Prostaglandin E₁ in Infants with Ductus Arteriosus–dependent Congenital Heart Disease

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SUMMARY  Between January 1976 and June 1979, 492 infants with ductus arteriosus–dependent congenital heart disease (385 cyanotic and 107 acyanotic) received prostaglandin E₁ (PGE₁) in 56 centers in the United States as part of a protocol sponsored by the Upjohn Company. In the infants with cyanotic congenital heart disease, the mean Pao₂ for the group increased from 26.7 mm Hg before to 38.5 mm Hg during infusion (p < 0.001). Infants older than age 4 days had a higher preinfusion Pao₂ and a smaller increase in Pao₂. Infants weighing more than 4 kg at birth and alkalotic infants (pH > 7.45) had a smaller increase in Pao₂. No differences in response were found with respect to mode of administration (intra-arterial or i.v.), gender, maternal age, or preinfusion PaCO₂. PGE₁ provides excellent palliation for infants with ductus arteriosus–dependent cyanotic congenital heart disease.

Of the 107 infants with acyanotic congenital heart disease, 46 had juxtaductal coarctation and 34 had interruption of the aortic arch. Clinical improvement occurred in about 80% in each group. In the infants with aortic interruption, descending aortic blood pressures increased and the pressure differences across the ductus arteriosus decreased markedly. In the infants with coarctation, descending aortic blood pressures increased and ascending aortic pressure decreased. The systolic pressure difference across the coarctation decreased markedly, from 45 to 9 mm Hg. Infants in whom the ductus arteriosus was closed before the infusion showed no beneficial effects. In infants in whom a constricted ductus arteriosus relaxed, the effect occurred more slowly than in infants with cyanotic heart disease. PGE₁ also provides excellent palliation in infants with aortic obstruction in which lower body perfusion is dependent on the ductus arteriosus.

IN 1973, Cocenia and Olley¹ showed that prostaglandins E₁ (PGE₁) and E₂ markedly relaxed the isolated ductus arteriosus of fetal lambs. This in vitro effect was confirmed in the fetal calf² and also was shown in vivo by Sharpe and Larsson³ in fetal rabbits. These observations led to several clinical trials in which PGE₁ was used to reduce arterial hypoxemia by maintaining patency of the ductus arteriosus after birth in infants with cyanotic congenital heart disease.⁴-⁵

Although Cocenia and Olley¹ suggested that PGE₁ would not dilate the ductus arteriosus in the presence of a Po₂ higher than that normally found in the fetus, Clyman et al.⁶ found equal efficacy at low and high Po₂. Therefore, PGE₁ infusion was considered suitable not only in infants with cyanotic congenital heart disease, but also in those with reduced systemic blood flow in whom Pao₂ might be normal.⁷

In 1976, the Upjohn Company started a collaborative study to evaluate the efficacy and complications of the use of PGE₁ to maintain patency of the ductus arteriosus in infants with ductus arteriosus–dependent congenital heart disease. Between January 1, 1976 and June 1, 1979, 492 infants in 56 centers (Appendix) in the United States received PGE₁ under this protocol. Because PGE₁ has been submitted for approval as a new drug, it seemed appropriate to review the data on efficacy and determinants of response as well as complications. In this report, we present the data on 385 infants with diminished effective pulmonary flow due to cyanotic congenital heart disease and 107 infants with reduced systemic flow associated with aortic arch anomalies, all of whom received PGE₁.

Patients and Methods

Cyanotic Congenital Heart Disease

Data on preinfusion Pao₂ were available in 372 of the 385 infants with cyanotic congenital heart disease. In 333 of these 372 infants, Pao₂ was recorded after PGE₁ was infused, so it was possible to compute the difference between pre- and postinfusion Pao₂ in these 333 infants only. One hundred twenty-five infants had pulmonary atresia (PA) and a ventricular septal defect (VSD) and 106 had PA and an intact ventricular septum, usually with hypoplasia of the right ventricle. Forty-seven infants had pulmonary stenosis; 25 had a VSD and 22 had an intact interventricular septum. Twenty-three infants had tricuspid atresia, 21 had transposition of the great arteries and 11 had miscellaneous lesions. At the onset of infusion, the infants were 5 hours to 3 months old (median 36 hours). Eighty-six percent were younger than 4 days of age.

PGE₁ was infused either through an intra-arterial (62%) or an i.v. (38%) catheter, usually placed at cardiac catheterization. One hundred ninety-six infants (59%) received PGE₁ at a dose of 0.1 μg/kg/min throughout the entire infusion. In 89 infants (27%), this dose was gradually decreased to as low as 0.002 μg/kg/min. In 11 infants (3%), the dose was gradually

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989
increased to as high as 0.5 μg/kg/min, whereas in 37 infants (11%), varying higher and lower doses were used.

The size of the ductus arteriosus was not measured consistently. Efficacy of PGE₁ in dilating the ductus arteriosus and in improving pulmonary or effective pulmonary blood flow was evaluated by changes in the Pao₂. The Pao₂ was usually measured immediately before and several times after the start of the infusion. When more than one value was obtained after the onset of the infusion, the value closest to 1 hour after the start of the infusion was used for this analysis.

After the infusions, data were collected on standardized forms and sent to the Cardiovascular Research Division of the Upjohn Company. Not all data were available on all patients. Data were collated, transferred to data cards and stored in an IBM 370/158 computer. At the end of the study, the data were analyzed by Statistical Analysis System 76 (SAS Institute, Inc.). Significance testing was by regression analysis or the t test, with a two-sided p value.

Acyanotic Congenital Heart Disease

One hundred seven infants had acyanotic congenital heart disease and restricted systemic blood flow. Forty-six had juxtaaortic coarctation of the aorta, 34 had an interrupted aortic arch, 19 had hypoplastic left-heart syndrome, and eight had miscellaneous lesions. At the onset of infusion, the infants were 1 day to 5 months old (median 5 days). Seventy percent were younger than 10 days of age.

PGE₁ was infused as described above. The efficacy of PGE₁ in dilating the ductus arteriosus and in improving systemic blood flow was evaluated as follows. Data were collected on the standardized forms, collated and analyzed as described above. However, certain data required to assess dilatation of the ductus arteriosus and improvement in descending aortic blood flow were not requested on the original forms. Therefore, questionnaires were sent to each investigator to obtain more data on infants with coarctation or interruption of the aorta.

The overall clinical effect of PGE₁ was graded as very useful, useful, no effect or harmful. Femoral arterial pulses were graded from 0 (absent) to 4+ (normal) and lower body perfusion from 1+ (poor) to 4+ (normal) before and during the infusion (after 30 minutes and maximal change). Urine flow was graded from 0 (none) to 4+ (normal). Arterial blood pH was usually measured immediately before and several times after the onset of the infusion; the value closest to 1 hour after the start of the infusion was used to evaluate improvement in perfusion as reflected by reduced acidemia. Reduction or discontinuation of base administration was assessed, also as an index of reduced acidemia and improved perfusion. Aside from changes in arterial blood pH, these are all subjective changes; the most accurate reflection of ductus arteriosus dilatation would be a measurement of the change in a resistance either across the ductus arteriosus in an infant with an interrupted aortic arch or across the coarctation. Because flow is extremely difficult to measure, changes in pressures were used to estimate changes in resistance. In infants with interruption of the aortic arch, the main pulmonary arterial and descending aortic pressures were assessed; in infants with coarctation, the ascending and descending aortic pressures were evaluated. In some infants, only descending aortic pressures were recorded; these gave some indication of changes in lower body perfusion.

Not all data were available on all patients. In view of the limited information available, the small numbers of infants in each group, and the large variability of the methods used for evaluating a response, statistical analysis was not attempted. Data are presented as mean and range.

Results

Cyanotic Congenital Heart Disease

The mean Pao₂ for the entire group increased from 26.7 mm Hg before infusion to 38.5 mm Hg during infusion (p < 0.001). There were no significant differences in the preinfusion Pao₂, Pao during infusion, or increase in Pao₂ (ΔPao₂) between infants with pulmonary atresia, pulmonary stenosis or tricuspid atresia; therefore, the data from these infants were pooled. The 21 infants with transposition had a lower preinfusion Pao₂ (22.9 vs 27.5 mm Hg, p < 0.025) and a lower Pao during infusion (31.8 vs 38.9 mm Hg, p < 0.01), although the overall increase in Pao₂ was similar to that in the other infants (9.0 vs 11.9 mm Hg, p = 0.25) (fig. 1). The transposition group was small

**Figure 1. Arterial blood Pao₂ before and during PGE₁ infusion in 333 infants with cyanotic congenital heart disease. No differences were found between infants with pulmonary stenosis (PS) and pulmonary atresia (PA), with or without a ventricular septal defect (VSD), tricuspid atresia (TA) or miscellaneous lesions (MICL) before or during PGE₁ infusion. Compared with these groups, infants with transposition of the great arteries (TGA) had a lower Pao before (p < 0.025) and during the infusion (p < 0.01), although the change in Pao was similar. Bar indicates mean ± SEM.**
(21 infants) and their Pao₂ values before and during PGE₁ infusion differed from those in the other infants. Therefore, the infants with transposition, as well as the 11 infants with miscellaneous lesions, were not analyzed further, leaving 301 infants in whom detailed analyses were performed.

The responsiveness of the ductus arteriosus to PGE₁ in the 301 infants with pulmonary atresia, pulmonary stenosis or tricuspid atresia was related to age. Compared with the 258 younger infants, the 43 infants greater than 96 hours old at the beginning of the infusion had a higher preinfusion Pao₂ (29.2 vs 26.5 mm Hg, p < 0.05), a lower Pao₂ during infusion (32.9 vs 39.2 mm Hg, p < 0.005), and a much smaller change in Pao₂ (3.8 vs 13.0 mm Hg, p < 0.001) (fig. 2). The distribution of anatomic defects was similar in the two age groups. In the 258 infants younger than 96 hours old, the improvement in oxygenation was inversely proportional to the initial Pao₂ (fig. 3). Infants with an initial Pao₂ less than 20 mm Hg had the greatest improvement (Δ Pao₂ 19.7 ± 1.7 mm Hg (± SEM); those with an initial Pao₂ greater than 40 mm Hg had virtually no response (Δ Pao₂ 0.5 ± 4.5 mm Hg). The differences in Pao₂ response between these two groups were highly significant (p < 0.001).

If one selects an increase in Pao₂ of 5 mm Hg or greater to define a clinically significant response, 88% of the infants younger than 96 hours old who had an initial Pao₂ less than 20 mm Hg responded. Conversely, only half of those older than 96 hours of age who had a preinfusion Pao₂ greater than 30 mm Hg had virtually no response (Δ Pao₂ 0.5 ± 4.5 mm Hg). The differences in Pao₂ response between these two groups were highly significant (p < 0.001).

There were no differences in preinfusion Pao₂, Pao₂ during infusion, or increase in Pao₂ with regard to route of administration, gender, maternal age, or Paco₂ in the 241 infants less than 96 hours old who had an initial Pao₂ less than 40 mm Hg. Birth weights were available for 237 of these infants, and those weighing more than 4 kg at the time of birth had a smaller increase in Pao₂ than those weighing less than 4 kg (5.9 vs 12.4 mm Hg, p < 0.02) (fig. 4). Infants who were alkalotic (pH > 7.45) at the time of infusion also had a lower Pao₂ during PGE₁ infusion (34.9 vs 39.1 mm Hg, p < 0.01) and a lower Δ Pao₂ (6.6 vs 12.3 mm Hg, p < 0.001).

**Acyanotic Congenital Heart Disease**

The mean preinfusion Pao₂ for the whole group was 67 mm Hg (table 3). No difference in clinical or arterial pressure response was apparent between infants with a low Pao₂ and those with a high Pao₂. Arterial blood pH was recorded before and during PGE₁ infusion in 89 infants. Thirty-seven had a preinfusion Pao₂ less than 20 mm Hg, and the remainder had a preinfusion Pao₂ of 20 mm Hg or more. Of the 37 infants who had an initial Pao₂ less than 20 mm Hg, 88% had a clinically significant response (Δ Pao₂ > 5 mm Hg) to the infusion of PGE₁. The arterial blood pH was usually normal before and during the infusion. The arterial blood pH was lower in those infants with the greatest change in Pao₂ (Δ Pao₂ > 10 mm Hg) compared with those with the smallest change in Pao₂ (Δ Pao₂ < 5 mm Hg) (fig. 5).

**TABLE 1. Percentages of Patients with an Increase in Pao₂ of 5 mm Hg or More During Infusion of Prostaglandin E₁**

<table>
<thead>
<tr>
<th>Age (hours)</th>
<th>&lt; 20</th>
<th>20-29</th>
<th>30-39</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤96</td>
<td>88%</td>
<td>76%</td>
<td>60%</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td>(n = 60)</td>
<td>(n = 113)</td>
<td>(n = 68)</td>
<td>(n = 17)</td>
</tr>
<tr>
<td>&gt;96</td>
<td>71%</td>
<td>57%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>(n = 7)</td>
<td>(n = 14)</td>
<td>(n = 18)</td>
<td>(n = 4)</td>
</tr>
</tbody>
</table>

Total number of patients is given in parentheses.
TABLE 2. Percentages of Patients with an Increase in Pao2 of 10 mm Hg or More During Infusion of Prostaglandin E1

<table>
<thead>
<tr>
<th>Age (hours)</th>
<th>Preinfusion Pao2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 20</td>
</tr>
<tr>
<td>≤ 96</td>
<td>77%</td>
</tr>
<tr>
<td>(n = 60)</td>
<td></td>
</tr>
<tr>
<td>&gt; 96</td>
<td>71%</td>
</tr>
<tr>
<td>(n = 7)</td>
<td></td>
</tr>
</tbody>
</table>

Total number of patients is given in parentheses.

fusion pH below 7.25, and among these, pH increased in 25 (68%), was unchanged in eight (22%), and decreased in four (11%). Because more detailed information was obtained only in the infants with aortic interruption or coarctation, the others were not analyzed further.

Interruption of the Aorta

Information was available on 25 of the 34 infants in this group. Not all data were available on each infant. In 10 infants, the infusion was considered very useful, in nine useful, and in six there was no effect; the infusion was not considered harmful in any infant. In two infants (ages 5 months and 2 weeks) in whom there was no apparent effect, the ductus arteriosus was considered closed at cardiac catheterization before the start of the infusion. These infants were excluded from further evaluation of the effects of PGE1 on the ductus arteriosus. In 19 of 23 infants, lower body perfusion and femoral arterial pulse volume improved during the infusion. In 11 of 15 infants, urine flow increased. In 11 of 17 infants receiving base to correct metabolic acidemia, the amount given could be reduced or stopped completely.

Adequate pressure measurements were reported in only 15 infants. During the PGE1 infusion main pulmonary arterial, systolic, diastolic and mean blood pressures (table 4) were slightly lower than before the infusion was started. Systolic, diastolic and mean blood pressures in the descending aorta increased in each infant, and the systolic, diastolic and mean pressure difference between the main pulmonary artery and the descending aorta decreased consistently.

Juxtaductal Coarctation of the Aorta

Detailed information was available on 30 of the 46 infants who had juxtaductal coarctation of the aorta. Not all data were available on each infant. In 16 infants, the infusion was considered very useful, in eight useful, and in six there was no effect; the infusion was not considered harmful in any infant. In four of the six infants in whom PGE1 had no effect (ages 3, 16, 24 and 28 days), the ductus arteriosus was considered closed at cardiac catheterization before the start of the infusion and they, therefore, were not considered further in the evaluation of the effect of PGE1 on the ductus arteriosus. Lower body perfusion in 19 of 21 infants and femoral arterial pulse volume in 18 of 21 infants improved during the infusion. In 17 of 20 infants, urine flow increased. In 11 of 13 infants receiving base to correct metabolic acidemia, the amount given could be reduced or stopped completely.

Adequate descending aortic blood pressure measurements were reported in 19 infants, but ascending aortic blood pressures were reported only in 11 of the infants (table 4). During the PGE1 infusion, ascending aortic systolic, diastolic and mean arterial blood pressures were slightly lower than before the infusion was started. Systolic, diastolic and mean blood pressures in the descending aorta increased markedly and the systolic pressure difference between the ascending and descending aorta decreased markedly.

Discussion

We have confirmed reports* that PGE1 is usually very effective in improving oxygenation in infants with cyanotic congenital heart disease and a closing ductus arteriosus. In these infants, the primary determinants of responsiveness were the postnatal age at the start of infusion and the preinfusion Pao2.

In infants with pulmonary atresia, pulmonary sten-
osis or tricuspid atresia, the increase in arterial oxygen content is probably due to increased pulmonary blood flow through the ductus arteriosus. In infants with transposition, dilatation of the ductus arteriosus probably increases the obligatory shunt from the high-pressure aorta to the lower pressure pulmonary artery, which must be balanced by an equivalent shunt from the left to the right atrium. This improved mixing between the systemic and pulmonary circuits increases the effective pulmonary flow and arterial saturation.11, 12

It is now thought that circulating or locally produced prostaglandins keep the ductus arteriosus patent during fetal life. What causes postnatal closure, however, is not completely understood.13 Closure of the normal ductus arteriosus is thought to occur in two steps: a functional closure due to constriction of the medial muscle layer that usually occurs within a few hours to days after birth, and an anatomic closure that involves infolding of the endothelium and disruption of the subintimal layers that is usually completed by the second week of life.

The decreased response of the ductus arteriosus to PGE1 infusion after 96 hours of age suggests either that anatomic closure is nearly complete by this time or that there is irreversible functional closure due to a lack of responsiveness of prostaglandin receptors by this age. Further research in this area is needed.

We also have shown that improvement in oxygenation is a function of preinfusion Pao2. Infants with the lowest preinfusion Pao2 had the greatest increase during PGE1 infusion, whereas those with a relatively high initial Pao2 failed to respond at all. This is consistent with the hypothesis that PGE1 can dilate the ductus arteriosus to a certain size, but no more. If the preinfusion Pao2 is low, the ductus arteriosus is probably very constricted,14 and PGE1 will dilate the ductus to a maximal size, thereby increasing pulmonary flow and Pao2 significantly. If, however, the Pao2 is high initially, the ductus arteriosus is probably maximally patent. PGE1 will not produce further dilatation and little improvement in oxygenation can be expected. Another possibility is that these infants had an additional source of pulmonary blood flow, such as other collaterals or forward flow through a severely stenotic pulmonary valve.

PGE1 has been shown to dilate the pulmonary vascular bed.15 Infants who have low Pao2 values initially are likely to have some pulmonary vasocstriction,16 and the PGE1 infusion may improve pulmonary blood flow by reducing pulmonary vascular resistance as well.

Most of the other variables analyzed were not useful for predicting responsiveness of the ductus arteriosus to PGE1. However, the lack of response to PGE1 in infants who weighed more than 4 kg at birth was highly significant. We cannot explain this phenomenon. Possibly some of these infants had diabetic mothers; such infants are large for gestational age and may develop hypoglycemia. Involutional changes in the wall of the ductus arteriosus may occur earlier in this subgroup or, alternately, hypoglycemia or some other biochemical or hormonal phenomenon may interfere with dilatation of the ductus arteriosus or the pulmonary vasculature induced by PGE1.

Because oxygenation improved dramatically in infants who were younger than 4 days old and had an initial Pao2 less than 30 mm Hg, we believe that PGE1 infusion is indicated for this group. We recommend starting with 0.05 μg/kg/min, preferably intravenously, for the route of administration does not appear to affect the response and complications are fewer with this route. The dose can be halved once stable improvement is achieved. An adequate response generally can be maintained at the lower dose.

In infants older than 4 days of age and those with a Pao2 greater than 30 mm Hg, PGE1 should be used more cautiously. Although some infants respond with an increase in Pao2, many show no effect. In these patients, PGE1 should be infused only when the risk-benefit ratio is favorable.

We also confirmed findings10, 17 that PGE1 usually improves descending aortic blood pressure and blood flow in infants with interruption of the aortic arch or juxtaductal coarctation and a closing ductus arteriosus. When the ductus arteriosus was considered closed during cardiac catheterization before the start of the infusion, reopening could not be accomplished in either group, regardless of age (3 days to 5 months). Improvement occurred in the majority of infants in whom the ductus arteriosus was partially constricted at angiography. Clinically, this improvement was
reflected by increased perfusion of the lower limbs, increased urine production and reduced metabolic acidemia. Preinfusion arterial blood PO₂, PCO₂ and pH did not influence the response. In infants with a cyanotic congenital heart disease, an increased Pao₂ response was not critical for a positive response (median age 5 days); one infant responded positively at 36 days of age. Another difference between infants with cyanotic and those with acyanotic congenital heart disease was the rapidity of the effect. In cyanotic infants, a maximal Pao₂ response generally was seen within 30 minutes. In the infants with interruption of the aortic arch, the maximal response occurred 1.5 hours (range 15 minutes to 4 hours) after the start of the infusion; in the infants with coarctation, the maximal response occurred 3 hours (range 15 minutes to 11 hours) after the start of the infusion. Thus, the infusion should be continued somewhat longer in cyanotic infants than in acyanotic infants before deciding that PGE₁ will not be effective.

In the infants with interruption of the aortic arch, the pressure differences between the main pulmonary artery and the descending aorta, particularly the systolic pressure difference, were reduced markedly, which directly indicates relaxation of the ductus arteriosus. In infants with juxtaductal coarctation of the aorta, closure of the ductus arteriosus has been considered an important factor in precipitating hemodynamic obstruction of the aorta. Reduction of the pressure differences between the ascending and descending aorta, therefore, also indicated relaxation of the ductus arteriosus, at least at its aortic end, in these infants.

PGE₁ is a major addition to medical management of these infants before, during and even after palliative or corrective surgery in infants with ductus arteriosus-dependent cyanotic congenital heart disease. PGE₁ infusion also is an effective method to improve systemic (lower body) perfusion in infants with interruption of the aortic arch or coarctation. Although many of these infants are older than 5 days of age, PGE₁ appears to be effective and therefore should be used, regardless of age, to dilate the ductus arteriosus and improve perfusion.

Acknowledgment

We gratefully acknowledge the effort and cooperation of the investigators listed in the Appendix, their co-investigators, and the fellows, house officers, nurses and technicians involved in the care of these infants. We also express our appreciation to Dr. David Huang for his assistance in the statistical analyses and to Susan Axelrod, Zilla Brye, Ann Marie Carpenito, and Terry McCarthy for their help in the preparation of the manuscript.

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Appendix

Data for this analysis were submitted by the following investigators:

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