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CASE REPORT

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Direct prostacyclin transition in pediatric patients with pulmonary hypertension

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Abstract

Pediatric patients with pulmonary arterial hypertension (PAH) are commonly treated with the prostacyclin analog treprostinil in IV, SQ, inhaled or oral form, or the prostacyclin receptor agonist selexipag. Patients who transition between these medications often follow recommendations for gradual up- and down-titrations that take place over several days in the hospital or several weeks as an outpatient. However, hospital resources are limited, and long transitions are inconvenient for patients and families. We report a case series of eight pediatric patients with PAH transitioned directly between prostacyclins with no overlapping doses. Direct medication transitions occurred in the cardiac intensive care unit (CICU), at home and in cardiology clinic. Equivalent doses for selexipag were estimated using information extrapolated from experience, published materials and selexipag study guidelines. All patients completed direct transition as planned and remained on transition dose for at least 1 week. In most cases selexipag was up-titrated at home after establishing initial transition dose. In select patients, direct prostacyclin transition in pediatric patients with PAH is safe, effective, convenient for families and reduces the use of hospital resources.

KEYWORDS

children, pulmonary vascular disease, selexipag, treprostinil

INTRODUCTION

Survival for pediatric patients with pulmonary arterial hypertension (PAH) has improved over the past several decades, beginning with the introduction of the prostacyclin intravenous IV epoprostenol in 1995.[1–3] Prostacyclins continue to be a mainstay of PAH therapy and are now available in other forms, including (IV), subcutaneous (SQ), inhaled or oral treprostinil.[1] The oral prostacyclin analog selexipag was introduced in 2015 and is increasingly used in children due to its longer half-life.[4] Patients may transition from one prostacyclin to another because of side effects, ease of dosing, or efficacy.

In 2002, the first reported transition between prostacyclins involved gradual down-titration of IV epoprostenol and gradual up-titration of SQ treprostinil over 1–3 days,[5] leading to package insert recommendation of 7 dose titration steps, in the hospital. As the

various treprostinil forms were introduced, reports described transitions using similar stepwise strategies, but with variable length of time, from days up to several weeks, usually longer in outpatient transitions.[6,7] Most "rapid" transitions between prostacyclins and selexipag in pediatric patients take place over 4–8 days, in the hospital.[8,9]

However, transitions over several days in the hospital are inconvenient for patients and families and use limited resources. Our center has previously performed successful rapid 1-day transitions in pediatric PAH patients and hypothesized that transitions with no steps, directly from one prostacyclin to the other, would be as safe and effective as longer transitions. Here, we describe our experience with direct transitions in eight patients.

CASE DESCRIPTION

See Table 1 for further case details.

Patient 1 with idiopathic PAH (IPAH) was started on IV treprostinil and sildenafil at 15 months old. Two years later, symptoms improved to World Health Organization functional class (WHO-FC) I, B-type natriuretic peptide (BNP) level was normal and mean PA pressure by catheterization was 20 mmHg. In the cardiac intensive care unit (CICU), patient received the first dose of selexipag at 10 a.m. and IV treprostinil was immediately stopped. Patient was observed overnight, and BNP was normal the following morning.

Patient 2 with IPAH was started on triple therapy with SQ treprostinil, sildenafil, and bosentan when diagnosed 14 months prior. Symptoms improved from WHO-FC IV to I and transition to selexipag from SQ treprostinil was pursued due to severe side effects, including site dislodgement and skin reactions. In the CICU, selexipag was given at 10 a.m. and SQ treprostinil was immediately stopped. The patient was observed for 10 h and discharged that evening. The following day echocardiogram and BNP was unchanged.

Patient 3 with IPAH on dual therapy with SQ treprostinil and tadalafil strongly requested a transition to oral prostacyclin due to poor tolerance (site pain) of SQ therapy. Before transition, the SQ treprostinil was down-titrated at home from 81 to 50 ng/kg/min[10] with BNP unchanged from 30 to 19 pg/mL. In the CICU, selexipag was given at 10 a.m. and the SQ treprostinil infusion was immediately stopped. The following day, he became dizzy and dyspneic at 5 min of a 6-min walk test, but BNP < 5. Despite these symptoms, the patient requested to remain on selexipag and was discharged. However, 3 weeks later, he transitioned directly back to SQ treprostinil.

Patient 4 with Eisenmenger syndrome on tadalafil and selexipag had worsening PH symptoms, and an inability to tolerate selexipag dose increases. A trial of SQ treprostinil was recommended. The patient took selexipag at 9 p.m. at home the night before. She was admitted to the CICU the next morning and SQ treprostinil was started at 9 a.m. There was brief complaint of headache.

Patient 5 with severe bronchopulmonary dysplasia on tadalafil and selexipag had pulmonary pressures that increased to suprasystemic. The patient was admitted to the CICU for transition from selexipag to SQ treprostinil. The last dose of selexipag was given at 8 p.m. the night before, and SQ treprostinil was initiated at 8 a.m. Patient was discharged the next day.

Patient 5 was referred for lung transplantation 2 years later and when a central line was placed for an outpatient milrinone infusion, he transitioned directly from SQ treprostinil to IV treprostinil. In the clinic, with assistance of a specialty pharmacy nurse, the IV infusion was initiated and the SQ infusion was immediately stopped. Patient was observed for 1 h and discharged.

Patient 6 with IPAH on SQ treprostinil, tadalafil and macitentan had a central line placed for home milrinone infusion while undergoing lung transplant evaluation. Patient underwent transition from SQ treprostinil to IV treprostinil, while in the clinic, for ease of administration. In the clinic, with assistance of a specialty pharmacy nurse, the IV infusion was initiated and the SQ infusion was immediately stopped. Patient was observed for 1 h and discharged.

Patient 7 with IPAH on oral treprostinil, ambrisentan and tadalafil, experienced bothersome side effects of oral treprostinil. At home, the usual dose of oral treprostinil was taken the night before transition. The next morning, the patient began selexipag in the presence of the specialty pharmacy nurse.

Patient 8 with PAH associated with delayed repair of a large VSD on tadalafil had an increase in pulmonary artery pressures by cardiac catheterization and the addition of a prostacyclin was recommended. Selexipag was initially denied by insurance, therefore inhaled treprostinil was started and up-titrated to 54 μg (9 breaths) 4 times daily. The patient developed increased school absence and depression associated with frequent dosing and with this information insurance granted selexipag approval. In anticipation of direct transition, inhaled treprostinil was decreased to 36 mcg (6 breaths) per dose. At home, the patient administered the last dose of inhaled treprostinil the night before transition, and the following morning, started selexipag in the presence of

TABLE 1 Transition doses.

Pt #	Age (years)	Sex	Weight (kg)	WHO diagnosis group	WHO-functional class	Location	Transitioned from	Transitioned to	Timing of further dose changes
1	4	F	13	1	I	CICU	IV treprostinil 34 ng/kg/min	Selexipag 400 mcg BID	Slow up-titration by 100 mcg BID to 800 mcg BID 1 year after transition
2	2	M	16	1	I	CICU	SQ treprostinil 76 ng/kg/min	Selexipag 800 mcg BID	Up-titrated to 1200 mcg BID over 3 months
3	14	M	85	1	IIIa	CICU (2 days)	SQ treprostinil 50 ng/kg/min	Selexipag 1600 mcg BID	3 weeks later, transitioned back to SQ
4	12	F	41	1	IIIb	CICU	Selexipag 1100 mcg BID	SQ treprostinil 30 ng/kg/min	Up-titrated by 2 ng/kg/min every 2–4 weeks beginning 1 month after starting
5	12	M	38	3	II	CICU	Selexipag 1600 mcg BID	SQ treprostinil 40 ng/kg/min	1 day later, decreased to 36 ng/kg/min due to headache. No change in dose for 3 months, then began up-titration
5	15	M	53	3	IV	Clinic	SQ treprostinil 50 ng/kg/min	IV treprostinil 50 ng/kg/min	
6	15	F	58	1	IV	Clinic	SQ treprostinil 116 ng/kg/min	IV treprostinil 116 ng/kg/min	
7	14	M	56	1	I	Home	Oral treprostinil 6 mg TID	Selexipag 1000 mcg BID	Continued usual up-titration to 1600 mcg BID
8	15	M	55	1	II	Home	Inhaled treprostinil 6 breaths (36 mcg) QID	Selexipag 200 mcg BID	Continued usual up-titration to 1600 mcg BID

Abbreviations: CICU, cardiac intensive care unit; WHO, World Health Organization.

the specialty pharmacy nurse. Due to poor compliance with inhaled treprostinil, selexipag was initiated at standard starting dose and up-titrated weekly.

DISCUSSION

We show that direct prostacyclin transitions are safe. Compared to longer stepwise transitions, direct prostacyclin transitions are more convenient for families and use fewer hospital resources. Direct transitions simplify the management of the transition by having only one medication to titrate for side effects and PH symptoms. As for all transitions, factors for success include appropriate patient selection and education, careful dose selection and transition planning.

Location of transition was chosen based on type of transition. Transitions including initiation or stopping of a continuous prostacyclin occurred in the hospital. The one exception was Patient 3 who transitioned directly back to SQ treprostinil while at home. Direct transitions from IV to SQ treprostinil occurred in the clinic. Transitions from oral or inhaled prostacyclin to selexipag occurred at home in the presence of a specialty pharmacy nurse. Medication teaching and insurance approval was obtained before all transitions.

Transition dosages chosen were adequate to avoid most side effects and no adverse events occurred. We used preliminary reports that parenteral treprostinil 10 ng/kg/min equaled selexipag 200 mcg twice daily in adults, and 100 mcg twice daily in children.[9] Doses were occasionally adjusted due to concerns for history of prostacyclin side effects. Target end dose of selexipag by mcg twice daily was chosen by weight: 1600 for patients >50 kg, 1200 for patients 25–50 kg, and 800 for patients 9–25 kg. Prostacyclin doses were titrated following transition to achieve a balance between PH signs/symptoms and side effects.

Only one patient, number 5, required a dose change within days of transition, and this was due to side effects. For Patients 4 and 5 who transitioned to SQ treprostinil, slow up-titrations were performed as per the general standard of care for up-titrations in pediatric patients for efficacy. For Patients 1 and 2, who transitioned to selexipag as small children, up-titrations to target doses were increased by a small increment. Target doses increased as children grew. For Patients 7 and 8, who were close to adult weight, selexipag was up-titrated per usual adult practice.

Patient 3, who transitioned from SQ treprostinil to selexipag, was the only patient who developed PH symptoms and transitioned back to SQ treprostinil 3 weeks after initial transition. We had suspected and discussed with the patient and family that he may not tolerate the transition from SQ treprostinil due to the higher treprostinil dose and WHO-FC IIIa. Although PH symptoms objectively increased on day 2 of transition, the teenage patient strongly requested to continue trial of selexipag and was discharged. He agreed to transition back to SQ treprostinil 3 weeks later when both PH symptoms and estimated pulmonary pressures by echocardiogram worsened.

To our knowledge, this is the first report of direct prostacyclin transitions in both the adult and pediatric population. The limitation of this series is that it reflects few patients in a single center. However, due to this result, our center now only performs direct transitions. We hypothesize that side effects and PH symptoms are minimized during direct transition due to the half-life of the prostacyclins providing an overlap of medication that maintains circulating drug concentrations of both medications. Direct prostacyclin transitions could be considered at other institutions.

AUTHOR CONTRIBUTIONS

Delphine Yung determined the indication and method for all transitions. Delphine Yung and Kelly Merrill drafted the manuscript, and all authors revised it critically for important intellectual content. All authors approved the final version of the article.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

Not applicable.

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