- Decide whether back-up epoprostenol bags or cassettes will be kept on the nursing unit.
- If a refrigerated medication dispensing system is available, then storage of epoprostenol on the unit is generally desirable so as to be available in an emergency.
- If only a common medication refrigerator is used, consider whether the risks of mix-up between patients outweigh the benefits.
- Ask the patient or caregiver to be involved in their care, and confirm name, concentration, dose and pump rate at each cassette or bag change or whenever a rate change is made.
- Each shift, document that pump is running correctly and at a rate that matches the order on the medication administration record, regardless of whether a new cassette or bag change is due.

Miscellaneous:

- Conduct regular, at least annual, pump training for all nurses in intensive-care and telemetry units and any other floors where pulmonary hypertension patients are likely to be admitted. This training may be provided in conjunction with specialty pharmacies, particularly when home infusion pumps are used in the hospital setting.
- If the hospital has a rapid response team, they should also be trained as experts in the use of the home infusion pumps.

Policy decisions where risk and benefit are less certain:

- Decide whether to keep patients on their home infusion pumps.
- Decide whether to standardize the prostacyclin concentration(s) or match the concentration used by the patient