Oral Administration of Prostaglandin E₂ in the Hypoplastic Left Heart Syndrome

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SUMMARY

Oral administration of prostaglandin E₂ resulted in marked clinical and hemodynamic improvement in patients with hypoplastic left heart syndrome. A lessening of metabolic acidosis and an increase in blood pressure were evident. These results indicate that the ductus arteriosus was effectively dilated by oral prostaglandin E₂ in patients with ductus-dependent *systemic* circulation, as in the case of ductus-dependent *pulmonary* circulation. Surgical risk will also be reduced by pretreatment with oral prostaglandin E₂.

Additional Indexing Words:

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INFUSIONS of prostaglandin E₂ (PGE₂) and PGE₁ are widely used to maintain postnatal patency of the ductus arteriosus in infants with severe right ventricular outflow obstruction and aortic arch anomalies. Recently, oral PGE₂ has also been used successfully in patients with ductus-dependent *pulmonary* circulation. However, clinical data regarding the oral administration of PGE₂ in the aortic obstruction, have not been reported. We describe the results of oral administration PGE₂ in 2 cases of hypoplastic left heart syndrome. Since corrective surgery in this malformation is theoretically feasible, orally administered PGE₂ may be of use to maintain the patency of the ductus arteriosus prior to surgical intervention.

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CASE REPORTS

Case 1 A 2.9 Kg boy was born following uneventful 37-week gestation. The Apgar score was 9 at 1 min. In the newborn nursery mild tachycardia and mild cyanosis were noted. The infant was transferred to our hospital at 6 days of age. On physical examination, he was mildly cyanotic and in mild respiratory distress. The pulse rate was 160/min, respiratory rate was 74/min and systolic pressure was 110 mmHg in the upper extremities. No cardiac murmur was heard. The liver edge was palpated 2 cm below the right costal margin. A chest roentgenogram showed mild cardiomegaly and pulmonary vascular congestion. The electrocardiogram revealed right ventricular hypertrophy with right axis deviation. An arterial blood sample obtained from the right radial artery disclosed a pH of 7.34, a P_{aO_2} of 48 mmHg and a P_{aCO_2} of 36 mmHg.

On the fourth day of hospitalization, generalized edema and poor feeding developed and the peripheral pulse was weak. An echocardiogram showed a small left ventricle, distorted mitral valve and moderate hypoplasia of the ascending aorta. Cardiac catheterization was performed to confirm the diagnosis on the eighth day of hospitalization. The cardiac study re-

Fig. 1. Aortograms revealed moderate (Case 1, A) and severe (Case 2, B) underdevelopment of the ascending aorta in these cases. The arrow indicates a markedly hypoplastic ascending aorta.

vealed aortic valve atresia, a hypoplastic ascending aorta, mitral atresia, and a restrictive foramen ovale (Fig. 1). Balloon atrioseptostomy was not performed because the catheter could not be inserted into the left atrium. The pressure difference of 10 mmHg between the main pulmonary artery (78/40 mmHg with mean pressure of 53 mmHg) and the descending aorta (68/52 mmHg with mean pressure of 46 mmHg) was interpreted as evidence of a closing ductus arteriosus. Clinical deterioration developed after the cardiac catheterization. Systemic blood pressure fell to 46 mmHg in the lower extremities, indicative of rapid closure of the ductus. Oral administration of PGE₂ (500 μ g) was initiated. The radial arterial sample revealed a pH of 7.41, a PaO₂ of 43 mmHg and a PaCO₂ of 38 mmHg before administration. Within 20 min after PGE₂, femoral pulses were palpated, capillary filling was markedly improved and urine output commenced. The patient's skin color and level of activity improved markedly.

Serial transcutaneous P_{O₂} values and systolic blood pressure in the lower extremities are shown in Fig. 2A. Blood pressure rose to 78 mmHg 30 min after oral PGE₂ administration. The radial blood pH was 7.41, the P_{O₂} was

A CASE 1

B CASE 2

Fig. 2. The blood pressure was elevated 10 min (Case 1, A) and 20 min (Case 2, B) after oral PGE₂ administration. The transcutaneous P_{O₂} was mainly dependent on oxygen administration.

Fig. 3. The electrocardiogram and descending aortic pressure before (a) and after (b) oral administration of PGE_2 in Case 2. The ST elevation on the ECG disappeared and phasic blood pressure trace was observed after oral PGE_2 administration.

43 mmHg and the PaCO_2 was 39 mmHg 1 hour after administration. Thereafter, PGE_2 was given hourly. However, the infant died of respiratory and cardiac failure 22 hours after the cardiac catheterization.

Case 2 A 3.02 Kg girl, full-term, uncomplicated pregnancy, was referred to our hospital when she was 23 hours old because of tachycardia, retractive breathing, and cyanosis. On physical examination, she was moribund with mottled skin, poor capillary filling, an absent peripheral pulse and gasping respiration. The heart rate was 136/min and the respiratory rate was 60/min. A grade 2/6 systolic murmur was heard along the left sternal border. The liver edge was palpable 5 cm below the right costal margin. A chest roentgenogram showed mild cardiomegaly and pulmonary vascular congestion. The electrocardiogram showed right ventricular hypertrophy with right axis deviation. An arterial sample obtained from umbilical catheter disclosed a pH of 7.15, a PaO_2 of 75 mmHg and a PaCO_2 of 21 mmHg. M-mode echocardiogram showed one A-V valve, one ventricle, and severe hypoplasia of the ascending aorta. The diagnosis of hypoplastic left heart syn-

drome was assumed and oral PGE₂ was started because systemic blood flow was dependent on a patent ductus arteriosus. There was no phasic waveform in the descending aorta but the mean pressure of 26 mmHg before oral PGE₂ administration (Fig. 3a). With ductus dilatation after oral PGE₂ administration, the descending aortic pressure increased to 51/22 mmHg with mean pressure of 32 mmHg, and a phasic trace in the descending aorta was observed (Fig. 3b). The ischemic changes on the electrocardiogram disappeared immediately (Fig. 3a, b), and the blood pressure increased within 20 min after oral PGE₂. One hour later, umbilical arterial sample showed a pH of 7.23, a PaO₂ of 57 mmHg, and a PaCO₂ of 23 mmHg. Serial transcutaneous PaO₂ values and systolic blood pressure are shown in Fig. 2B. PGE₂ was given hourly in doses of 500 µg. Emergency cardiac catheterization demonstrated aortic atresia, mitral atresia, and a closing ductus, with a 20 mmHg pressure gradient from the main pulmonary artery (65/34 mmHg with mean pressure of 49 mmHg) to the descending aorta (45/20 mmHg with mean pressure of 29 mmHg). Balloon atrioseptostomy was performed to reduce pulmonary congestion. PGE₂ was continued during the cardiac catheterization and an operation was performed 6 hours later. A 6 mm polytetrafluoroethylene graft was placed from the proximal main pulmonary artery to the descending aorta. The ductus arteriosus was ligated and a band was placed around the main pulmonary artery distal to the graft. The initial postoperative course was uneventful. PGE₂ was discontinued and the systolic pressure remained at 60 mmHg. However, the patients became oliguric on the third postoperative day and developed renal failure. The band on the pulmonary artery was tightened again in order to increase the systemic flow on the fifth postoperative day. She died of renal failure 29 hours after the second operation.

DISCUSSION

Many reports concerning the effectiveness of E-type PGs have been exclusively in cases of infants with restrictive *pulmonary* blood flow and a closing ductus-arteriosus with low PaO₂.¹⁾⁻³⁾ The relaxant effect of PG on the ductus is most striking under these hypoxic conditions.⁴⁾ However, Clyman et al observed the same relaxant action, even under high PaO₂, in an experimental study.⁵⁾ The PaO₂ during aortic obstructions such as an interrupted aortic arch, hypoplastic left heart syndrome or coarctation of the aorta is either normal or slightly below normal. In these malformations, the maintenance of systemic blood flow or provision of adequate blood flow to the descending aorta after birth depends on right-to-left ductal shunting. In the hypoplastic

left heart syndrome, the systemic blood-supply depends entirely upon a patent ductus arteriosus. With ductal closure after birth, the blood flow to vital organs decreases, resulting in clinical deterioration and unstable hemodynamics. These infants usually die of congestive heart failure, renal failure, hepatic necrosis, respiratory failure, and severe metabolic acidosis.

Some investigators^{(6)–(11)} have described the efficacy of PG in infants with aortic obstructions. PG was administered from the descending aorta via an umbilical catheter just above the ductus arteriosus, pulmonary artery, inferior vena cava or a peripheral vein. However, the most effective route for PG administration was not determined. Silove et al⁽¹²⁾ employed oral PGE₂ in ductus-dependent pulmonary circulation. They found that PGE₂ was easier to administer orally and, if the regimen was started, PGE₂ continued to be effective for about 3 months. They recommended an initial regimen of 30–40 $\mu\text{g}/\text{Kg}/\text{hour}$ in the case of restrictive pulmonary flow.

PGs are chiefly inactivated through the pulmonary circulation.⁽¹³⁾ As pulmonary flow is decreased in ductus-dependent pulmonary circulation, the PG catabolism in the lungs may be decreased. Conversely, if the pulmonary flow is increased in ductus-dependent systemic circulation, the PG catabolism in the lungs may be increased. Therefore, the circulating PGE level may be lower in aortic obstruction than in restrictive pulmonary flow. Linday et al⁽¹⁴⁾ reported that PGE₂ was not effective in infants with restrictive systemic flow.

In light of these data, we used a higher dose (500 μg of PGE₂/hour) in cases of hypoplastic left heart syndrome. Rapid clinical and hemodynamic improvement was documented by a reversal of systemic hypotension, metabolic acidosis, and coronary ischemia. This report presents the first cases where oral PGE₂ improved the clinical and hemodynamic status of infants with restrictive *systemic* flow. The ductal dilatation improved the clinical condition of these patients. We did not observe complications such as hypotension, bradycardia, diarrhea, apnea, and pyrexia.

Until recently, it was considered meaningless to use PG in infants with no prospect of corrective surgery, such as hypoplastic left heart syndrome^{(10), (15)} because satisfactory methods of management for these infants has not been established. However, corrective surgery in this syndrome seems to be feasible, and some reports of surgical procedures^{(16)–(18)} encourage the use of PG in the hypoplastic left heart syndrome. Based on our experience with 2 infants and the demonstrated relative safety of oral PGE₂, we recommend the pre-operative use of oral PGE₂ in infants with hypoplastic left heart syndrome and a closing ductus. Surgical intervention in the face of vascular collapse and severe metabolic abnormalities caused by ductal constriction has usually

been futile. However, it may be possible to improve the management of these patients with oral administration of PGE₂.

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