E-Type Prostaglandins
A New Emergency Therapy for Certain Cyanotic Congenital Heart Malformations

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SUMMARY Prostaglandin E2 (PGE2) has been used to maintain patency of the ductus arteriosus in four neonates with cyanotic congenital heart disease due to obstructive right heart malformations. PGE2 was infused prior to surgery, and in three patients, during surgery until a satisfactory aorto-pulmonary shunt was established. PGE2 produced consistently an immediate and persistent rise in arterial oxygen saturation, which could be ascribed to dilation of the ductus arteriosus. No major side effects occurred, except for pyrexia in two infants. All patients recovered well from surgery. We propose this treatment as preparation for surgery in any infant with congenital heart defects and ductus-dependent pulmonary blood flow. The same treatment may be useful preoperatively in patients with aortic interruption who also depend on continued patency of the ductus for blood supply to the lower half of the body.

CONGENITAL HEART DEFECTS which include pulmonary atresia, critical pulmonary stenosis or a severely hypoplastic right ventricle as part of the malformation are frequently almost entirely dependent on persistence of the ductus arteriosus for the maintenance of pulmonary blood flow. Likewise, interruption of the aortic arch requires ductus patency for blood flow to the lower half of the body. Patients in either group usually become extremely sick in the first few days of life as the ductus constricts and without intervention they generally die within the first month. Even when referred to an investigative center, they are frequently so ill by the time investigation is undertaken that subsequent palliative surgery carries a high mortality.

The original demonstration by Cocceani and Olley that E-type PGs are potent relaxants of the ductus arteriosus, confirmed by subsequent animal studies by others in vitro and in vivo, suggested their use in these patients. Administration of PG to reverse ductus constriction and increase pulmonary blood flow should improve tissue oxygenation, permit correction of metabolic acidosis, and improve the chances of successful surgery. Similar reasoning was followed by Elliott et al. when they infused PGE2 in two infants with cyanotic heart disease in whom surgery was refused by the parents.

In this paper we describe the use of PGE2 as a preparation for surgery in three patients and postoperatively in one patient in whom surgery was unsuccessful. Part of this work has been reported briefly.

Materials and Methods

PGE2 (Prostin E2, Upjohn Co.) has been used in all patients. Its effectiveness was first evaluated during diagnostic cardiac catheterization. Once the diagnostic procedure was completed, an infusing catheter introduced into the femoral vein was placed as close to the aortic end of the ductus as possible, either being in the left ventricle via the foramen ovale or in the aortic root through a ventricular septal defect. PGE2 (0.5 mg in 0.5 ml ethanol) was diluted in a dextrose 3.3%-sodium chloride 0.3% solution to give a final concentration of PGE2 of 0.4 µg/ml and was infused at the rate of about 1 ml/min using a Harvard pump (model 940). Prior to commencing the infusion, arterial blood gases and oxygen saturation were measured using an Instrumentation Laboratory gas analyzer and a Waters oximeter. Inspired oxygen concentration was kept constant during the initial infusion. Three patients were breathing room air spontaneously and the fourth patient was being ventilated with 40% oxygen. None of the patients had received sedation and there was no change from their resting state during the test infusion. Systemic blood pressure, heart rate, and respiration were monitored. At the end of a 10 min infusion, arterial blood gases were remeasured. If PaO2 and oxygen saturation were higher, by 5 mm Hg tension or 10% saturation, a cannula was positioned in the inferior vena cava, either via the umbilical vein or the long saphenous vein, for further PGE2 infusion on the ward. A more concentrated PGE2 solution (1.6 µg/ml) was used to reduce the fluid load to 15 ml/hour, or less. Blood pressure was monitored every 30 min and rectal temperature checked hourly. The ECG was monitored continuously and blood gases measured as often as possible (max. interval, 3 hours). The babies were observed for apneic spells. In all but one patient (Case 1), PGE2 infusion was continued up to and during surgery until a satisfactory aortopulmonary anastomosis was established.

Patient Histories and Results

Case 1

This full-term male infant was delivered vaginally after a normal pregnancy. Birth weight 3.27 kg. Cyanosis was noted 24 hours later and was associated with tachypnea. Cardiac catheterization on the third day demonstrated tetralogy of Fallot with pulmonary atresia, the only pulmonary blood flow being via a small patent ductus arteriosus. PGE2, 0.13 µg/kg/min, was infused into the aortic root while arterial blood pressure was monitored intermittently through the same catheter. Arterial oxygen saturation increased from 62 to 84% within 10 min of the infusion while the blood pressure remained constant. No ill effects were observed. Subsequently, the infusion was maintained for a four-hour period after which time the infant developed a pyrexia of 39.5°C and the treatment was discontinued. Three hours later, the
pyrexia subsided but the child became deeply cyanosed and a
ductus murmur which had developed during the initial infu-
sion period disappeared. PGE$_2$ was given again with a
dramatic improvement in the baby's color and the
appearance of a loud ductal murmur. Two hours later, the
baby underwent a successful Waterston anastomosis be-
tween the ascending aorta and right pulmonary artery.

Case 2

This baby girl was the product of a normal pregnancy and
delivery. Birth weight 2.7 kg. Cyanosis developed shortly
after birth. Cardiac catheterization at the age of 26 hours
confirmed the clinical diagnosis of tricuspid atresia with a
hypoplastic right ventricle and severe pulmonary stenosis.
Pulmonary blood flow was almost exclusively via a small
ductus arteriosus. PGE$_2$, 0.13 $\mu$g/kg/min, was infused into
the left ventricle (LV) through a #5 NIH catheter while
arterial blood pressure was monitored via an indwelling um-
bilical artery catheter. Three minutes after starting the infu-
sion, profound bradycardia developed, the infusion was
stopped and the catheter withdrawn from the LV. Subse-
quent attempts to re-enter the LV again caused bradycardia and
PGE$_2$ was therefore infused into the left atrium without
further slowing. The bradycardia was therefore felt to be due
to placement of the catheter in the LV rather than to the
PGE$_2$ infusion. Blood gases were measured before and after
a 10-min infusion. Oxygen saturation rose from 50 to 82%.
The infusion was then discontinued to permit balloon septo-
tomy. On the basis of the favorable response to PGE$_2$
during catheterization, treatment was continued overnight
for 12 hours until the infant underwent a Potts anastomosis
(descending aorta to left pulmonary artery). During PGE$_2$
therapy, the infant had several apneic spells which even-
tually necessitated intubation and ventilation. The PGE$_2$
was not discontinued. At surgery, the ductus was found to be
widely patent and no special intraoperative difficulties were
encountered. The change in PaO$_2$ in response to PGE$_2$ is
shown in figure 1.

Case 3

This full-term female infant was noted to be deeply
cyanoosed from birth. Birth weight 3.1 kg. Cardiac catheteri-
ation at 12 hours confirmed the clinical diagnosis of
pulmonary atresia with an intact ventricular septum and
small right ventricle. Pulmonary blood flow was pre-
dominantly through a small patent ductus arteriosus. No
significant bronchial vessels were demonstrated angiog-
raphically. PGE$_2$, 0.11 $\mu$g/kg/min, was infused into the
LV. Arterial oxygen saturation increased from 65 to 77%.
Subsequently the infusion was maintained for four hours un-
til the baby underwent a Potts anastomosis combined with
pulmonary valvotomy. At surgery, the ductus was found to
be quite large externally, with the exception of its pulmo-
nary end which appeared narrowed. There was no thrill over
the vessel. No untoward effects were observed in this infant.

Case 4

This baby boy resulted from a full-term, normal preg-
nancy and delivery and was noted to be cyanosed at
birth. Birth weight 3.2 kg. Cardiac catheterization at 12
hours demonstrated critical pulmonary stenosis with a
hypoplastic right ventricle and a patent ductus arteriosus.
Pulmonary valvotomy was performed two hours after
catheterization. During the subsequent 12 hours, while in the
Intensive Care Unit, the baby became increasingly hypoxic
despite assisted ventilation and high inspired oxygen con-
centrations. This was presumed to be due to an inadequate
pulmonary blood flow which was clearly ductus-dependent.
PGE$_2$, 0.13 $\mu$g/kg/min, was infused into the inferior vena
cava while arterial blood pressure was monitored. Arterial
oxygen saturation rose from 58% to 84% within 10 min. On
the basis of this satisfactory initial response, a reduced dose
of PGE$_2$, 0.08 $\mu$g/kg/min, was given during the next three
hours. During this period, the child became pyrexial (rectal
temperature 39°C). The dose was further reduced to 0.04
$\mu$g/kg/min, but shortly afterwards, the baby developed a
pneumothorax as a complication of his assisted ventilation.
PaO$_2$ fell to 16 mm Hg and subsequent effectiveness of
PGE$_2$ became difficult to evaluate. After chest tubes had
been placed, the PGE$_2$ dose was again increased to 0.08
$\mu$g/kg/min and PaO$_2$ rose to 37 mm Hg. How much of this
rise was due to relief of the pneumothorax and how much to
PGE$_2$ could not be assessed. The same evening, 24 hours
after the initial operation, the patient was returned to the
operating room and a descending aorta to left pulmonary
artery anastomosis performed successfully. On visual ex-
amination, the ductus appeared widely patent.

All four patients are doing well postoperatively. The max-
imum follow-up to date is four months.

Figure 2 summarizes the findings with the four patients.
As shown, arterial oxygen tension and saturation rose within
10 min of PGE$_2$ infusion. This effect was sustained as long as
the infusion was continued. In one patient (Case 3), angiog-
raphic evidence of increased size of the ductus was obtained
(fig. 3).

Discussion

Several lines of investigation suggest that the muscle tone
of the fetal ductus arteriosus is controlled by the endogenous
production of PGE compounds. PGEs are a normal con-

![Figure 1. Effect of PGE$_2$ treatment on arterial oxygen tension in a patient with tricuspid atresia and severe pulmonary stenosis (Case 2).](http://circ.ahajournals.org/)}
stent of the vessel. The same PGs markedly relax the ductus both in vitro and in vivo. Their in vitro action is fully developed only in a low oxygen environment. Indomethacin and eicosa-5,8,11,14-tetraynoic acid, both blockers of PG synthesis in tissues (for a review, see Flower), produce intense and persistent contraction of the hypoxic ductus arteriosus in vitro. Indomethacin action has been confirmed in vivo. Finally, reduced glutathione, a known stimulator of PGE synthesis, relaxes the ductus arteriosus in vitro. These data, while suggesting that PGs may be responsible for maintaining the patency of the ductus arteriosus in the fetus, also afford a new approach to the treatment of certain congenital heart defects.

Two groups of patients may be considered: 1) Infants with certain cyanotic malformations which have in common dependency on the ductus arteriosus for their pulmonary blood flow, e.g., pulmonary atresia with an intact ventricular septum and insignificant bronchial collaterals. Despite this dependency, the ductus frequently closes during the first week of life, which leads to progressive hypoxia, metabolic acidosis, and eventually to death. In these patients, hypoxia from birth, an E-type PG can be used to maintain or increase ductus patency and therefore increase pulmonary blood flow and arterial oxygen saturation. 2) Premature infants with a persistent ductus arteriosus, complicating the respiratory distress syndrome or causing congestive failure, in whom it may be possible to produce ductus closure by the administration of a blocker of PG synthesis.

To date, we have infused PGE in four patients who fall into the first group with excellent results. A significant rise in arterial oxygen saturation appeared directly related to the infusion and could be ascribed to the dilation of the ductus arteriosus and the resulting increase of pulmonary blood flow. Possible complications of PG administration require further evaluation but have not seriously limited therapy in any of these patients.

Hypotension is to be expected in view of the systemic vasodilating effect of E-type PGs. However, the sensitivity of the ductus smooth muscle to PGE is greater than that of ordinary vascular smooth muscle, and systemic hypotension has been mild (< 5 mm Hg) and has posed no problems. Bradycardia was not observed except in one patient in whom it was related to the location of the catheter in the left ventricle rather than to the PGE infusion.

Pyrexia due to a central action of PGs (for a review, see Coceani) has been reported as a complication of the clinical use of PGs in adults. Two of our patients (Cases 1 and 4) developed fever, but interruption of PGE infusion in one patient (Case 1) proved that this effect is reversible. No long-term sequelae occurred in either patient.

Apneic spells and bradycardia occurred in one infant (Case 2). Such phenomena are common in these seriously ill patients and it is not yet clear whether they result from PGE administration, although PGs are known to have a direct action on respiratory centers.

Slight muscular twitching was also observed (Case 3). However, it seems unlikely that PGE was responsible because there are several recent reports proving that PGs are not epileptogenic, at least in adults.

These potential complications require further evaluation with more clinical experience. Possibly, PGE can be used in a lower dose without altering its effectiveness on the ductus arteriosus. However, even if side effects occur, they should be reversible because circulating PGE compounds are rapidly degraded in the newborn.

To date, we have used PGE because this was the only compound available for clinical trials. However, recent work indicates that whereas PGE is a weak vasoconstrictor, PGE is a weak vasodilator on pulmonary vessels. From this, it would follow that PGE, as used by Elliott et al., is a better choice. Yet, the rise in oxygen saturation brought about by the two PGs is comparable.

On the basis of this preliminary experience, we believe
that PG treatment should be considered in infants in whom it is potentially important to maintain patency of the ductus arteriosus. Specific indications include: 1) Pulmonary atresia with an intact ventricular septum; 2) critical pulmonary valve stenosis with intact ventricular septum; 3) tetralogy of Fallot with pulmonary atresia or extreme pulmonary stenosis; 4) tricuspid atresia with small right ventricle, pulmonary stenosis and/or restrictive ventricular septal defect; 5) double outlet right ventricle, single ventricle complexes and transposition complexes which include severe pulmonary stenosis as part of the lesion. In these patients, patency of the ductus arteriosus is usually vital in maintaining pulmonary blood flow. Two additional conditions may benefit from prostaglandin treatment, namely, 6) simple transposition of the great arteries where balloon septostomy has failed and in which blood mixing occurs only through a patent ductus arteriosus and 7) interrupted aortic arch in which blood reached the lower half of the body via the ductus arteriosus. Prostaglandin treatment may be initiated during transfer of the patient from an outlying hospital to a major center; during diagnostic cardiac catheterization; while awaiting emergency surgical treatment; or if surgery has to be delayed or is technically impossible because of unfavorable anatomy (e.g. small size of the pulmonary artery or malpositions with widely separated great arteries). The treatment may also be helpful postoperatively if the aortopulmonary shunt is inadequate and pulmonary blood flow is still ductus-dependent.

In conclusion, we are currently evaluating the usefulness of PGs in the management of these conditions. Our present philosophy is to use PGE_1 (or PGE_2) as an emergency treatment in preparation for surgery. The compound is first infused during diagnostic cardiac catheterization, and if the appropriate response is obtained, infusion is continued up to and during surgery. The future availability of long-acting PG analogues with the ductus-dilating activity of PGE compounds, and no adverse side effects, may afford a new medical approach to the management of the newborn with cyanotic heart disease, permitting the physician to defer operation until the infant is older and better able to tolerate surgery.

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