Palliation of Cyanotic Congenital Heart Disease in Infancy with E-Type Prostaglandins


SUMMARY Prostaglandin-E (PGE) infusions have been used in an attempt to increase ductal patency in 11 infants aged one to 99 days with cyanotic heart disease. PGE1 was used in nine infants and PGE2 in two. Five patients had pulmonary atresia, four extreme pulmonary stenosis, one Ebstein's anomaly and one simple transposition of the great arteries. All but the oldest infant showed a satisfactory increase in oxygen saturation (average 36%) attributed to dilatation of the ductus. The failure in one infant may have been due largely to hypoplasia of the left pulmonary artery. The only important side effect was apnea in one infant receiving PGE2. The efficacy of this form of treatment is confirmed in infants dependent on ductal patency for survival. PGE is an important asset in saving the lives of neonates requiring an aortopulmonary shunt operation. The recommended starting dose is 0.1 µg/kg/min of PGE1 given by constant infusion.

MOST DUCTUS-DEPENDENT INFANTS die in the first three months of life, many in the first few weeks. A reasonable prognosis can be offered many of these infants by reconstructive surgery, if necessary using a conduit. Such surgery is possible at any age, but the mortality in the first month is unacceptably high (B.G. Barratt-Boytes, unpublished data). Palliation with a shunt operation also incurs a relatively high mortality in the first three months of life. Of the many factors responsible for this, marked hypoxia during the operation is probably the most important. In vitro1-2 and in vivo3-4 demonstrations that E and A-type prostaglandins dilate the ductus were therefore of considerable interest, and clinical studies5-6 have shown this property to be useful in humans. We now report experience with E-type prostaglandins in 11 infants aged one to 99 days.

Patients and Methods

Clinical details of the 11 patients are shown in table 1. Cases 1 and 2 have been reported previously.6 Nine cases had pulmonary atresia or extreme pulmonary stenosis and were heavily or entirely dependent on ductal patency for survival. Case 8 with Ebstein's anomaly probably received most or all of his pulmonary blood flow from the ductus. Case 9 with simple transposition, who had undergone cardiac catheterization at one day of age, was thought to have little if any ductal flow at the start of the prostaglandin trial. All patients were assessed clinically with electrocardiograms and chest X-rays.

All but case 8 (who was moribund at the time of initial assessment) underwent cardiac catheterization. The prostaglandin infusion was begun during cardiac catheterization in two infants and after catheterization in the remainder. PGE2 was given to cases 7 and 8, and PGE1 to the remainder. An arterial cannula was inserted via the femoral or umbilical artery and an intravenous infusion was commenced. Prostaglandins were dissolved in 5% dextrose and infused at a dose of 0.1-0.75 µg/kg/min with a Harvard constant infusion pump. Respiratory rate, pulse rate and blood pressure were recorded and any side effects were noted. Oxygen saturations and blood gases were measured before and during treatment, saturations being measured with a Kipp & Zonen hemoreflector and blood gases with an ABL1 acid-base laboratory machine.

Results

Changes in oxygen saturation and other measurements are shown in figure 1. In case 5 a preliminary trial of PGE1 had been carried out when the ductus was widely patent and the arterial saturation 70%. No change occurred with this infusion. Twelve hours later the arterial saturation had fallen to 53% and the changes from this point are recorded in the figure. In all other cases the results shown are those of the first infusion. In cases 1, 2, 3 and 7 repeat infusions were given at a later time, the results being comparable to those shown.

In nine infants improvement in the arterial oxygen saturation was evident within 10 minutes. In case 9 with simple transposition, there was no change in arterial saturation at 13 hours but the level had risen by 18 hours. In case 11 with transposition and pulmonary atresia, there was no response after 12 hours infusion.

In the ten patients showing a rise in arterial oxygen saturation the increase varied from 13 to 53%, with an average of 36% (fig. 1A). Because of the position of values on the oxygen dissociation curve, changes in arterial PO2 were less impressive. Changes in arterial PCO2, arterial pH, arterial pressure and pulse rate (fig. 1B-E) were variable. There was no relation between the change in arterial oxygen saturation and ambient oxygen (fig. 1F).

Case 7 who received PGE2 became apneic after 10 minutes of infusion and was ventilated for the remainder of the infusion. Cases 5 and 8 were ventilated before the infusion began and ventilation continued throughout. No patient showed important hypotension, pyrexia or muscle twitching.

Discussion

The rise in arterial oxygen saturation must have been due to dilatation of the ductus in the four infants with pulmonary atresia and was probably due entirely to ductus dilatation in the four infants with extreme pulmonary stenosis and the one example of Ebstein's anomaly. The situation is less clear in case 9, the 25-day-old infant with simple transposition, but it is suspected that ductal flow may have increased here also. The reason for the failure of case 11 to show any

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Footnotes:
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response is uncertain. The tortuous ductus was narrowed where it joined the left pulmonary artery which in turn joined the main pulmonary artery by a long hypoplastic segment. The hypoplasia of the left pulmonary artery would probably prevent any significant increase in ductal blood flow even if the ductus dilated. Whether or not the ductus will respond at this age remains to be determined.

Improved oxygenation permitted a palliative operation in four infants and an atrial baffle repair in one under optimal conditions. The ability to dilate the ductus should reduce the mortality of palliative surgery even in young infants to a very low level. A further advantage is demonstrated in case 4. After cineangiographic studies it was thought that a pulmonary valvotomy might provide adequate palliation. This judgment proved incorrect, however, as arterial oxygen saturation fell to 20% after valvotomy and withdrawal of PGE infusion. Satisfactory oxygenation was restored with a further infusion and a Waterston shunt was carried out on the following day as an elective procedure.

Palliative surgery was not undertaken in two patients (1 and 5) for whom the long-term prognosis appeared hopeless. In a third infant permission for operation was denied by the parents and it was not thought justifiable to invoke the legal procedures required to override their wishes. Although we accept that this is a controversial area, it is not the policy of this clinic to undertake palliative surgery unless a reasonable long-term prognosis appears possible. PGE infusions were used as long as required to complete investigations, discuss the problem with parents and decide on management. Even in this situation the infusions were useful as they allowed us to maintain the infant in satisfactory clinical condition while an unhurried decision was made.

In two other infants (6 and 8) the technique was useful even though it did not lead to surgical palliation. Brain damage resulting from prolonged hypoxia was suspected prior to treatment but this assessment is extremely difficult in a markedly hypoxic infant. When satisfactory oxygenation had been maintained for 48 hours in one case and 15 hours in the other, it was clear that extensive brain damage had occurred and no further steps were taken.
In cases 1, 2, 3 and 7 serial infusions were carried out over a period of 70, 80, 27 and 39 hours, and a satisfactory response was obtained with each infusion. It appears that PGE infusion remains effective at least over a period of several days.

Cases 8 and 9 are of particular interest. The mortality in the neonatal period of patients with Ebstein's anomaly is high. Although some patients are probably untreatable, a number may be capable of survival if they can be kept alive until the pulmonary vascular resistance falls, enabling the
right heart to maintain an adequate pulmonary blood flow. The trial of PGE infusion in case 8 was carried out with this in mind and the response was encouraging. The apparent response of case 9 with simple transposition was also encouraging. In those infants showing an unsatisfactory response to balloon septostomy, PGE infusion may well be useful either to tide them through the initial difficult period or to maintain their clinical status until a palliative or corrective operation is undertaken. In most cases improved oxygenation should result from dilatation of the ductus. Where pulmonary vascular resistance is high, the pulmonary vasodilating effect of PGEs\textsuperscript{10, 11} could also be beneficial as a relatively high pulmonary flow is necessary for optimal intracardiac mixing in transposition.\textsuperscript{12, 13}

Although the response of the ductus to PGE1 and PGE2 appears similar, apneic spells appear more common with PGE2.\textsuperscript{7} Although apnea may result from loss of the hypoxic drive to ventilation, a direct effect is also possible. PGE1 is therefore preferred but even with this agent facilities for ventilation should be available. The drug should be introduced cautiously, the usual starting dose being 0.1 \(\mu\)g/kg/min by constant infusion. Animal experiments have shown that hypotension is most marked at the onset of infusion\textsuperscript{4} and a subsequent increase in dosage is well tolerated. It appears, however, that a dosage greater than 1 \(\mu\)g/kg/min will rarely be necessary.

Addendum

Since submitting this manuscript we have given PGE1 to an infant with simple transposition in whom we suspected that the therapeutic effect arose from lowering of pulmonary vascular resistance. At 24 hours of age this infant, who had no signs of important lung disease, had an arterial oxygen saturation of 38% in ambient oxygen of 70%. At cineangiography the ductus had a minimum diameter of 2.8 mm and bidirectional shunting through the ductus showed that pulmonary vascular resistance was high. Despite satisfactory balloon atrial septostomy, the arterial oxygen saturation fell to 26% 18 hours later. With an intravenous infusion of 0.1 \(\mu\)g/kg/min of PGE1, the oxygen saturation rose to 43% in 70 minutes and 63% in 240 minutes.

The infant had septicemia, treated simultaneously with antibiotics. The age and clinical status of the infant made it unlikely that changes in ductal caliber were responsible for the changes in oxygen saturation and the slow response to PGE1 was compatible with an effect on pulmonary vascular resistance. Probably unwisely the PGE1 infusion was stopped after 24 hours' treatment and following two hours on a lower dose (saturation 51%). Three hours later the saturation had fallen to 28%. Although treatment was recommenced the baby died and the ductus was widely patent at autopsy.

Acknowledgment

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