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Safety and tolerability of subcutaneous treprostinil in newborns with congenital diaphragmatic hernia and life-threatening pulmonary hypertension☆

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ABSTRACT

Background: Prolonged pulmonary hypertension (PH) is highly predictive for pulmonary morbidity and death in infants with congenital diaphragmatic hernia (CDH).
Objectives: To report the effects and tolerability of subcutaneous treprostinil in newborns with severe CDH and late life-threatening PH.
Methods: We recorded clinical and echocardiography data before and after starting subcutaneous treprostinil, on patients with severe CDH and late PH, refractory to inhaled nitric oxide and oral sildenafil.
Results: 14 patients were treated with treprostinil (gestational age: 39.1 ± 2.0 weeks; birth weight: 3200 ± 600 g). Prior to treatment, the pre- and post-ductal SpO2 difference (Δ SpO2) was 14 ± 10%. Treprostinil was initiated at a median age of 12 days [5–157]. After starting treprostinil, ΔSpO2 decreased to 3% at day 7 ($p < 0.05$), and the mean blood flow velocities in the right pulmonary arteries increased by 110% ($p < 0.05$). 2 of the 14 patients died. At the age of follow up (12 months to 3 years), the 12 surviving infants were all weaned from respiratory support and discharged home.
Conclusion: The subcutaneous treprostinil improves pulmonary hemodynamics and outcomes in infants with CDH and life-threatening PH. We suggest that the treatment should be considered in infants with severe CDH and late PH.
Type of study: Case series with no comparison group.
Level of evidence: Level IV.

Infants with CDH are prone to develop profound hypoxemia related to lung hypoplasia and pulmonary hypertension (PH) [1]. Although increased pulmonary artery pressure (PAP) is almost a universal finding in CDH at birth [2], late PH is associated with a strikingly poor prognosis. Low survival rates have been reported when systemic PH is prolonged beyond the age of 2 weeks [3,4]. Late PH is the main cause of mortality after the neonatal period in infants with CDH [5]. Therefore, there is clearly a need for new therapeutic strategies in this particular subgroup of infants with severe CDH.

In clinical practice, inhaled NO (iNO) is the first-line pulmonary vasodilator used in newborn infants with PH [6]. Phosphodiesterase inhibitors such as sildenafil may reduce the degradation of cGMP that is produced by NO [7]. However, there is currently no evidence that iNO or sildenafil change the outcome in CDH [3].

The use of prostacyclin and analogues is an established therapy for children and adults with primary PH. Prostacyclin is a potent pulmonary vasodilator and prevents pulmonary vessel remodeling [8]. In a population-based study, use of prostacyclin at birth has been associated with a high survival rate in infants with CDH [9]. Because of its very short half-life and its physicochemical incompatibilities, however, intravenous (IV) epoprostenol must be continuously infused through

Abbreviations: PH, pulmonary hypertension; CDH, congenital diaphragmatic hernia; PAP, pulmonary artery pressure; iNO, inhaled NO; SpO_2, oxygen saturation; IV, intravenous; y, year; d, day; DA, ductus arteriosus; FO, foramen ovale; RV, right ventricle; IVS, interventricular septum; D0, day 0; D1, day 1; D7, day 7; D30, day 30; LPA, left pulmonary artery; RPA, right pulmonary artery; SD, standard deviation; ECMO, Extracorporeal membrane oxygenation; GA, gestational age; BW, birth weight; BP, blood pressure; HR, heart rate; PVR, pulmonary vascular resistance.

☆ None of the authors has any potential conflict of interest.

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an indwelling dedicated central catheter. Prolonged central venous line exposes infants to potential severe accidents (embolism/thrombosis, infections, delivery system malfunctions) in cases of prolonged infusion for late PH in CDH. Alternatively, treprostinil is a prostacyclin analog that can be delivered subcutaneously. It has been approved for the treatment of chronic PH in most countries. Its elimination half-life is approximately 4 h, thus reducing the possible consequences of inadvertent brief tubing disconnection [10]. A recent case report in 2 infants suggests that treprostinil may decrease pulmonary artery pressure and improve oxygenation in infants with CDH and late PH [11].

In this study, we report the effects and tolerability of treprostinil in 14 newborn infants with CDH and life-threatening late PH.

1. Population and method

In the North Pas-de-Calais area of France (4.5 million inhabitants, 55OOO births/y), all infants with a diagnosis of isolated CDH are referred at Lille University teaching hospital and are systematically enrolled in a prospective follow-up study (cohort). The CDH management procedures follow the guidelines of the CDH Euro Consortium Consensus [6].

Subcutaneous treprostinil has been used after surgical repair in cases of late life-threatening PH that failed to respond to iNO and oral sildenafil. The infants were treated with treprostinil in cases of hypoxemic respiratory failure (post-ductal $SpO_2 < 88\%$), or symptoms of right cardiac failure. PH, as assessed by a qualitative evaluation of pulmonary artery pressure using Doppler echocardiography, was defined by right to left shunting through the ductus arteriosus (DA) and/or the foramen ovale (FO), or a dilated right ventricle (RV) with right to left curvature of the interventricular septum (IVS).

To evaluate the safety and tolerability of subcutaneous treprostinil, we prospectively collected data on all patients with a diagnosis of CDH treated with treprostinil who were admitted from January 2009 through December 2014. The study was approved by the Regional Ethical Committee and the National Registry for Data Processing and Liberty. Written informed consent for use of the data was obtained from the parents.

Treprostinil (Remodulin®, 1 ml = 1 mg, Bioprojet Pharma, Paris) was infused through a 22G catheter (Accu-check® Tenderlike, Roche Diagnostics, Vilvoorde, Belgium) that was placed subcutaneously via an in-house Insulin micropump (Accu-chek® Spirit Combo) with a 3-mL syringe (Accu-chek® Spirit). Infusion catheters were originally introduced to the lateral thighs after local anesthesia was achieved (Emla® cream, Astrazeneca). Other infusion sites included the abdomen or lateral arms. The length and the internal volume of the connecting tubing were 30 cm and 0.15 ml, respectively. The rate of infusion was titrated upward within the first 24 h of treatment to a range of 10 to 20 ng/kg/min based on clinical response and tolerability. Special care was taken to prevent microbubbles in the tubing through the careful flushing of tubing and catheters. This is because with the flow rates usually ranging between 0.2 and 0.5 μl/h, even one microbubble could stop the drug infusion for a clinically significant period of time. The syringe of treprostinil was switched every 3 days as recommended. The subcutaneous catheter was replaced at another site every 15 days or earlier in the case of excessive local inflammation, infection, bleeding or leakage.

We recorded clinical and echocardiography data before (D0) and after starting treprostinil at D1, D7 and D30, arbitrarily chosen dates. Two well-trained senior consultants were involved in the Doppler echocardiographic assessments. The following variables were measured: internal diameter of the DA, orientation of the shunting in the DA, mean blood flow velocities in the left and right pulmonary arteries (LPA, RPA), shape of the IVS during diastole and systole from a transverse subcostal view (scored as 3 points for right to left curvature, 2 points for a flat shape and 1 point for left to right curvature). Averages of five consecutive readings of vessel diameter and flow velocity integrals were used. The angle of insonation was less than 20°. Clinical data were collected at the time of the echocardiographies. FiO_2 was set to maintain a post-ductal SpO_2 from 88 to 95%.

Local side effects (color, inflammatory nodule, sensitivity) and tolerability (pain score by using EDIN scale every 8 h, systemic hypotension, feeding intolerance, oral aversion and diarrhea) were systematically monitored by the nurses.

The outcomes at 6 months, 1, 2 and 3 and half years were also measured.

The data are presented as the mean ± SD or median according the variables. The analyses were performed using ANOVA with repeated measure and post hoc analyses (Fisher test). All analyses were carried out using SPSS® software (IBM SPSS® v22, USA). The limit of significance was $p < 0.05$.

2. Results

Over the 5-year study period, 76 newborn infants with CDH were admitted. Sixty-five (85%) survived to the time of follow-up. Two infants required ECMO and survived.

Among this population, 14 patients were treated with subcutaneous treprostinil (GA = 39.1 ± 2 weeks, BW = 3200 ± 600 g). Four patients had right-sided CDH. The umbilical cord blood pH was 7.16 ± 0.17. At 1 h after birth, severe PH was clinically obvious in all infants with a pre- and post-ductal SpO_2 difference > 10% and confirmation by Doppler echocardiography. Surgical repair was performed at 1.4 ± 1 days [0–4] after birth (performed during normal working hours, as soon as pre-ductal $SpO_2 > 90\%$ and $FiO_2 < 50\%$). A large prosthetic patch was required in 8 patients with diaphragmatic agenesis. A gastrostomy was also placed in these 8 infants, as protocolized at Lille's University Hospital in order to anticipate the management of oral aversion. Diagnostic of CDH was performed prenatally in all cases. No patient needed tracheotomy.

Treprostinil was initiated at a median age of 12 days [5–157]. Treprostinil was used for late severe PH refractory to iNO (20 ppm), oral sildenafil (Revatio®, 3 mg/kg/d, Pfizer Laboratory, USA), and optimized mechanical ventilation and hemodynamic support. Before starting treatment, the mean blood pressure (BP) and heart rate (HR) were 53 ± 11 mmHg and 155 ± 18beats/min, respectively. Arterial blood gases showed a pH = 7.34 ± 0.07, $PaCO_2$ = 63 ± 12 mmHg, and PaO_2 = 35 ± 11 mmHg. The plasma lactate concentration was 1.65 ± 0.83 mmol/l. The post-ductal SpO_2 and the pre- and post-ductal SpO_2 difference were, respectively, 80 ± 17% and 14 ± 10%. FiO_2 was 43.14 ± 23.53%. Echocardiography confirmed PH in all infants with bidirectional flow through the DA and a flat or right to left curved shape of the IVS during both systole and diastole (respectively shape score 3 ± 0 and 2.6 ± 0.9).

Treprostinil was initiated at 3 ng/kg/min and titrated up to reach 10 ± 5 ng/kg/min over the first 24 h of treatment. The subsequent doses of treprostinil infusion are shown in Table 1. HR and BP did not change significantly during the study. An episode of hypotension lasting 3 h, which was associated with symptoms of vasoplegia (blushing, low diastolic pressure, tachycardia, high blood flow, as assessed by Doppler echocardiography), was attributed to a treprostinil bolus because of an inadvertent manipulation of the bolus function of the pump while the catheter was still connected to the catheter. Except for this case, no episodes of hypotension required a change in infusion rate. The changes in pre- and post-ductal SpO_2, and in FiO_2 are shown in Fig. 1. Although the pre-ductal SpO_2 did not change, post-ductal SpO_2 increased and the difference between the pre- and post-ductal SpO_2 decreased after starting treprostinil ($p < 0.05$). Despite the persistence of bidirectional shunting through the DA, the mean blood flow velocities in the LPA and RPA increased after beginning treprostinil (Table 1) ($p < 0.05$). The score for the curvature of the IVS decreased after starting treprostinil (Table 1) ($p < 0.05$).

Monitoring of side effects showed mainly a mild inflammation at the site of infusion. However, the EDIN score did not change during the study period and remained low (Table 1). Difficulties in oral feeding