



Terlipressin as rescue therapy for refractory pulmonary hypertension in a neonate with a congenital diaphragmatic hernia

Lefteris Stathopoulos^a, Claire Nicaise^a, Fabrice Michel^{a,c,*}, Laurent Thomachot^a, Thierry Merrot^{b,c}, Pierre Lagier^a, Claude Martin^{a,c}

^aRéanimation Pédiatrique et Néonatale, Brûlés Pédiatriques, Pôle RAUC, Centre Hospitalo-Universitaire Nord, Marseille, France

^bService de Chirurgie Infantile, Pôle Parent Enfant, Centre Hospitalo-Universitaire Nord, Marseille, France

^cFaculté de Médecine de Marseille, Université de la Méditerranée, France

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Abstract We report the case of a 38-week gestational age neonate, with isolated congenital diaphragmatic hernia presenting with refractory persistent pulmonary hypertension, systemic hypotension, and hypoxemia, resistant to usual therapeutics. Arginine vasopressin is responsible for systemic vasoconstriction and decreases pulmonary hypertension. We theorized that terlipressin, its long-acting analogue, could have the same properties. We used terlipressin as rescue therapy after parental and local ethics committee acceptance. After a bolus of terlipressin 20 $\mu\text{g}/\text{kg}$ and continuous infusion at a rate of 5 $\mu\text{g}/\text{kg}$ per hour, blood oxygen saturation improved from 75% to 98%, oxygen requirements fell from fraction of inspired oxygen 100% to 40%, and mean arterial pressure rose from 28 to 46 mm Hg, allowing a decrease of vasopressor infusion. Terlipressin may be useful in the management of neonates with congenital diaphragmatic hernia and refractory pulmonary hypertension.

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Management of neonates with congenital diaphragmatic hernia is still a challenging clinical problem. Overall mortality rate for liveborn infants with isolated congenital diaphragmatic hernia remains as high as 20% to 50% [1]. Congenital diaphragmatic hernia is a complex syndrome

characterized by pulmonary hypoplasia and pulmonary vascular abnormalities that contribute to high pulmonary vascular resistance after birth. Persistent pulmonary hypertension (PPH) can cause extrapulmonary right-to-left shunting and cardiac failure despite pulmonary vasodilator therapy. Vasoactive properties of terlipressin, a long-acting vasopressin agonist, are used in various conditions especially in the treatment of hypotension in patients with catecholamine-resistant septic shock [2]. In addition, in animal models of hypoxic pulmonary constriction, vasopressin has been shown to decrease pulmonary artery pressure [3].

* Corresponding author. Département d'Anesthésie-Réanimation, Unité de Réanimation Pédiatrique et Néonatale et Unité de Brûlés Pédiatriques, Centre Hospitalo-Universitaire Nord, 13915 Marseille Cedex 20, France. Tel.: +33 04 91 96 86 59; fax: +33 04 91 96 46 61.

E-mail address: fabrice.michel@ap-hm.fr (F. Michel).

We report a case of a neonate with congenital diaphragmatic hernia who received terlipressin to treat severe systemic hypotension and PPH with hypoxemic respiratory failure refractory to initial management.

1. Case report

During a normal course gestation of a male infant, a routine prenatal ultrasound examination at 22 weeks gestational age (GA) detected a left-sided diaphragmatic hernia. Diagnosis was confirmed by magnetic resonance imaging at 24 weeks GA, the estimated lung volume was 8 mL, and there was intrathoracic herniation of the liver. Lung-to-head ratio was 0.85. After birth (38 weeks GA, 3000 g), neonatal management included tracheal intubation, surfactant administration, high frequency oscillatory ventilation, and inhaled nitric oxide. Sedation was achieved with intravenous fentanyl and midazolam. Inotropic support was started with adrenaline. Pulmonary hypertension developed rapidly. Echocardiography showed PPH and right ventricular dysfunction. Pulmonary hypertension was suprasystemic with an approximate pressure gradient of 70 mm Hg. During the first hours, the clinical condition worsened with refractory hypoxemia, under fraction of inspired oxygen 100%, and systemic arterial hypotension despite inotropic agents at increasing doses (dobutamine up to 20 $\mu\text{g}/\text{kg}$ per minute and noradrenalin up to 3 $\mu\text{g}/\text{kg}$ per minute) and epoprostenol (up to 60 $\mu\text{g}/\text{kg}$ per minute). Milrinone treatment led to no improvement.

After approval from the parents and the local ethics committee, a bolus of terlipressin (20 $\mu\text{g}/\text{kg}$) was administered intravenously at 38 hours of life. Within 2 hours, there was a dramatic improvement of blood oxygen saturation (from 70% to 98%), decreased oxygen requirements (from 100% to 40%), and normalization of mean arterial pressure

(from 28 to 46 mm Hg) (Fig. 1). Pulmonary hypertension fell to 50 mm Hg and was isosystemic. Therapy with terlipressin was continued with boluses given every 4 hours followed by a continuous infusion of 5 $\mu\text{g}/\text{kg}$ per hour, to avoid arterial pressure variations. Dobutamine and noradrenalin could be stopped within the next 3 days. The neonate remained stable and had the diaphragmatic hernia repaired on day 5. Terlipressin was then progressively decreased and stopped at day 8. Hyponatremia appeared after the beginning of treatment and was managed by fluid restriction and intravenous sodium supplementation. Unfortunately, after progressive improvement, the newborn died at the age of 4 months because of septic shock.

2. Discussion

Approved use of arginine vasopressin for esophageal variceal bleeding is based on its ability to increase systemic vascular resistance, particularly in the splanchnic bed [4]. Effects of arginine vasopressin and the arginine vasopressin analogue (terlipressin) occur via vascular V1 and renal V2 receptors. Besides the vasoconstrictor effect, animal experiments show that arginine vasopressin infusion decreased mean pulmonary pressure and increased systemic pressure in normal [3] and chronically hypoxic rats [5]. Pulmonary vasodilation in response to arginine vasopressin may be mediated through endothelium-derived nitric oxide release [6]. Scheurer et al [7] presented a case report where arginine vasopressin infusion reduced pulmonary hypertension and improved systemic blood pressure after correction of obstructed total anomalous pulmonary venous return in neonates.

Vasopressin has a short contextual half-life and is administered by continuous infusion. Dose is titrated according to clinical effect. However, arginine vasopressin is not available in many European countries, and physicians have

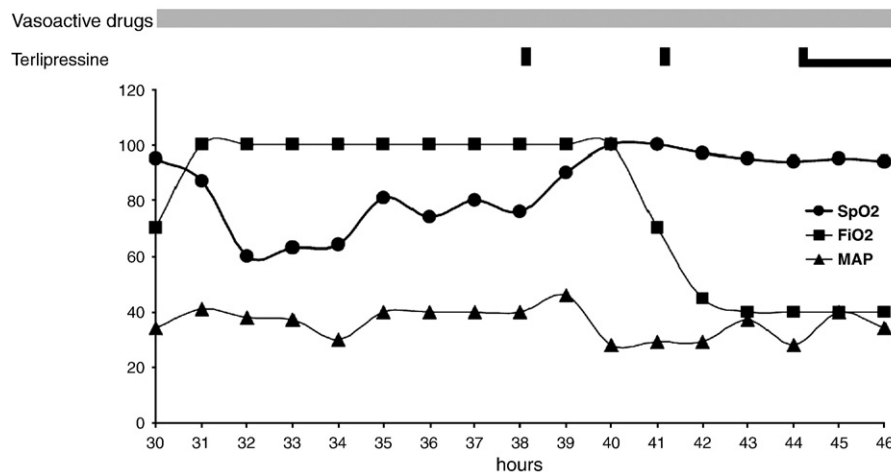


Fig. 1 Mean arterial pressure, fraction of inspired oxygen, and productal peripheral oxygen saturation (SpO₂) during terlipressin and vasoactive drug administration.

then substituted the analogue terlipressin in clinical practice [8]. Several authors have shown its efficacy for treating serious arterial hypotension. We hypothesized that terlipressin, which has previously been used as rescue therapy for septic shock [9], would be an effective agent to ameliorate pulmonary hypertension and decrease the need for vasopressor support in neonates with congenital diaphragmatic hernia with hypoxemia, PPH, and high risk of cardiac failure.

Landry et al [10] first reported the beneficial use of arginine vasopressin in critically ill patients with hypotensive septic shock refractory to catecholamines. Terlipressin was effective in children with hypotension in catecholamine resistant septic shock [11]. In neonates, terlipressin [12] was reported to correct hypotension in vasodilatory shock. Recently, Papoff et al [13] described a similar case of congenital diaphragmatic hernia and PPH managed with terlipressin.

The optimal dose of terlipressin required to manage catecholamine-resistant hypotension remains to be determined. In instances of hypotension caused by septic shock, most clinicians used a bolus of terlipressin between 7 and 20 $\mu\text{g}/\text{kg}$ [9]. Excessive vasoconstriction and rebound vasodilation have been reported when infusion is discontinued [2]. We first used a bolus of 20 $\mu\text{g}/\text{kg}$ followed by a continuous terlipressin infusion. Using this regimen, systemic arterial pressure remained stable.

We noted skin pallor but no obvious digital, cutaneous, or splanchnic ischemia. The hyponatremia that appeared during treatment was related to the antidiuretic property of terlipressin and was treated accordingly.

Our case report shows that terlipressin infusion increased systemic arterial pressure and decreased oxygen requirements. This observation suggests that terlipressin may be an effective pharmacologic rescue treatment of refractory pulmonary hypertension in neonates with congenital diaphragmatic hernia. Further studies are required to assess the

effectiveness and safety of terlipressin in congenital diaphragmatic hernia and to define the optimal dosage.

References

- [1] Brownlee EM, Howatson AG, Davis CF, et al. The hidden mortality of congenital diaphragmatic hernia: a 20-year review. *J Pediatr Surg* 2009;44:317-20.
- [2] O'Brien A, Clapp L, Singer M. Terlipressin for norepinephrine-resistant septic shock. *Lancet* 2002;359:1209-10.
- [3] Walker BR, Haynes J, Wang HL, et al. Vasopressin-induced pulmonary vasodilation in rats. *Am J Physiol* 1989;257:H415-22.
- [4] Levacher S, Letoumelin P, Pateron D, et al. Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. *Lancet* 1995;346:865-8.
- [5] Eichinger MR, Walker BR. Enhanced pulmonary arterial dilation to arginine vasopressin in chronically hypoxic rats. *Am J Physiol* 1994;267:H2416-9.
- [6] Evora PR, Pearson PJ, Schaff HV. Arginine vasopressin induces endothelium-dependent vasodilation of the pulmonary artery. *Chest* 1993;103:1241-5.
- [7] Scheurer MA, Scott MB, Atz AM. Vasopressin to attenuate pulmonary hypertension and improve systemic blood pressure after correction of obstructed total anomalous pulmonary venous return. *J Thorac Cardiovasc Surg* 2005;129:464-6.
- [8] Leone M. Terlipressin or eopressin? *Crit Care* 2009;13:192.
- [9] Michel F, Thomachot L, David M, et al. Continuous low-dose infusion of terlipressin as a rescue therapy in meningococcal septic shock. *Am J Emerg Med* 2007;25:863.e1-e2.
- [10] Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 1997;95:1122.
- [11] Yildizdas D, Yapicioglu H, Celik U, et al. Terlipressin as a rescue therapy for catecholamine-resistant septic shock in children. *Intensive Care Med* 2007;34:511-7.
- [12] Filippi L, Poggi C, Serafini L, et al. Terlipressin as rescue treatment of refractory shock in a neonate. *Acta Paediatr* 2008;97:500-2.
- [13] Papoff P, Caresta E, Versacci P, et al. The role of terlipressin in the management of severe pulmonary hypertension in congenital diaphragmatic hernia. *Paediatr Anaesth* 2009;19(8):805-6.