OPEN

Unexpected Interruptions in the Inhaled Epoprostenol Delivery System: Incidence of Adverse Sequelae and Therapeutic Consequences in Critically Ill Patients

Jason M. Block, MD[1]
Jai Madhok, MD, MSE[2]
Clark G. Owyang, MD[3]
Kristen R. Merriman, RRT, MS[4]
Stephen J. Ruoss, MD[5]
Vidya K. Rao, MD, MBA[2]

OBJECTIVES: Inhaled epoprostenol is a continuously delivered selective pulmonary vasodilator that is used in patients with refractory hypoxemia, right heart failure, and postcardiac surgery pulmonary hypertension. Published data suggest that inhaled epoprostenol administration via vibrating mesh nebulizer systems may lead to unexpected interruptions in drug delivery. The frequency of these events is unknown. The objective of this study was to describe the incidence and clinical consequences of unexpected interruption in critically ill patients.

DESIGN: Retrospective review and analysis.

SETTING: Stanford University Hospital, a 605-bed tertiary care center.

PATIENTS: Patients receiving inhaled epoprostenol in 2019.

INTERVENTIONS: No interventions.

MEASUREMENTS AND MAIN RESULTS: Clinical indication, duration of inhaled epoprostenol delivery, mode of respiratory support, and documented unexpected interruption. In 2019, there were 493 administrations of inhaled epoprostenol in 433 unique patients. Primary indications for inhaled epoprostenol were right heart dysfunction (n = 394; 79.9%) and hypoxemia (n = 92; 18.7%). Unexpected delivery interruptions occurred in 31 administrations (6.3%). Median duration of therapy prior to unexpected interruption was 2 days (interquartile range, 2–5 d). Respiratory support at the time of unexpected interruption was mechanical ventilation (61.3%), high-flow nasal cannula (35.5%), and noninvasive positive pressure ventilation (3.2%). Adverse sequelae of unexpected interruption included elevated pulmonary artery pressures (n = 12), systemic hypotension (n = 8), hypoxemia (n = 8), elevated central venous pressure (n = 4), and cardiac arrest (n = 1). Therapeutic interventions following unexpected interruption included initiation of inhaled nitric oxide (n = 21), increase in vasoactive medication (n = 2), and increase in respiratory support (n = 2). Most of the adverse events were Common Terminology Criteria for Adverse Events grade 3 and 4 (93.5%).

CONCLUSIONS: A retrospective review of patients receiving inhaled epoprostenol via vibrating mesh nebulizer in 2019 revealed interruptions in 6.3% of administrations with most of these interruptions requiring therapeutic intervention. The true incidence of unexpected interruption and subsequent rate of unexpected interruption's requiring intervention is unknown due to the reliance on unexpected interruption identification and subsequent documentation in the electronic medical record. Sudden interruption in inhaled epoprostenol delivery can result in severe cardiopulmonary compromise, and on rare occasion, death.

KEY WORDS: aerogen; inhaled epoprostenol; medical device safety; nitric oxide; vibrating mesh nebulizer

DOI: 10.1097/CCE.0000000000000548

Inhaled epoprostenol (iEpo) is a synthetic prostacyclin analog that is used off-label as a selective pulmonary vasodilator (SPV) in critically ill patients with refractory hypoxemia, right ventricular failure, and postcardiac surgery pulmonary hypertension (PH) (1, 2). By relaxing pulmonary vascular smooth muscle in ventilated portions of the lung, iEpo improves ventilation-perfusion (V/Q) matching and reduces pulmonary vascular resistance (PVR) (3, 4). Published studies suggest that SPV therapy decreases pulmonary artery pressures, augments cardiac output, and improves oxygenation (2, 5). While the physiologic effects of iEpo are accepted, the reliability of current iEpo delivery methods remains uncertain.

Vibrating mesh nebulizers (VMNs) are widely used to deliver iEpo. The Aerogen Solo (Aerogen, Galway, Ireland) is approved by the Food and Drug Administration to continuously nebulize medications such as albuterol. It is the only single-patient use VMN that is compatible with invasive mechanical ventilation (MV) and is used by many health systems. Published data, however, have reported concerns with the reliability of this technology. In a survey of respiratory therapists, 22% noted frequent or occasional drug delivery interruption due to device failure (6). Additionally, Gowda et al (7) reported unexpected cessation in the delivery of normal saline and distilled water in 12 of 40 (30%) experimental runs using the Aerogen Solo.

Given the use of iEpo in patients with severe physiologic compromise, coupled with its short half-life of 2–3 minutes, unexpected interruptions (UIs) in delivery can result in cardiopulmonary decompensation due to rebound increases in PVR and/or changes in V/Q matching (8). We report the incidence, subsequent physiologic adverse events (AEs), and clinical consequences of unplanned UIs identified by bedside clinicians in patients receiving iEpo via the Aerogen Solo VMN.

METHODS

After obtaining approval from the Stanford University Institutional Review Board (Number 55025), all administrations of iEpo in 2019 were reviewed using pharmacy records. If iEpo was terminated and subsequently reinitiated on an individual patient, this was regarded as two separate administrations. The electronic health record (EHR) was reviewed to obtain demographic information, indication for use, mode of delivery, duration of use, and date of UI when applicable. A UI refers to an abrupt, unplanned cessation in iEpo delivery due to device malfunction. UIs were identified by the clinical team who directly examined the Aerogen Solo nebulizer system when patients experienced abrupt clinical deterioration. Furthermore, transducer position, laboratory studies, and hemodynamic data were taken into consideration in determining the etiology of physiologic compromise. Clinical deterioration was attributed to interruptions in iEpo delivery when there were abrupt changes in clinical condition, visual inspection of the iEpo delivery system revealed pooling of fluid and a lack of nebulization, and the reinitiation of iEpo resulted in physiologic improvement. If an AE was noted, two reviewers independently assessed the EHR documentation to identify physiologic events and therapeutic maneuvers. The AE severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), a system initially developed for chemotherapy-related clinical events that was adapted to describe AEs (9) (**Supplemental Table 1**, http://links.lww.com/CCX/A812). Discordant assessments were adjudicated by a third reviewer.

The iEpo formulation used at Stanford University Medical Center during this time period was VELETRI (Actelion Pharmaceuticals US, South San Francisco, CA). The delivery system consisted of a Becton Dickinson Alaris (Becton Dickinson, San Jose, CA) syringe pump that infused epoprostenol through pump tubing to the Aerogen Solo, which delivered epoprostenol to the patient via high-flow nasal cannula (HFNC), noninvasive positive pressure ventilation (NIV), or MV modes (**Fig. 1*A***). The default initial dose of iEpo was 0.05 μg/kg/min (10 mL/hr into the nebulizer cup). The Aerogen Solo was exclusively used by the institution for continuous nebulization during the study period.

RESULTS

There were 493 administrations of iEpo to 433 unique patients, with 31 instances of UI (6.3%) (**Table 1**). The median (25–75th interquartile range [IQR]) duration of iEpo use was 3 days (2–6 d), with a total of 2,398 iEpo-days/yr. Forty-three percent of patients receiving iEpo were mechanically ventilated. Among

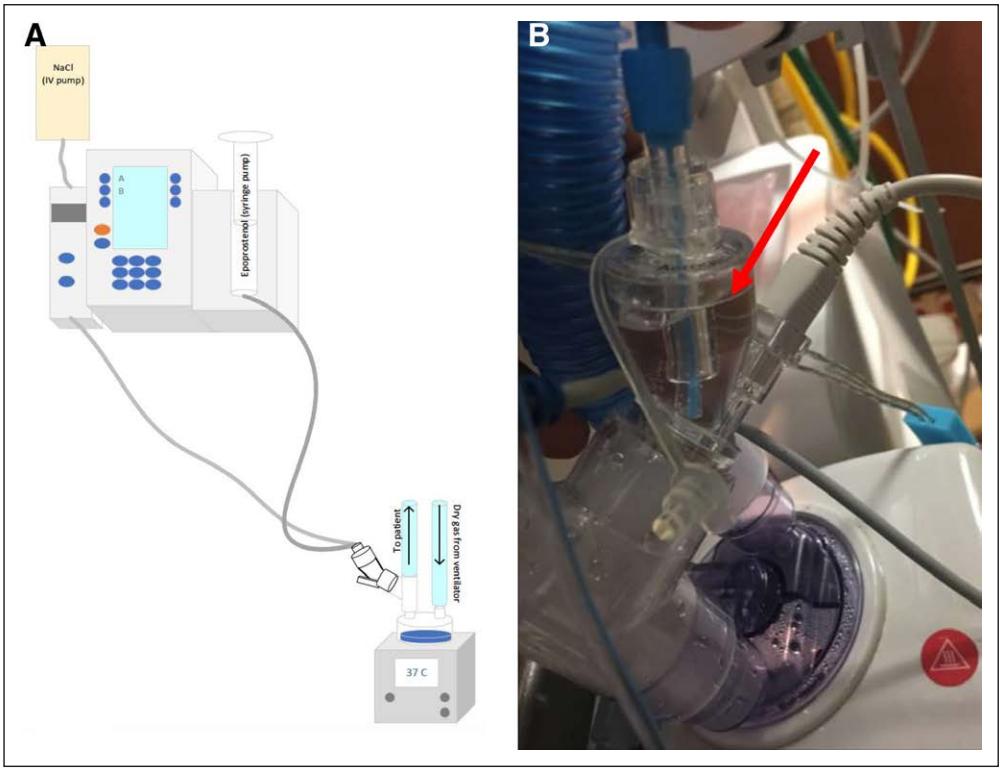

Figure 1. Inhaled epoprostenol delivery system and example of an unexpected interruption in medication delivery. **A**, Schematic of inhaled epoprostenol delivery system with syringe pump delivering epoprostenol to Aerogen Solo. **B**, Epoprostenol accumulation in Aerogen Solo delivery chamber. The *red arrow* indicates accumulation in the medication chamber with no aerosol delivery to the patient. NaCl = sodium chloride.

UIs, 19 (61.3%) occurred with use of MV, 11 (35.5%) with HFNC, and 1 (3.2%) with NIV. There was no significant difference between observed and expected frequencies of UI by mode of respiratory support χ^2 (2, n = 493 = 1.88; p = 0.39).

The most frequently documented physiologic AEs were elevated pulmonary artery pressures (n = 12), hypotension (n = 8), and hypoxemia (n = 8). One patient sustained cardiac arrest related to iEpo UI (**Table 2**). Therapeutic interventions employed to manage the physiologic consequences of UI included transitioning to inhaled nitric oxide (iNO) (n = 21), increasing vasoactive agents (n = 2), and increasing respiratory support (n = 2). The CTCAE scores ranged from 2 to 5, with the majority constituting life-threatening AEs, CTCAE 4 (n = 18; 58.1%).

DISCUSSION

This study describes the incidence and AEs associated with iEpo delivery interruption when using the Aerogen Solo in critically ill patients. We noted a UI rate of 6.3%, which is much lower than a 30% failure rate of Aerogen VMN devices in a 2017 study (7). Due to the short half-life of this medication, UI in iEpo delivery may cause severe cardiopulmonary compromise secondary to an abrupt increase in PVR and loss of V/Q matching. The AEs of UI ranged from clinically silent to profound hypoxemia and hemodynamic instability. This is of particular importance given the use of the Aerogen Solo for continuous nebulization in many institutions.

The majority of the UIs were classified as life-threatening AEs. Despite the potentially serious outcomes, iEpo delivery interruptions have not been widely reported in the literature. There was only one interruption using an Aerogen device reported to the Manufacturer and User Facility Device Experience (MAUDE) database in 2019 (10). The off-label use of this medication and the Aerogen Solo delivery system may preclude reporting of AEs via the MAUDE database.

In 67.7% of patients with UI, we transitioned from iEpo to iNO. iNO is an alternative SPV and is delivered as a gas, while iEpo is a nebulized liquid. In contrast to iEpo, the iNO delivery system is equipped with interruption alarms and reserve delivery mechanisms (11), which may result in more reliable delivery. While these medications have been found to have similar efficacy in managing refractory hypoxemia and postcardiac surgery PH (12–15), the cost of iNO precludes its widespread use. The estimated cost of iEpo is approximately $1.30–$6.52/hr, while iNO is approximately $220.46/hr (16).

This study has several limitations. First, our reported UI rate is likely underestimated (i.e., many UIs were likely not identified) due to the retrospective

TABLE 1.
Patient Demographics and Summary Characteristics of Inhaled Epoprostenol Delivery and Interruptions via the Aerogen Solo Nebulizing System

Characteristic	iEpo Instances (*n* = 493)	iEpo Interruptions (*n* = 31)	No Interruptions (462)
Age (yr), median (IQR)	60 (48–69)	62 (55–68)	59 (47–69)
Male, *n* (%)	303 (61.5)	20 (64.5)	283 (61.3)
Race, *n* (%)			
Non-Hispanic/Latino	323 (65.5)	24 (77.4)	299 (64.7)
Hispanic/Latino	67 (13.6)	3 (9.7)	64 (13.9)
African American	32 (6.5)	1 (3.2)	31 (6.7)
Asian	58 (11.8)	2 (6.5)	56 (12.1)
American Indian, Pacific Islander, or Alaska native	6 (1.2)	1 (3.2)	5 (1.1)
Unknown	7 (1.4)	0	7 (1.5)
Indications for iEpo, *n* (%)			
RV dysfunction, RV protection, or pulmonary hypertension	394 (79.9)	29 (93.5)	365 (79.0)
Hypoxemic respiratory failure	92 (18.7)	2 (6.5)	90 (19.5)
Other	7 (1.4)	0	7 (1.5)
Mode of delivery, *n* (%)			
MV	215 (43.6)	19 (61.3)[a]	202 (43.7)
HFNC	71 (14.4)	11 (35.5)[a]	68 (14.7)
NIV	7 (1.4)	1 (3.2)[a]	7 (1.5)
MV, HFNC[c]	172 (34.9)		162 (35.1)
MV, NIV[c]	3 (0.6)		3 (0.7)
HFNC, NIV[c]	6 (1.2)		6 (1.3)
MV, HFNC, NIV[c]	19 (3.9)		14 (3.0)
Duration of iEpo administration (d), median (IQR)	3 (2–6)	2 (2–5)[b]	3 (2–6)

HFNC = high-flow nasal cannula, iEpo = inhaled epoprostenol, IQR = interquartile range, MV = mechanical ventilation, NIV= noninvasive ventilation, RV = right ventricle.

[a]Mode of delivery at the time of iEpo dispensing failure.

[b]Days on iEpo prior to dispensing failure.

[c]Patients who received iEpo via more than one modality during their ICU stay.

study design, challenging recognition, and the general under-reporting of safety events. Short of a high index of suspicion for iEpo delivery interruption, clinical deterioration may have been attributed to other etiologies. The absence of a medication delivery failure alarm system further contributes to under-recognition.

Due to overall under-recognition of UIs, the estimated incidence of AEs classified as severe in our study likely overestimates the proportion of events that were life-threatening. However, it should be noted that as our institutional awareness of UIs of iEpo expanded, clinicians were able to recognize delivery interruptions and intervene in an expeditious fashion, mitigating further decompensation. In such cases, the severity of sequelae was likely minimized due to clinician vigilance and immediate troubleshooting of the delivery system. Detection of iEpo interruption is performed by inspecting the nebulizer cup for the presence of pooled liquid and the absence of aerosol in the chamber (**Fig. 1*B***). Troubleshooting the Aerogen Solo VMN may include gentle agitation of the nebulizer cup to resume aerosolization, replacement of the nebulizer, controller and/

TABLE 2.

Common Terminology Criteria for Adverse Events Scores, Physiologic, and Therapeutic Consequences in Patients Who Had Unexpected Interruptions due to Aerogen Solo Nebulizing System Failure

Common Terminology Criteria for Adverse Events Score, *n* (%)		Physiologic Sequelae, *n*[a]		Therapeutic Consequences, *n*[a]	
1	0	↓Oxygen saturation	8	↑Vasoactive support	2
2	1 (3.2)	↑Pulmonary artery pressure	12	↑Respiratory support	2
3	11 (35.5)	↑Central venous pressure	4	Switch to inhaled nitric oxide	21
4	18 (58.1)	↓Mean arterial pressure	8		
5	1 (3.2)	Cardiac arrest	1		

[a]Physiologic and therapeutic sequelae were not available for all interruptions, only those that were explicitly documented in the electronic health record or event reporting system are included.

or the controller cable, dabbing the cup to get rid of possible bubble lock, and finally transitioning to an alternative SPV. In our institution, we commonly transition patients with tenuous hemodynamics from iEpo to iNO due to the presence of safety features incorporated into delivery system. We preferentially use iEpo as our first-line SPV but have transitioned to the High Output Extended Aerosol Respiratory Therapy continuous nebulizer, which we have found to be more reliable. Institutions that continue to administer iEpo via the Aerogen Solo should incorporate safety protocols to ensure assessment of the delivery system at regular intervals and implement efforts to promote clinician awareness of interruptions. However, the most important risk mitigation strategy would be for the manufacturer to incorporate safety measures such as a delivery interruption alarm.

The results of this study are particularly relevant as many institutions exclusively use the Aerogen Solo for administration of iEpo in critically ill patients. However, the reliability of iEpo delivery in a physiologically fragile patient population should remain an important consideration. Clinicians caring for patients receiving iEpo via VMNs should be vigilant for UI. In the absence of an effective alarm system, frequent bedside evaluations of the delivery system or a change to a different device are required.

CONCLUSIONS

In this retrospective study, we find iEpo administered via the Aerogen Solo is prone to UI that can result in severe, acute cardiopulmonary compromise. The intensivist should be familiar with the possibility of iEpo delivery interruption and understand troubleshooting techniques, alternative SPV delivery systems, and alternative SPVs. Further investigations are required to fully understand the clinical burden of iEpo delivery failure in critically ill patients.

1 Department of Anesthesiology, Pain, and Perioperative Medicine, Division of Critical Care Medicine, Stanford University School of Medicine, Stanford, CA.

2 Department of Anesthesiology, Pain, and Perioperative Medicine, Divisions of Critical Care Medicine and Adult Cardiothoracic Anesthesiology, Stanford University School of Medicine, Stanford, CA.

3 Department of Medicine, Division of Pulmonary and Critical Care Medicine, New York-Presbyterian/Weill Cornell Medical Center, New York, NY.

4 Department of Respiratory Care Services, Stanford Healthcare, Palo Alto, CA.

5 Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Stanford University School of Medicine, Stanford, CA.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: blocja02@luther.edu

REFERENCES

1. Actelion Pharmaceuticals US: VELETRI (Epoprostenol) [package insert]. US Food and Drug Administration website. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022260s005lbl.pdf. Accessed October 20, 2020

2. De Wet CJ, Affleck DG, Jacobsohn E, et al: Inhaled prostacyclin is safe, effective, and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery. *J Thorac Cardiovasc Surg* 2004; 127:1058–1067
3. Haché M, Denault A, Bélisle S, et al: Inhaled epoprostenol (prostacyclin) and pulmonary hypertension before cardiac surgery. *J Thorac Cardiovasc Surg* 2003; 125:642–649
4. Peter M, Jaffe B, Gilbert C, et al: Effect of inhaled epoprostenol on oxygenation, outcome, and diuresis in critically ill patients. *Chest* 2011; 140:287A
5. Fuller BM, Mohr NM, Skrupky L, et al: The use of inhaled prostaglandins in patients with ARDS: A systematic review and meta-analysis. *Chest* 2015; 147:1510–1522
6. Kauffman GW: RT Awareness and Preferences Regarding Pulmonary Hypertension Treatment. 2018. Available at: https://rtmagazine.com/products-treatment/pharmaceuticals/rt-awareness-preferences-regarding-pulmonary-hypertension-treatment/. Accessed November 23, 2020
7. Gowda AA, Cuccia AD, Smaldone GC: Reliability of vibrating mesh technology. *Respir Care* 2017; 62:65–69
8. Dzierba AL, Abel EE, Buckley MS, et al: A review of inhaled nitric oxide and aerosolized epoprostenol in acute lung injury or acute respiratory distress syndrome. *Pharmacotherapy* 2014; 34:279–290
9. US Department of Health and Human Services: Common Terminology Criteria for Adverse Events (CTCAE) v5.0. National Institute of Health. 2017. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Accessed October 30, 2020
10. US Food and Drug Administration: Manufacturer and User Facility Device Experience (MAUDE). Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM. Accessed June 10, 2020
11. U.S. Department of Health and Human Services Food and Drug Administration Center for Devices and Radiological Health: Guidance Document for Premarket Notification Submissions for Nitric Oxide Delivery Apparatus, Nitric Oxide Analyzer and Nitrogen Dioxide Analyzer. 2000. Available at: https://www.fda.gov/media/71766/download. Accessed April 12, 2020
12. Hawn JM, Wanek M, Bauer SR, et al: Effectiveness, safety, and economic comparison of two inhaled epoprostentol products (Flolan and Veletri) in cardiothoracic surgery patients. *Ann Pharmacother* 2018; 52:956–964
13. Torbic H, Szumita PM, Anger KE, et al: Inhaled epoprostenol vs inhaled nitric oxide for refractory hypoxemia in critically ill patients. *J Crit Care* 2013; 28:844–848
14. Khan TA, Schnickel G, Ross D, et al: A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. *J Thorac Cardiovasc Surg* 2009; 138:1417–1424
15. Winterhalter M, Simon A, Fischer S, et al: Comparison of inhaled iloprost and nitric oxide in patients with pulmonary hypertension during weaning from cardiopulmonary bypass in cardiac surgery: A prospective randomized trial. *J Cardiothorac Vasc Anesth* 2008; 22:406–413
16. Rao V, Ghadimi K, Keeyapaj W, et al: Inhaled nitric oxide (iNO) and inhaled epoprostenol (iPGI2) use in cardiothoracic surgical patients: Is there sufficient evidence for evidence-based recommendations? *J Cardiothorac Vasc Anesth* 2018; 32:1452–1457