Side Effects of Therapy with Prostaglandin E₁ in Infants with Critical Congenital Heart Disease

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SUMMARY The case reports of 492 infants with critical congenital cardiac disease treated with prostaglandin E₁ (PGE₁) were reviewed to determine the nature and incidence of intercurrent medical events. Forty-three percent of the infants had at least one such event, but only half of these were related to PGE₁ and the majority required only minor changes in management. Cardiovascular events were the most common (18% incidence), with cutaneous vasodilatation and edema occurring more frequently during intraaortic infusion than during i.v. infusion. Central nervous system events were reported in 16% of the patients. Respiratory depression was reported in 12%, and was particularly common in infants weighing less than 2.0 kg at birth (42%). Hematologic, infectious and renal events appeared for the most part to be unrelated to PGE₁. The overall mortality (excluding 19 patients with hypoplastic left-heart syndrome) was 31%; the mortality for the patients with critical coarctation or interruption of the aortic arch was nearly twice that for the cyanotic infants (50% vs 27%). No death was attributed to PGE₁ administration.

During infusion of PGE₁, arterial blood pressure and respiratory activity should be monitored carefully and appropriate supportive steps taken if hypotension or respiratory depression occurs. The development of fever or jitteriness may require reduction of the infusion rate and, in view of the possible increased incidence of infections, the prophylactic use of antibiotics is recommended.

AFTER Coceani and Olley showed that PGE₁ and PGE₂ were potent dilators of the fetal ductus arteriosus, numerous independent reports of their efficacy in treating infants with ductus arteriosus-dependent cyanotic and acyanotic congenital cardiac defects appeared in the literature. However, data on the side effects of PGE₁ have been difficult to gather because so few patients were treated by each group. Therefore, we have examined the experiences of all 56 investigators in the United States who administered PGE₁ under the investigational new drug protocol of the Upjohn Company between January 1976 and June 1979.

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Patients and Methods

The case reports of 492 infants treated with PGE₁ were reviewed and all intercurrent medical events (IMEs) were recorded. An IME was defined as any unanticipated or undesirable incident that occurred during the course of treatment and might have necessitated an alteration in therapy. Several categories listed as IMEs in the original reports were deleted because they were either expected responses to the underlying cardiac anomaly, other congenital anomalies, or were undocumented. These included "cyanosis" in patients with pulmonary atresia or tetralogy of Fallot, "congestive heart failure" (CHF) in infants with left ventricular (LV) outflow obstruction, "possible sepsis" without any confirmatory clinical or laboratory evidence, and associated congenital anomalies, e.g., "hypoplastic lungs."

Each IME was counted separately to determine the total number of reactions. Patients who had more than one IME were counted only once, thereby permitting the incidence of IMEs to be calculated.

The data were analyzed using the chi-square test and the probability was obtained from a cumulative
distribution of chi-square tables. A value of \( p < 0.05 \) was considered statistically significant.

**Results**

Of the 492 infants, 385 were classified as having cyanotic and 107 as having acyanotic congenital heart disease. There were 298 males (61%) and 194 females (39%). The mean gestational age was 39.2 ± 2.1 weeks (± SD) and the mean birth weight was 3.1 ± 0.7 kg. Infusion of \( \text{PGE}_1 \) was begun within 48 hours of birth in 59% of the infants and within 96 hours of birth in 78%.

Two hundred thirteen patients (43%) were reported as having had at least one IME (table 1). Eighty infants (16%) had two or more IMEs. There was no difference in the overall incidence of IMEs between the cyanotic and acyanotic groups (fig. 1).

The IMEs were organized into eight categories: cardiovascular events (cutaneous vasodilation or edema, rhythm or conduction disturbances, and hypotension), central nervous system (CNS) events (seizure-like activity, temperature elevation, irritability or lethargy), respiratory depression (apnea or hypventilation), metabolic abnormalities (hypoglycemia or hypocalcemia), infections (sepsis, wound infections), gastrointestinal disturbances (diarrhea, necrotizing enterocolitis, hyperbilirubinemia), hematologic abnormalities (hemorrhage, disseminated intravascular coagulation and thrombocytopenia), and renal failure or insufficiency.

Cardiovascular IMEs were most frequently reported and had an overall incidence of 18% (table 2). Infants with critical cyanotic lesions were more likely to have a cardiovascular reaction than were acyanotic patients \( (p < 0.05) \) This difference may be the result of the more common use of intraaortic (IA) infusion of \( \text{PGE}_1 \) in cyanotic infants and the significantly greater incidence of cutaneous vasodilatation \( (p < 0.005) \) with this route of administration (table 3). There were no other significant differences in the incidence of IMEs between i.v. and IA administration. Cardiovascular IMEs were also more likely to occur in patients who weighed less than 2.0 kg (fig. 2) or when the duration of \( \text{PGE}_1 \) infusion exceeded 48 hours (table 4). The incidence of cardiovascular events was not affected by the age of onset of \( \text{PGE}_1 \) therapy, the dose regimen or preinfusion pH. When preinfusion \( \text{Pao}_2 \) was greater than 40 mm Hg, the incidence of cardiovascular events was lower (10%), which reflects less use of IA \( \text{PGE}_1 \) in acyanotic patients with coarctation or interrupted aortic arch.

The incidence of CNS events was 16%, and did not appear to be influenced by patient type, route of administration, birth weight or preinfusion arterial \( \text{Po}_2 \). CNS events were observed more often, however, in patients in whom the preinfusion pH was 7.15 or less \( (p < 0.05) \) (table 5) and when the duration of infusion (table 4) exceeded 48 hours \( (p < 0.025) \).

Respiratory depression was reported in 12% of the infants. It was significantly more common among cyanotic infants \( (p < 0.01) \) and among infants weighing less than 2.0 kg at birth \( (p < 0.005) \). In contrast, respiratory depression was less commonly reported in infants in whom the preinfusion pH was less than 7.15 \( (p < 0.05) \). More infants in this group probably had mechanically assisted ventilation before \( \text{PGE}_1 \) administration, thereby masking further respiratory depression, but this information is not available. The incidence of respiratory depression was not related to the route of \( \text{PGE}_1 \) administration, the duration of infusion, or the preinfusion \( \text{Po}_2 \).

The other five categories of IMEs each had an incidence of approximately 2% (table 2).
Metabolic abnormalities, i.e., hypoglycemia or hypocalcemia, were not associated with patient type, route of administration, birth weight, duration of infusion or preinfusion blood gases.

Infections were more common in babies who weighed less than 2.0 kg at birth ($p < 0.025$) (fig. 2). However, no associations between infections and the other variables analyzed were detected. Most infants received antibiotics before or soon after the PGE$_1$ infusions were commenced.

Diarrhea was the most common gastrointestinal disturbance. Necrotizing enterocolitis and hyperbilirubinemia were reported as isolated occurrences.

Hematologic IMEs appeared to be slightly more common among acyanotic infants (table 2), but the difference was not statistically significant ($0.05 < p < 0.1$). Disseminated intravascular coagulation, however, was observed in four of 107 acyanotic patients (3.7%) but in only two of 385 cyanotic infants (0.5%) ($p < 0.01$). Associations with other variables were not evident.

Renal insufficiency or failure occurred in a slightly higher percentage of patients with acyanotic lesions (4% vs 1%), but the difference was not statistically significant. This difference undoubtedly reflects the poor systemic perfusion and compromised renal blood flow in infants with severe coartation or interruption of the aortic arch.

The incidence of IMEs was not influenced by the age at onset of infusion or the dose regimen. In the opinion of the individual principal investigators, 49% of all IMEs were either "related" or "probably related" to PGE$_1$, 37% were "probably not related," and 14% were unknown or unrecorded. Respiratory depression was thought to be related to PGE$_1$ administration in 68% of the occurrences. Cardiovascular IMEs were thought to be related to PGE$_1$ therapy in 54% of the occurrences. Hematologic and renal IMEs generally were not considered to be related to infusion of PGE$_1$.

The infusion rate of PGE$_1$ was decreased (to $< 0.1 \mu g/kg/min$) because of the development of an IME in 24 patients (5%) and discontinued in 44 (9%). Of the 90 reported cardiovascular IMEs, 14 (16%) pre-
FIGURE 2. Comparison of the incidence of intercurrent medical events (IMEs) by birth weight. Infants weighing less than 2.0 kg were more likely to develop respiratory depression or cardiovascular IMEs than were infants weighing more than 2.0 kg at birth. CV = cardiovascular; CNS = central nervous system disorders; Resp = respiratory depression; Metab = metabolic abnormalities; Inf = infection; GI = gastrointestinal disturbances; Heme = hematologic abnormalities; Renal = renal failure or insufficiency.

Interpreted a subsequent decrease in dosage. Respiratory depression, however, was the most common reason for discontinuing the infusion. PGE₁ was stopped in 22 of 58 instances of respiratory depression (38%); it was restarted in seven instances without any reported recurrence.

Minor changes were noted in the mean hemoglobin concentration, hematocrit, and neutrophil and lymphocyte counts between the preinfusion baseline values and measurements during or after PGE₁ administration. No other hematologic or biochemical differences were evident.

There were no reports of morphologic abnormalities of the ductus arteriosus during intraoperative or postmortem examination. Further, no pathologic or histologic changes attributable to PGE₁ administration were reported by any of the investigators, although it is uncertain how carefully such changes were sought.

**Mortality**

The reported in-hospital mortality for the 492 patients was 34% (table 6). Excluding 19 patients with hypoplastic left-heart syndrome and four patients considered inoperable, the net mortality was 31%. One hundred five cyanotic infants (27%) died, whereas 44 of 88 acyanotic infants (50%) (excluding those with hypoplastic left-heart syndrome) died. No death was attributed to PGE₁ administration.

**Discussion**

Despite the numerous reports of the successful administration of the E-type prostaglandins to infants with ductus-dependent critical congenital cardiac defects that restrict pulmonary or systemic blood flow,⁴⁻¹⁰ data on the various side effects are incomplete. Several investigators have observed occasional episodes of peripheral vasodilation,³⁻⁷ seizure-like activity,¹¹ apnea,⁸ and temperature elevation¹² associated with PGE₁ infusion, but the incidence of such reactions has not been reported because of the small number of patients treated at each institution. We reviewed the data from 492 infants treated with PGE₁ at 56 centers throughout the United States over a 3-year period to determine the incidence of side effects in a large number of patients.

Forty-three percent of the infants were reported to have had at least one IME. Only 49% of these reactions, however, were believed to be either "related" or "probably related" to PGE₁ administration, and most of these were minor. Several types of IMEs clearly appear to be related to PGE₁, e.g., respiratory depression or apnea, cutaneous vasodilation, and temperature elevation. In contrast, the hematologic and renal IMEs reported are probably unrelated to PGE₁ infusion. Potential infectious complications almost certainly would have been masked because the majority of infants received prophylactic antibiotic therapy. The critical condition of many of these infants may predispose to the development of cardiovascular instability (e.g., hypotension, bradycardia), metabolic abnormalities, seizure-like activity, and renal insufficiency.

Cutaneous vasodilation was the only IME related to the route of administration. PGE₁ is a potent vasodilator, particularly when infused into a regional arterial circulation, such as the left carotid or left subclavian artery. Although rapidly reversed by repositioning the IA catheter or changing to i.v. administration, the vasodilation may be associated with local edema requiring up to 24-36 hours to resolve. Because IA administration of PGE₁ does not appear to have any therapeutic advantage over the IV route,¹³ i.v. infusion appears to be the preferred mode of therapy.

Respiratory depression or apnea appeared to be the most worrisome IME, and resulted in discontinuation of therapy in 38% of the reported occurrences. It was most often observed in babies weighing less than 2.0 kg at birth (42% incidence). The etiology of

**TABLE 4. Incidence of Intercurrent Medical Events in Cyanotic and Acyanotic Patients Treated with PGE₁ for more than 48 Hours**

<table>
<thead>
<tr>
<th>Event</th>
<th>Cyanotic (n = 56 pts)</th>
<th>Acyanotic (n = 6 pts)</th>
<th>Total (n = 62 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>18 (32%)</td>
<td>2 (33%)</td>
<td>20 (32%)</td>
</tr>
<tr>
<td>CNS</td>
<td>15 (27%)</td>
<td>4 (67%)</td>
<td>19 (31%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>11 (20%)</td>
<td>0 (0)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>2 (4%)</td>
<td>0 (0)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Infectious</td>
<td>0 (0)</td>
<td>1 (17%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>GI</td>
<td>5 (9%)</td>
<td>1 (17%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>0 (0)</td>
<td>1 (17%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1 (2%)</td>
<td>0 (0)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>None</td>
<td>19 (34%)</td>
<td>2 (33%)</td>
<td>21 (34%)</td>
</tr>
</tbody>
</table>

* p < 0.05 vs patients treated for less than 48 hours.

**p < 0.025 vs patients treated for less than 48 hours.

Abbreviations: see table 3.
respiratory depression is probably related to the action of PGE₁ on the CNS. Since respiratory depression secondary to PGE₁ therapy may require assisted ventilation, we recommend that PGE₁ be administered in a setting where assisted ventilation is readily available.

Temperature elevation and seizure-like activity described as "myoclonic jerks" have been attributed by Fariello et al.¹¹ to the CNS effect of the E-type prostaglandins. Minor alterations in the electroencephalogram were observed during PGE₁ infusion in three infants and appeared to reflect a "sedative action" that subsided after treatment was stopped. There was no evidence, however, of epileptiform discharges from the cerebral cortex. They suggested, therefore, that the myoclonic phenomena in patients receiving PGE₁ originated in subcortical, bulbo-spinal structures. PGE₁ was discontinued in nine infants because of seizure-like activity or fever (1.8%), but in four it was resumed without recurrence of any IME.

Sepsis has been reported in several infants treated with PGE₁.¹³ The overall incidence of infection reported by the 56 contributing centers, however, was only 2%. A survey conducted in September 1979 showed that infants at 21% of the participating institutions were routinely given antibiotics by the cardiologist, whereas they were routinely given antibiotics postoperatively by the surgeons at 92% of the hospitals (Reischer S: unpublished data). Only one institution related infection to PGE₁ administration, and they now routinely use antibiotics in all infants receiving PGE₁.

Gittenberger-DeGroot et al.¹⁴ reported histologic changes in the ductus arteriosus wall and Haworth et al.¹⁸ reported changes in the small pulmonary arteries of patients treated with PGE₁. We do not have enough data to confirm these findings. Nevertheless, there were no reports of structural abnormalities of the ductus arteriosus or pulmonary vasculature at surgery or at autopsy. Further, unimpeded closure of the ductus arteriosus has occurred after completion of PGE₁ therapy, even in patients who received long-term infusions.⁸

It is difficult to determine whether treatment with PGE₁ before surgery has reduced the mortality of critical congenital cardiac lesions. The combined reported in-hospital mortality in both the cyanotic and acyanotic groups, excluding 19 patients with hypoplastic left-heart syndrome, was 31%. The mortality for the patients with interruption of the aortic arch was greater than twice that for cyanotic patients and may reflect both the technical difficulties in reconstructing the aortic arch and the high association with other intracardiac defects, e.g., ventricular septal defect or single ventricle. The accumulated mortality reported in the literature for infants with pulmonary atresia and intact ventricular septum treated before the use of PGE₁ (1967-1976) was 68% (140 of 207).¹⁸⁻²¹ The early mortality for the 251 infants with pulmonary atresia treated with PGE₁ was half (34%) that reported previously. This improvement may reflect not only the use of PGE₁, but also recent advances in surgical techniques and the overall medical management of critically ill neonates. Nevertheless, to the extent that PGE₁ has been effective in improving systemic oxygenation and perfusion in these babies, it is

### Table 5. Intercurrent Medical Events vs Preinfusion pH

<table>
<thead>
<tr>
<th>Event</th>
<th>≤ 7.15 (n = 49 pts)</th>
<th>7.16-7.30 (n = 132 pts)</th>
<th>7.31-7.45 (n = 275 pts)</th>
<th>≥ 7.46 (n = 25 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>8 (16%)</td>
<td>14 (11%)</td>
<td>63 (23%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>CNS</td>
<td>14 (29%)*</td>
<td>18 (14%)</td>
<td>43 (16%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>1 (2%)</td>
<td>17 (13%)</td>
<td>34 (12%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>2 (4%)</td>
<td>4 (3%)</td>
<td>6 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Infectious</td>
<td>1 (2%)</td>
<td>3 (2%)</td>
<td>8 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>GI</td>
<td>1 (2%)</td>
<td>5 (4%)</td>
<td>11 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Hematologic</td>
<td>2 (4%)</td>
<td>3 (2%)</td>
<td>4 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2 (4%)</td>
<td>1 (&lt; 1%)</td>
<td>6 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>31 (4%)</td>
<td>65 (4%)</td>
<td>175 (6%)</td>
<td>14 (4%)</td>
</tr>
</tbody>
</table>

*p < 0.05.
Abbreviations: see table 3.

### Table 6. Mortality vs Primary Cardiac Diagnosis

<table>
<thead>
<tr>
<th>Cyanotic</th>
<th>No. of pts</th>
<th>No. of deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary atresia</td>
<td>251</td>
<td>85 (34%)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>59</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>23</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>D-transposition</td>
<td>50</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>385</td>
<td>105 (27%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acyanotic</th>
<th>No. of pts</th>
<th>No. of deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarctation of aorta</td>
<td>50</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>Interrupted aortic arch</td>
<td>32</td>
<td>21 (66%)</td>
</tr>
<tr>
<td>Hypoplastic left heart</td>
<td>19</td>
<td>19 (100%)</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>5</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>107</td>
<td>63 (59%)</td>
</tr>
<tr>
<td>Total patients</td>
<td>492</td>
<td>168 (34%)</td>
</tr>
</tbody>
</table>
likely that the increased survival is in part due to PGE$_1$
therapy.

In conclusion, PGE$_1$ is effective in improving pulmonary or systemic blood flow in neonates with ductus arteriosus-dependent critical congenital cardiac lesions. Although 43% of all infants were reported to have had at least one IME, only half of these events were believed to be related to PGE$_1$ infusion. The majority of the IMEs were relatively minor, initiating a change in PGE$_1$ administration in only 14% of patients. Intra-arterial infusion is associated with a greater incidence of regional peripheral vascular dilatation. Infants who weighed less than 2.0 kg at birth, however, appear to be at significantly higher risk of developing respiratory depression than are larger infants. Therefore, assisted ventilation should be readily available before initiating therapy with PGE$_1$.

References
Side effects of therapy with prostaglandin E1 in infants with critical congenital heart disease.

A B Lewis, M D Freed, M A Heymann, S L Roehl and R C Kensey

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