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Atrial natriuretic peptide infusion for a neonate undergoing repair of congenital diaphragmatic hernia

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Introduction

Atrial natriuretic peptide (ANP) is an endogenous and clinically available substance that regulates water and electrolyte balance [1] and is present in both premature and full-term infants [2]. ANP has recently been used for patients with congestive heart failure because of its diuretic and vasodilator actions in adults [3,4]. Pediatric use of ANP [5] during or after operation is increasing in Japan [6–8]. However, little information concerning the use of ANP in neonates is available. We describe a neonate with congenital diaphragmatic hernia (CDH) coexisting with patent ductus arteriosus (PDA) and patent foramen ovale (PFO) who had anuria before and during surgical repair of CDH and was resistant to the administration of conventional diuretics. The anuria of the patient was successfully treated with continuous infusion of ANP.

Case report

The patient was a 3260-g female infant born at 41 weeks of gestation and was less than a day old. The Apgar score was 3, 7, and 8 at 1, 5, and 10 min, respectively. She showed obvious respiratory distress and was diagnosed as having CDH with coexisting PDA and PFO. After 6 h, she was transferred to our neonatal intensive care unit (NICU) and intubated. Although she had been treated with mechanical ventilation and fluid therapy ($3\,ml\cdot kg^{-1}\cdot h^{-1}$ of crystalloid solution and $0.8\,ml\cdot kg^{-1}\cdot h^{-1}$ fresh frozen plasma solution), her urinary output showed only a trace amount through the urinary catheter. Analysis of arterial blood gases sampled from the left radial artery found pH 7.368, PaO_2 73.7 mmHg, $PaCO_2$ 31.0 mmHg, and base excess $-6.3\,mmol\cdot l^{-1}$ (FiO_2 0.3, inspiratory pressure 22 cmH_2O, positive end-expinatory pressure (PEEP) 4 cmH_2O, and ventilatory frequency 40 bpm). On echocardiographic examination, she had PDA and PFO with left to right shunt, and her left venticular function was slightly depressed. On the first day of life, she was scheduled for surgical repair of CDH. The preoperative physical examination revealed wet mucous membrane, normal skin turgor, and normal anterior fontanel. The serum urea nitrogen and creatinine levels were $20\,mg\cdot dl^{-1}$ and $0.8\,mg\cdot dl^{-1}$, respectively. The other preoperative laboratory data were within normal limits. Anuria persisted for 12 h before surgery, despite intravenous administration of dopamine ($3\,\mu g\cdot kg^{-1}\cdot min^{-1}$) and furosemide ($0.3\,mg\cdot kg^{-1}$).

Anesthesia was induced and maintained with fentanyl ($10\,\mu g\cdot kg^{-1}$) and isoflurane (0.5%–1.0%) in an air–oxygen mixture (FiO_2 0.4–1.0, pressure-controlled mode 20 cmH_2O, PEEP 2 cmH_2O, and respiratory frequency 40 bpm). Pancuronium ($0.1\,mg\cdot kg^{-1}$) was given as a supplement. After the induction, catheters were inserted into the right radial artery and the internal jugular vein for continuous measurement of arterial and central venous pressures. The intraoperative heart rate was within the range of 170–180 bpm, and arterial and central venous blood pressure were within the ranges of 75/50–60/40 mmHg and 5–6 mmHg, respectively. The serum Na^+ and K^+ concentrations were 134.4 and $3.5\,mEq\cdot l^{-1}$, respectively. After crystalloid solution ($6.3\,ml\cdot kg^{-1}\cdot h^{-1}$) and an additional 20 ml of 5% albumin were infused for 1.5 h, the anuria persisted. Despite little blood loss, the hematocrit decreased from 46.4% to 38.2%. The heart rate and blood pressure were stable. The mucous membrane was moist. Skin turgor

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Table 1. Course of fluids, urine output, and hemodynamics

Time	Fluids ($ml \cdot kg^{-1} \cdot h^{-1}$)		Urinary output ($ml \cdot kg^{-1} \cdot h^{-1}$)	BP (mmHg)	CVP (mmHg)	HR (bpm)
	Crystalloid	Colloid				
Before operation	3.0	0.8	0.0	75/45		180
Before ANP started	6.3	4.0	0.0	70/50	6	175
After ANP started	6.2	4.0	3.3	70/50	5	170
After ANP stopped	3.0	0.0	1.8	65/45		160

BP, Blood pressure; CVP, central venous pressure; HR, heart rate; ANP, atrial natriuretic peptide

and the anterior fontanel remained stationary, with warm extremities. The patient did not appear hypovolemic. Intravenous administration of $0.6\,mg \cdot kg^{-1}$ furosemide for 1 h was ineffective. Continuous intravenous infusion of ANP (Hanp; Zeria Pharmaceutical, Tokyo, Japan) at a rate of $0.05\,\mu g \cdot kg^{-1} \cdot min^{-1}$ was started. Fifteen minutes after the start of ANP infusion, urinary output began and increased to 24 ml in 2 h ($3.3\,ml \cdot kg^{-1} \cdot h^{-1}$). The heart rate and arterial pressure remained stable, and serum Na^+ and K^+ levels also remained unchanged. Surgery was completed uneventfully, and ANP infusion was discontinued. Urinary output was continuously obtained, even after termination of ANP infusion (Table 1). Blood loss was minimal. The patient required mechanical ventilatory support without PEEP for another 24 h, and her hemodynamics remained stable within normal limits. Postoperative urinary output was shown to be adequate (1.8–$3.5\,ml \cdot kg^{-1} \cdot h^{-1}$), while fluid infusion was maintained at $80\,ml \cdot kg^{-1} \cdot day^{-1}$ without any diuretics. The postoperative laboratory data, including serum electrolytes and blood gas analysis, were also within normal limits.

Discussion

Our patient had anuria despite fluid infusion and respiratory therapy. A suspected cause of anuria of the neonate is renal hypoperfusion secondary to low cardiac output due to congenital heart disease or hypovolemia. Although the possibility of low cardiac output could not be excluded, salient low cardiac output seemed unlikely according to the hemodynamic data and blood gas analysis. The physical findings as to skin turgor and anterior fontanel, and central venous pressure values ranging from 5 to 6 mmHg during surgery, were not suggestive of obvious hypovolemia. Further, the neonatal kidney has immature glomerular and tubular functions in association with high renal vascular resistance [9]. Glomerular hypoperfusion caused by a slightly low cardiac output and by immaturity of the renal functions might have contributed to the anuria. In fact, urinary output was continuously obtained without positive treatment, even after discontinuation of ANP infusion. The most important reason for using ANP was that the patient did not respond to the conventional diuretics furosemide and dopamine. The present case shows that ANP is an effective diuretic agent and is a useful alternative in neonates.

Several mechanisms underlying the increased urinary output induced by ANP infusion have been suggested [10]. ANP produces an increase in renal filtration fraction and glomerular filtration rate without changing renal blood flow. The change in peritubular hemodynamics causes a decrease in proximal tubular sodium reabsorption, i.e., the inhibition of countercurrent mechanisms [10]. ANP acts on its specific receptors, which are distributed preferentially in the renal and pulmonary vasculature [11], to activate particulate guanylyl cyclase to form 3′,5′-cyclic guanosine monophosphate (cGMP), resulting in vasodilation [12]. Further, ANP inhibits renin release from the juxtaglomerular apparatus [13], which in turn inhibits sodium and water retention derived from the angiotensin-aldosterone system.

Compared with that in the adult, the neonatal renal natriuretic response to acute volume expansion is limited [14] because of the increased activity of endogenous angiotensin II. ANP may antagonize the effects of circulating angiotensin II, because the early natriuretic response appears to be the cause of suppression of angiotensin II following acute volume expansion [14,15]. The success of ANP infusion may be related not only to its natriuretic and diuretic potential, but also to suppression of renin secretion and of aldosterone and vasopressin synthesis when the immature kidney is less susceptible to diuretics.

Hamawaki et al. reported that, following ANP infusion at incremental doses of $0.05–0.24\,\mu g \cdot kg^{-1} \cdot min^{-1}$ for neonates and early infants who developed congestive heart failure after surgical repair of congenital heart disease, urinary output and hemodynamics improved [8]. Murakami et al. reported that infusion of 0.08–$0.2\,\mu g \cdot kg^{-1} \cdot min^{-1}$ ANP and furosemide after cardiac surgery in neonates and infants increased urine volume more than furosemide alone, whereas systemic arterial

pressure, central venous pressure, and renal function were unchanged [6].

Our previous study in infants undergoing cardiac surgery [7] found that ANP infusion at a rate of $0.02\,\mu g \cdot kg^{-1} \cdot min^{-1}$, only one fifth of the dose used for the treatment of congestive heart failure in adult patients [4], produced adequate urinary output without a fall in systemic arterial pressure and electrolyte abnormality such as hypokalemia during and after cardiopulmonary bypass.

There are few reports of the direct effect of ANP on PDA opening after birth. However, a highly significant correlation exists between the secretion of ANP and the magnitude of the left-to-right shunt in PDA [16,17]. The ANP level is significantly higher when the ductus is open than when it is closed in preterm infants with respiratory distress [16].

ANP tends to decrease pulmonary capillary wedge pressure and right atrial pressure more than mean arterial pressure in patients with congestive heart failure [4].

Despite the presence of left-to-right shunt observed by preoperative echocardiography, intraoperative surgical stress may evoke spasms of the pulmonary artery, which causes right-to-left shunting followed by hypoxia. Preferential pulmonary vasodilation, as well as natriuresis caused by ANP, is beneficial to CDH.

In conclusion, we reported a case of effective treatment with continuous intravenous infusion of ANP in a neonate who had anuria before and during surgery for congenital diaphragmatic hernia and was resistant to conventional diuretics. Although further studies are necessary, our experience will provide a way for safe and useful application of ANP in the treatment of critically ill neonates.

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