Cardiology in the Young

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Transition from intravenous treprostinil to enteral selexipag in an infant with pulmonary arterial hypertension

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Brief Report

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Abstract

Selexipag is an enteral, selective prostacyclin IP receptor agonist approved for pulmonary hypertension in adults. There are few reports of its use in children and none in infants. We report the first transition of an infant (11.5 months, 8.6 kg) from intravenous treprostinil (40 ng/kg/minute) to enteral selexipag (400 mcg twice daily) with a good response and no adverse effects.

Case report

Our patient was a twin, born at 30-weeks gestational age (424 g). He was intubated after birth and had evidence of pulmonary hypertension, which required inhaled nitric oxide for a short time. He was discharged home at approximately 4 months old in room air, without evidence of pulmonary hypertension by echocardiography. Shortly thereafter, he was readmitted due to acute respiratory failure, requiring non-invasive mechanical ventilation. His echocardiogram showed pulmonary hypertension, and he was started on sildenafil. He was not able to wean from ventilatory support, and, at 6 months old, he was transferred to our hospital for tracheostomy placement.

After tracheostomy placement, he developed respiratory deterioration. He was placed on inhaled nitric oxide and high frequency oscillatory ventilation. Echocardiography showed suprasystemic pulmonary hypertension with right heart hypertrophy and enlargement. NT pro-BNP values were between 2500 and 4000 pg/ml. Sildenafil was converted to an intravenous infusion (0.067 mg/kg/hour), and dopamine was initiated. He was receiving 100% inspired oxygen, and his oxygen saturation was difficult to maintain over 80%. His liver enzymes were elevated, and he had evidence of cholestasis due to prolonged parenteral nutrition after necrotizing enterocolitis; therefore, bosentan was not initiated. Dopamine was transitioned to milrinone, and a furosemide infusion was initiated.

At 7.5 months old (6.4 kg), an intravenous treprostinil infusion was initiated. Over the course of several weeks, the infusion was titrated to a maximal dose of 50 ng/kg/minute. He showed significant improvement in echocardiographic evidence of pulmonary hypertension, NT pro-BNP, and inspired oxygen requirement. His dose of treprostinil was held at the current dose and was not adjusted for weight gain. At approximately 11 months old, his NT pro-BNP was 85 pg/ml and he underwent cardiac catheterization. Hemodynamic assessment revealed a pulmonary vascular resistance (PVRi) of 1.8 woods units * m^2, while receiving 40 ng/kg/minute of treprostinil, adjusted for his current weight. He was tolerating full enteral feeds via gastrostomy tube, though his liver function testing remained elevated (supplemental figure 1). At this point, he was approaching readiness for discharge to a long-term care facility, but no local facility would accept the patient with a continuous treprostinil infusion, whether intravenously or subcutaneously administered. For this reason and with the recent positive reports of transition to enteral selexipag in children, the decision to attempt transition to enteral selexipag in our patient was made.

At 11.5 months old (8.6 kg), our patient began transition from continuous intravenous treprostinil to twice daily enteral selexipag. Transition occurred over an 8-day period and was well tolerated. The transition process is described later. He has been receiving enteral selexipag for over 12 months (since 3/30/2018) and continues to improve. He is now receiving 21% inspired oxygen and is weaning from ventilator support. His NT pro-BNP remains low (28 pg/ml), and his echocardiogram has shown no more than mild septal flattening (Fig 1 and supplemental figure 2).

Discussion

We report the first use of enteral selexipag in an infant with a history of severe pulmonary hypertension. Although transition to subcutaneous treprostinil before discharge has been successful

Table 1. Suggested paediatric dosing protocol.

Starting selexipag dose: <7.5 kg = 25–50 mcg PO Q12H 7.5–15 kg = 50 mcg PO Q12H 15–30 kg = 100 mcg PO Q12H >30 kg = 200 mcg PO Q12H (adult dose)
Dose escalation protocol during transition from IV treprostinil: <7.5 kg = Increase by 25–50 mcg/dose daily 7.5–15 kg = Increase by 50 mcg/dose daily 15–30 kg = Increase by 100 mcg/dose daily >30 kg = Increase by 200 mcg/dose daily
De novo dose escalation protocol: <7.5 kg = Increase by 25–50 mcg/dose every 1–2 weeks 7.5–15 kg = Increase by 50 mcg/dose every 1–2 weeks 15-30 kg = Increase by 100 mcg/dose every 1–2 weeks >30 kg = Increase by 200 mcg/dose every 1–2 weeks
Target selexipag dose: <7.5 kg = 200–400 mcg PO Q12H 7.5–15 kg = 400 mcg PO Q12H 15–30 kg = 800 mcg PO Q12H >30 kg = 1600 mcg PO Q12H (adult dose)

and is becoming a more viable option in infants receiving prostacyclin therapy, our patient was unable to be discharged on this medication; therefore, the decision to undertake the transition to enteral selexipag was made.[1–3] Selexipag is the first in a new generation of long-acting enteral selective prostacyclin IP receptor agonists approved for the treatment of pulmonary arterial hypertension in adults.[4] There have been few reports of its use in the children to date. Geerdink and colleagues report the first use in a 12-year-old child, weighing approximately 30 kg.[5] This patient tolerated the full adult dose of 1600 mcg twice daily. Gallotti then reported the first single-centre series of children.[6] Although they present 10 patients, only 5 are children (<18 years old). The children ranged in age from 7 to 16 years. The youngest child apparently tolerated the full adult dose of 1600 mcg twice daily as well. Three children in this series were also transitioned from continuous treprostinil infusions.

The following sections describe the process used to select the proper preparation method, dose, transition process, and follow-up monitoring.

Preparation

To determine the proper method of medication preparation, the European Medicines Agency Assessment Report on selexipag was reviewed.[7] Selexipag is manufactured as immediate-release film-coated tablets of various strengths. Preparations with sterile water, Ora-Sweet®, and Ora-Plus® with various methods of suspension/dissolution were tested to find the optimal mixing procedure. The final method involves dissolving the tablet in sterile water over a 10–15-minute period. We tested 200 and 400 mcg tablets.

(1) Halve tablet.
(2) Pull out syringe plunger and place tablet halves in open syringe.
(3) Replace syringe plunger and fill to 4 ml with sterile water per tablet. Cap syringe.
(4) Intermittently shake and agitate syringe until tablet is dissolved (10–15 minutes).
(5) Administer required dose. Discard remaining solution.

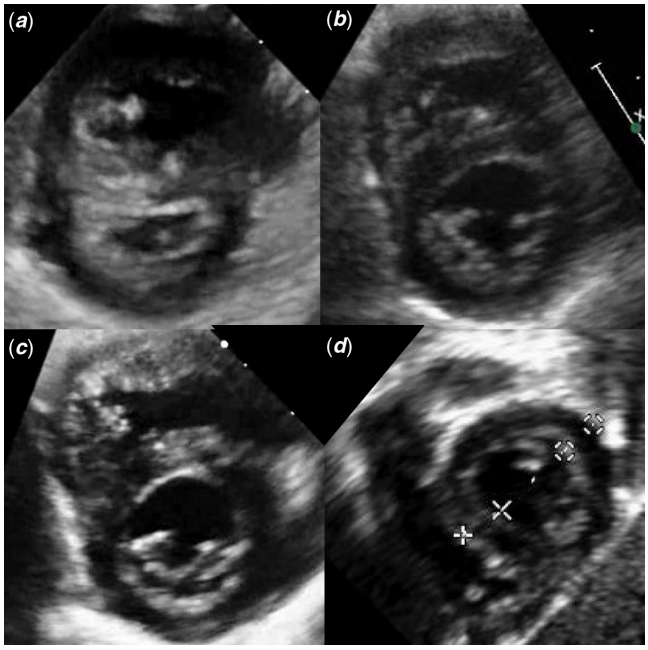

Figure 1. Parasternal short-axis end-systolic echocardiogram images over the course of therapy. (***a***) Severe septal flattening before administration of treprostinil. (***b***) Trivial septal flattening while receiving treprostinil 50 ng/kg/minute. (***c***) No septal flattening after transition to enteral selexipag. (***d***) Mild septal flattening 11 months after transition to enteral selexipag.

Dose selection

Prior reports in children utilized the full final adult dose of 1600 mcg twice daily for children as young as 7 years old and 30 kg. With this information, we extrapolated our initiation and goal doses (Table 1). Our patient (8.6 kg) initially received 50 mcg twice daily, with a goal dose of 400 mcg twice daily.

Transition process

At transition, our patient was receiving 40 ng/kg/minute of intravenous treprostinil, adjusted for weight. He was receiving an H1- and H2-blocker to minimize systemic side effects as well. His pulmonary hypertension was well treated with his current therapies. Transition occurred over an 8-day period as follows. After each new dose strength was begun, the treprostinil infusion was decreased by 1 ng/kg/minute every 2 hours for 10 hours (5 ng/kg/minute over 10 hours), then held at that dose for the following 14 hours. This transition protocol continued daily until full dose selexipag (400 mcg twice daily) was achieved, and treprostinil was discontinued.

Monitoring and follow-up

During the initial cross-titration, vital signs were monitored continuously and recorded hourly. No significant changes to vital signs were observed during the transition. Echocardiography and NT pro-BNP were obtained throughout the transition and were similar to the previous testing.

The patient was subsequently discharged and follows up with a Cardiology office visit, echocardiogram, electrocardiogram, NT pro-BNP, comprehensive metabolic panel, and blood counts every 3 months. After 12 months of follow-up while receiving selexipag, his NT pro-BNP has remained low and his echocardiogram has

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shown no more than mild pulmonary hypertension. At his last visit, his dose was decreased from 400 to 200 mcg twice daily, which he has tolerated well. We plan to continue weaning selexipag slowly based on his echocardiogram, NT pro-BNP, and clinical symptoms. A follow-up catheterization will be performed after withdrawal of the medication to assure tolerance and assess vascular resistance.

Conclusions

We report the first transition from intravenous treprostinil to enteral selexipag in an infant with pulmonary hypertension. The medication transition was well tolerated, without significant adverse effects or worsening of his underlying disease. Although more testing in this population is needed, this report is encouraging regarding the potential role of enteral prostacyclin agonists in infants.

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Conflicts of interest. None.

Ethical standards. This research did not involve human or animal experimentation. This research was exempt from IRB review.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951119001082

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