JPPT | Case Report

Inpatient Transition From Intravenous to Inhaled Treprostinil in a Pediatric Patient

David Procaccini, PharmD, MPH; Dennis Delany, MD; Abigail Self, CRNP; Patricia Lawrence Kane, CRNP; and John D. Coulson, MD

We report a case of a 7-year old male with idiopathic pulmonary arterial hypertension, successfully transitioned from an intravenous infusion to inhaled treprostinil during inpatient admission, after his intentional removal of multiple central venous catheters. He had no clinical, echocardiographic, or serum biomarker evidence of loss of control of pulmonary arterial hypertension during the 4-day transition. The patient was discharged home without complications, and 3 weeks after discharge the patient's pulmonary hypertension remained well controlled per clinical and echocardiographic evidence, including a significantly improved 6-minute walk distance test.

ABBREVIATIONS CVC, central venous catheter; FiO_2, fraction of inspired oxygen; iNO, inhaled nitric oxide; IV, intravenous; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro–brain-type natriuretic peptide; PAH, pulmonary arterial hypertension; RV, right ventricular; 6MWD, 6-minute walk distance; SQ, subcutaneous; TR, tricuspid regurgitation; WHO, World Health Organization

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Introduction

Pulmonary arterial hypertension (PAH) is a rare, progressive, and life-threatening disease that may result in right heart failure and death when unmanaged.[1] Pharmacologic modalities for treatment remain limited. However, prostacyclin analogs are now a standard of care for chronic management and are often used as part of combination therapy with other agents.[1] Clinical benefits of prostacyclin therapy include improved exercise capacity and hemodynamics, and overall survival in both adult and pediatric patients.[1,2] Of the prostacyclins available, treprostinil has become a preferred agent because of a longer half-life of approximately 4.5 hours in adult patients.[3,4] Treprostinil clearance may be enhanced in pediatric patients compared with adults, but the half-life still exceeds that of other available agents (epoprostenol, 3–6 minutes; iloprost, 20–30 minutes).[5–9] Treprostinil is most often provided as a continuous intravenous (IV) or subcutaneous (SQ) infusion, although administration via these routes has been associated with complications, including central line infections and infusion site pain.[9–11] In 2009, an inhaled, sterile formulation of treprostinil (Tyvaso; United Therapeutics Corp, Research Triangle Park, NC) delivered via an Optineb inhalation device (United Therapeutics) became available.[12] Given the need for 4-times-daily administration compared with iloprost (6–9 times/day), and the favorable outcomes (improved 6-minute walk distance [6MWD], N-terminal pro–brain-type natriuretic peptide [NT-pro BNP] concentrations, and quality of life) of a randomized clinical trial, inhaled treprostinil is now an appealing treatment option for PAH in adults.[13] Although use in pediatric patients remains off-label, inhaled treprostinil has been used effectively in patients as young as 3 years of age, and was associated with improvement in exercise capacity and World Health Organization (WHO) functional class when added to background targeted PAH therapy, without significant adverse effects.[13,14] Although product information provides recommendations for initiating inhaled treprostinil for prostacyclin-naive patients, information on transitioning patients from established IV or SQ to inhaled therapy remains limited.[12] We describe a case of successful transition from an IV infusion to inhaled treprostinil in a pediatric patient during inpatient admission.

Case Report

A 7-year-old, 50-kg African American male with a significant medical history, including autism spectrum disorder with associated developmental and speech delay (not receiving pharmacologic treatment), neurofibromatosis type 1, exotropia, obstructive sleep apnea, and obesity, initially presented to our institution 4 weeks after an asymptomatic COVID-19 infection because of development of dyspnea upon exertion, decreased exercise tolerance, intermittent vomiting, and presyncope during ambulation. An echocardiogram revealed paradoxic systolic interventricular septal positioning, severe right atrial and right ventricular (RV) dilation, moderately diminished RV function, and a peak

Table 1. Cardiac Catheterization and Pulmonary Vasoreactivity Testing Measurements

Measurement*	100% FiO_2 and iNO 20 ppm	100% FiO_2, off iNO
RA, mean pressure	9	9
RPA pressure		
Systolic/Diastolic	57/30	63/32
Mean	43	47
LPA pressure		
Systolic/Diastolic	60/30	
Mean pressure	45	
PCW pressure	9	9
Left radial artery pressure		
Systolic/Diastolic	58/31	86/49
Mean	43	60
CI, L/min/m^2	3.18	3.13
PVRi, Wood units × m^2	11.01	12.16
SVRi, Wood units × m^2	16.98	16.32
PVR/SVR	0.65	0.75

CI, cardiac index; FiO_2, fraction of inspired oxygen; iNO, inhaled nitric oxide; LPA, left pulmonary artery; PCW, pulmonary capillary wedge; PVRi, pulmonary vascular resistance index; RA, right atrium; RPA, right pulmonary artery; SVRi, systemic vascular resistance index

* All pressures measured as millimeters of mercury (mm Hg).

tricuspid regurgitation (TR) gradient of 72 mm Hg, all consistent with PAH. The patient also had an elevated blood N-terminal pro–brain-type natriuretic peptide (NT-proBNP) concentration of 7275 pg/mL (reference range, 0–125 pg/mL). Given the history of neurofibromatosis type 1, with concomitant recent COVID infection and obstructive sleep apnea, he was classified as group 5, pulmonary hypertension with unclear and/or multifactorial mechanisms, per the Sixth WHO World Symposium on Pulmonary Hypertension.[15–17] The patient was admitted to the pediatric cardiac intensive care unit for management, including supplemental oxygen, inhaled epoprostenol, inhaled nitric oxide (iNO), and IV milrinone infusion. The blood NT-proBNP concentration decreased to 4571 pg/mL within 48 hours; however, repeat echocardiogram remained consistent with severe pulmonary hypertension and RV dysfunction. The patient was then initiated on sildenafil orally 5 mg every 8 hours for 24 hours, which was titrated to 20 mg orally every 8 hours over the next 9 days. At the time of sildenafil initiation, a peripherally inserted central catheter line was also placed in anticipation of initiation of a continuous infusion of IV treprostinil. Repeat echocardiography immediately prior to initiation of IV treprostinil showed severe dilatation of the RV, severely diminished RV systolic function, and a TR gradient of 62 mm Hg, still consistent with pulmonary hypertension. After the first titration of oral sildenafil to 10 mg orally every 8 hours, IV treprostinil was initiated at 2 ng/kg/min and titrated by 1 ng/kg/min every 6 to 8 hours, to 18 ng/kg/min. On day 13 of treatment, the patient underwent diagnostic cardiac catheterization with pulmonary vasoreactivity testing with iNO. The patient presented to the cardiac catheterization suite receiving milrinone 0.5 mcg/kg/min, IV treprostinil 18 ng/kg/min, 100% fraction of inspired oxygen (FiO_2), iNO 20 ppm, sildenafil 20 mg orally 3 times daily, and furosemide 10 mg orally daily. Hemodynamic instability occurred during the induction of anesthesia, but responded favorably to 2 IV doses of epinephrine. The measurements obtained during the procedure are outlined in Table 1. The first set of measurements was obtained with delivery of both 100% FiO_2 and iNO 20 ppm. The findings are consistent with severe, precapillary PAH (mean pulmonary arterial pressure, [mPAP] >20 mm Hg, pulmonary arterial wedge pressure ≤15 mm Hg, pulmonary vascular resistance ≥3 Wood units × m^2).[18] Discontinuation of the iNO did not indicate positive vasoreactivity to iNO, defined as a change of mPAP ≥10 mm Hg or an overall change of mPAP by 20% with unchanged or increased cardiac output.[18,19] The continuation of IV treprostinil and sildenafil during the catheterization may have influenced the apparent lack of vasoreactivity to iNO. After cardiac catheterization, ambrisentan 5 mg orally daily was initiated, and then increased to 10 mg orally once daily after 5 days. Twenty-four hours after ambrisentan initiation, the patient was transitioned from sildenafil to tadalafil 20 mg orally once daily for 24 hours, prior to increasing to 40 mg once daily. A 6MWD test was then performed. The patient walked a distance of 700 feet, but stopped before 6 minutes had elapsed. There was no significant change in oxygen saturation by pulse oximetry from baseline to completion of test, but there was a nadir of 92%. The IV treprostinil was then further increased by 1 ng/kg/min every 24 hours to a dose of 30 ng/kg/min. A central venous catheter (CVC; Broviac, Bard Access Systems, Salt Lake City, Utah) was placed and the peripherally inserted central catheter line was removed, in preparation for discharge. After the patient received 24 hours of treprostinil at 30 ng/kg/min, he was discharged home.

Forty-one days after the initial discharge, the patient presented to the emergency department after his intentional removal of the CVC. Intravenous treprostinil was infused via a peripheral line, a new CVC was placed within 24 hours of presentation, and the patient was discharged home after 24 hours. Twelve days following discharge, the patient presented again to the emergency department after intentional removal of the second CVC, and a peripheral line was placed to continue IV treprostinil therapy. Because of the behavior-related difficulty maintaining stable IV

Table 2. Dosing Transition From Intravenous (IV) to Inhaled Treprostinil in Our Patient

Step*	IV Treprostinil Dose, ng/kg/min	Inhaled Treprostinil Dose†
1	27	
2	18	24 mcg QID (4 inhalations)
3	12	36 mcg QID (6 inhalations)
4	6	48 mcg QID (8 inhalations)
5	Off	54 mcg QID (9 inhalations)

* 24 hours between each step.
† 1 inhalation = 6 mcg. Subsequent increase in inhaled treprostinil made 2 hours after reduction of the IV dose.

access, alternative modalities for prostacyclin therapy were considered and discussed among the Pediatric Pulmonary Hypertension care team, consisting of a cardiac intensivist, a pediatric interventional cardiologist, a nurse practitioner, and a clinical pharmacy specialist. Oral treprostinil was considered; however, it was rejected as an option because of 1) the lack of published experience with use in pediatric patients; 2) the potential need for many tablets to achieve a therapeutic dose; and 3) given the osmotic, extended-release formulation of the tablets, concern for rapid rise in serum concentrations and adverse hemodynamic effects if chewed or crushed prior to swallowing.[20] After extensive deliberation, the decision was made to transition the patient from IV to inhaled treprostinil therapy during the hospital admission. After prior authorization from the patient's insurance company was obtained, an inhaled treprostinil (Tyvaso) starter kit was ordered from a specialty pharmacy and delivered to the hospital. In preparation for the transition and to assess whether the patient would tolerate dose reductions of IV therapy, we first decreased the IV treprostinil infusion by 1 ng/kg/min every 24 hours from 30 to 27 ng/kg/min and observed no changes in symptoms. The patient and caregivers received education and training on use of the Tyvaso system during the course of 2 hours. The patient was able to consistently demonstrate acceptable use of the system. The transition from IV to inhaled treprostinil commenced 3 hours later. The full transition, outlined in Table 2, occurred over 4 days following a similar approach described by Enderby et al.[21] The patient experienced no adverse effects from use of inhaled treprostinil during initiation or titration of therapy. Twenty-four hours after completion of the transition, the patient's blood NT-proBNP was 174 pg/mL and echocardiography displayed mild dilatation of the RV with normal RV systolic function and a TR gradient of 48 mm Hg, essentially unchanged from previous values while on IV treprostinil. A repeat 6MWD test was performed. The patient covered a distance of 800 feet, with no significant change in oxygen saturation by pulse oximetry from baseline to completion of the test. During the patient's first outpatient clinic visit (7 days after discharge), the echocardiogram displayed low-normal RV function (tricuspid annual plane systolic excursion, 1.8), with a reduced pulmonary regurgitation gradient (to 14 mm Hg from 36–39 mm Hg originally), and there was a substantial increase in distance walked during the 6MWD (1379 feet) compared with the previous test. The patient also continued to demonstrate appropriate use of the Tyvaso system, with no reported side effects from inhaled treprostinil, during the next several weeks. The echocardiographic, blood NT-proBNP, and 6MWD test changes, and full pharmacologic treatment course are outlined in Table 3.

Discussion

There remains a paucity of literature regarding the use of inhaled treprostinil in pediatric patients, specifically with transition from IV or SQ infusions, although there are previously published reports of this transition in adult patients. In a multicenter retrospective case series in adult patients, de Jesus Perez et al[22] describe the transition of 18 WHO group 1 PAH patients from IV treprostinil or epoprostenol (n = 18) to inhaled treprostinil.[22] The specific transition methods were not explicitly outlined and varied among centers. However, the most common strategy was initiation of inhaled treprostinil at 3 breaths (18 mcg) every 6 hours and increased daily as tolerated to a final goal of 9 breaths (54 mcg) 4 times daily, while there was simultaneous weaning off the IV or SQ prostacyclin. Although most patients who transitioned to inhaled treprostinil demonstrated no statistically significant worsening of hemodynamics or 6MWD, a subset of patients demonstrated worsening of New York Heart Association functional class during a 7-month period. Of note, the mean ± SD dose of IV treprostinil prior to the transition was 73 ± 39.7 ng/kg/min, 2.4-fold greater than the maximum dose our patient received. Raina et al[23] described transition of 2 patients from IV or SQ to inhaled treprostinil: a 69-year-old woman with idiopathic PAH receiving a maximum treprostinil dose of 38 ng/kg/min and a 46-year-old man with PAH secondary to β-thalassemia and cirrhosis, and receiving a maximum treprostinil dose of 61 ng/kg/min. Both patients were initiated on inhaled treprostinil at 3 breaths (18 mcg) every 6 hours and increased by 3 breaths daily to a maximum of 9 breaths (54 mcg) every 6 hours during a period of 3 days. Simultaneously, the treprostinil infusion dose was decreased by 5 ng/kg/min every 6 hours until cessation of therapy. No deterioration in hemodynamic parameters was reported, and longer-term post–inhaled treprostinil hemodynamic data at 5 months continued to show benefits of inhaled therapy per observations of 6MWD, functional class, and NT-pro BNP concentrations. Finally, Enderby et al[21] described 3 adult patients transitioned from IV or SQ treprostinil or epoprostenol

Table 3. Echocardiogram, Blood NTproBNP Concentration, 6-Minute Walk Distance Test, and Pharmacologic Management Course for Our Patient

Parameter	Therapy Day									
	7	10	12	19	25	43	68	82	93	103
RA dilatation	Mild	Mild	Mild	None	Mild	Mild	None	None	Mild	NA
RV dilatation	Severe	Severe	Moderate	Mild	Mild	Mild	Mild	Mild	Mild	Mild
RV systolic function	Severely diminished	Severely diminished	Moderately diminished	Mildly diminished	Mildly diminished	Mild–moderately diminished	Mildly diminished	Mildly diminished	Normal	Low–normal
TR	Trivial	Trivial	Trivial	Trivial	Mild	Mild	Mild	Trivial	Mild	Trivial
TR gradient, mm Hg*	62	49	51	NA	57	NA	63	56	48	NA
PR gradient, mm Hg†	28	17	28	16	24	25	NA	NA	20	14
Blood NT-proBNP, pg/mL	2398	NA	652	378	957	NA	245	77	174	NA
Baseline Borg score‡	—	—	—	0	—	—	—	—	NA	6
Baseline SpO_2, %	—	—	—	98	—	—	—	—	100	100
Termination Borg score‡	—	—	—	NA	—	—	—	—	NA	7
Termination SpO_2, %	—	—	—	99	—	—	—	—	100	98
Total distance walked, feet	—	—	—	700	—	—	—	—	800	1379
FiO_2, %	100	100	100	21	21	21	21	21	21	21
O_2 delivery method	8 L/min HFNC	6 L/min HFNC	2 L/min HFNC	NR	NR	NR	NR	NR	NR	NR
iNO, ppm	20	20	20	NR	NR	NR	NR	NR	NR	NR
Inhaled epoprostenol, ng/kg/min	50	50	50	NR	NR	NR	NR	NR	NR	NR
IV milrinone, mcg/kg/min	0.5			NR	NR	NR	NR	NR	NR	NR
Sildenafil, mg	15 PO TID	15 PO TID	20 PO TID	NR	NR	NR	NR	NR	NR	NR
Tadalafil, mg	NR	NR	NR	40 PO daily	40 PO daily	40 PO daily	40 PO daily	40 PO daily	40 PO daily	40 PO daily
Ambrisentan, mg	NR	NR	NR	10 PO daily	10 PO daily	10 PO daily	10 PO daily	10 PO daily	10 PO daily	10 PO daily
IV treprostinil, ng/kg/min	4	12	16	24	30	30	30	30	NR	
Inhaled treprostinil, mcg	NR	NR	NR	NR	NR	NR	NR	NR	54 QID	54 QID

FiO_2, fraction of inspired oxygen; HFNC, High Flow Nasal Cannula; iNO, inhaled nitric oxide; IV, intravenous; NA, not available; NR, not receiving; NT-proBNP, N-terminal pro–brain-type natriuretic peptide; PR, pulmonary regurgitation; RA, right atrium; RV, right ventricle; SpO_2, oxygen saturation by pulse oximetry; TR, tricuspid regurgitation; —, not obtained

* Estimated per modified Bernoulli of peak TR jet velocity.

† Estimated per modified Bernoulli of end-diastolic PR jet velocity.

‡ Estimated physical activity intensity per the Borg Rating of Perceived Exertion scale.[24,25]

to inhaled treprostinil. All patients were first titrated down to a dose of 25 ng/kg/min or less prior to being admitted to the intensive care unit for pulmonary artery catheter placement and monitoring and a baseline hemodynamic profile. The transition then commenced by decreasing the IV or SQ prostacyclin therapy in 33% steps with concomitant increases in 3 breaths 4 times daily increments, until 9 breaths (54 mcg) 4 times daily was reached and IV or SQ prostacyclin therapy was terminated. All patients concurrently received oral PAH

medications prior to and after conversion. No patients discontinued inhaled treprostinil following transition, and functional class remained stable at WHO functional class II or better during long-term follow-up. Although inhaled treprostinil has an established, dose-dependent bioavailability of 64% to 72%, which could be used to determine a dose conversion from the IV infusion, we chose to follow the transition process described by Enderby et al[21] because 1) our patient's IV treprostinil dose was similar to the doses described in that study; 2) our patient was also receiving oral PAH therapy, which may augment the response to the treprostinil; and 3) this coincided with the standard dosing formulations of inhaled treprostinil solution, and we felt this was pragmatic.[12,21]

Conclusion

This case describes safe and effective transition from IV to inhaled treprostinil during inpatient admission and may be valuable for providers who manage pediatric patients with PAH. Transitioning from IV or SQ to inhaled treprostinil was achieved successfully with the described approach applied in a controlled intensive care unit environment.

Article Information

Affiliations. Department of Pharmacy (DP), The Johns Hopkins Hospital, Baltimore, MD; Department of Anesthesiology & Critical Care Medicine (DD, AS), The Johns Hopkins Hospital, Baltimore, MD; Department of Pediatric Cardiology (PLK, JDC), The Johns Hopkins Hospital, Baltimore, MD.

Correspondence. David Procaccini, PharmD, MPH; dprocac1@jhmi.edu

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