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# Aerosolized $PGE_1$: A Selective Pulmonary Vasodilator in Neonatal Hypoxemic Respiratory Failure Results of a Phase I/II Open Label Clinical Trial

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## ABSTRACT

Twenty term/near term neonates with hypoxemic respiratory failure and oxygenation index ≥20 were enrolled in a Phase I/II feasibility, safety and dose escalation study of inhaled $PGE_1$ ($IPGE_1$). Incremental doses of $IPGE_1$, delivered by a jet nebulizer over a 2-h period, followed by weaning over 1 h, were given to 13 patients before receiving inhaled nitric oxide (INO) (Group I), and to seven patients, who failed to respond to INO (Group II). Response was defined as an increase in $P_aO_2$ of either ≥ 25 (full) or 10–25 (partial) torr. Exit criteria included an acute deterioration in oxygenation status, a persistent oxygenation index above 35 in Group I, or the availability of extracorporeal membrane oxygenation (ECMO) in Group II. The mean (SD) increase in $P_aO_2$ at the end of $IPGE_1$ administration was 63 (62.3) in Group I ($p = 0.024$), and 40 (62.1) in Group II ($p > 0.05$). In Group I, 8 of 13 neonates had a full response, but 4 deteriorated following discontinuation of $IPGE_1$. Of these four, two responded to INO and two were placed on ECMO. Five patients deteriorated before or during $IPGE_1$, and none of them responded to INO. In Group II, three of seven patients had a full response to $IPGE_1$. One patient with a partial response and all patients exiting before or during $IPGE_1$ administration were placed on ECMO. The results of our study indicate that $IPGE_1$ may be a safe, selective pulmonary vasodilator in neonatal hypoxemic respiratory failure. **(*Pediatr Res* 56: 579–585, 2004)**

**Abbreviations**

**BPD,** bronchopulmonary dysplasia
**ECMO,** extracorporeal membrane oxygenation
**HUS,** head ultrasound
**INO,** inhaled nitric oxide
**IPCKD,** infantile polycystic kidney disease
**$IPGE_1$,** inhaled Prostaglandin $E_1$
**MRI,** magnetic resonance imaging
**OI,** oxygenation index
**$P_aO_2$,** arterial oxygen tension
**PG,** prostaglandin
**$PGE_1$,** prostaglandin $E_1$
**$PGI_2$,** prostaglandin $I_2$
**PPHN,** persistent pulmonary hypertension of the newborn
**PVL,** periventricular leukomalacia

Hypoxemic respiratory failure in the newborn is usually associated with potentially reversible pulmonary hypertension that causes right-to-left shunting and profound hypoxemia. The goal of therapy is to selectively lower the pulmonary vascular resistance (PVR). Intravenously administered vasodilators lack pulmonary selectivity leading to systemic side effects. Inhaled nitric oxide (INO), a selective pulmonary vasodilator, has revolutionized the treatment of hypoxemic respiratory failure. However, there is lack of sustained improvement in 30–46% of infants (1–4); moreover, INO is a highly toxic molecule requiring expensive monitoring and scavenging systems for administration, making the treatment expensive and limiting availability. Aerosolized prostaglandins $I_2$ and $E_1$ have been reported to be effective selective pulmonary vasodilators in animals and human adults (5–19). In addition, inhaled $PGI_2$ ($IPGI_2$) has also been reported to be effective in preterm and term newborns and children with pulmonary hypertension (20–26). Although i.v. $PGE_1$ is widely used in neonates, the use of the inhaled form has not been reported in newborns with

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pulmonary hypertension. The high pulmonary clearance of $PGE_1$ (70 to 90%) contributes to its selectivity as a pulmonary vasodilator when administered as an aerosol (17). Compared with $PGI_2$, $PGE_1$ has a shorter half-life, lower pKa (6.3 *versus* 10.5), bronchodilator action, anti-proliferative and anti-inflammatory effects on the alveolar, and interstitial and vascular spaces of the lung (17,27–31). Prostaglandin nebulization can be used without the sophisticated technical equipment needed for controlled NO inhalation and hence is less expensive. It has no known toxic metabolites or toxic effects. Prostaglandins and nitric oxide relax the vascular smooth muscles through two different second-messenger systems; therefore, in combination, INO and $IPGE_1$ may have synergistic effect (32).

The existing literature suggests that inhaled $PGE_1$ is a potential effective vasodilator in the treatment of pulmonary hypertension of the newborn. We report the results of a phase I-II open-label pilot study of escalating doses of aerosolized $PGE_1$ in term/near-term neonates with hypoxemic respiratory failure. Our objectives were to establish the feasibility and safety of $PGE_1$ administered as an aerosol and to determine the effective dose.

## METHODS

***Subjects.*** The study was conducted at five centers in the metropolitan Detroit area. The IRB at all five hospitals approved the study. All of the patients in this report were recruited at two of the five centers (Children's Hospital of Michigan and Hutzel Women's Hospital). INO was available only during transport to and at Children's Hospital of Michigan. Newborn infants born at $\geq$34 wk gestation requiring assisted ventilation for hypoxemic respiratory failure in the first 2 weeks of life were eligible to participate after an oxygenation index (OI) of $\geq$ 20 on two arterial blood gases at least 15 min apart in the preceding 12 h. Additional requirements were an indwelling arterial catheter and informed parental consent. Although an attempt was made to obtain a head ultrasound and cardiac echocardiogram before enrollment, this was not a requirement for study participation. Neonates with congenital diaphragmatic hernia, congenital heart disease other than ductal or septal shunts, thrombocytopenia, or those in whom a decision to not provide full treatment (including ECMO) were considered ineligible for the study.

Two groups of patients were defined based on disease severity and prior treatment with INO at the time of enrollment. Patients in Group I (Pre-INO Group) were enrolled before they received INO. Group II patients (Post-INO Group) were enrolled after they were found to be refractory to INO. A patient was labeled as being "refractory to INO" if there was no response to INO one hour after initiation or if there was a failure to sustain a response in $P_aO_2$ $\geq$25 mm Hg above baseline at any time without weaning of INO or ventilator. Many of the patients in Group II were eligible and were waiting for the availability of ECMO.

Management of eligible infants was optimized before treatment with aerosolized $PGE_1$ by the clinical team. This included management decisions about the use of conventional or high frequency oscillatory ventilation, induction of alkalosis, administration of volume, surfactant, pressors, sedation and paralysis. Surfactant therapy was initiated before the initiation of $IPGE_1$. The mode of ventilation remained unchanged for the duration of the study.

***Drug dosing and administration of aerosolized $PGE_1$.*** $PGE_1$ solution for aerosolization was prepared from 500 $\mu$g synthetic $PGE_1$ dissolved in 1 mL ethanol (Gensia Sicor Pharmaceuticals, Irvine, CA) by dilution in 0.9% saline. Once diluted, the solution was used within 24 h. Four different doses of aerosolized $PGE_1$ (25, 50, 150, and 300 ng/kg/min) were prepared. These trial doses were selected based on the recommended i.v. dose of 50 to 100 ng/kg/min (0.05 to 0.1 $\mu$g/kg/min) for ductal patency in neonates with congenital cardiac lesions. The dose was varied by a factor of three from the recommended i.v. dose of 100 ng/kg/min. The $PGE_1$ concentration in the solution was varied to keep the nebulized volume constant at 2.2 to 2.6 mL/h. Inhalation was begun at the lowest dose and each dose was administered for 30 min in all infants. Once the maximal dose was achieved (300 ng/kg/min), $IPGE_1$ was weaned in 15 min steps (weaning phase). The entire study lasted for 3 h unless the infant met exit criteria before completion.

The $PGE_1$ dosage refers to the total amount of nebulized drug placed in the nebulizer. It has previously been shown that the fraction deposited in the alveolar space during mechanical ventilation is less than 10 to 20% of the dose administered (10). The alveolar dose is even smaller in newborn infants as there is proportionally larger dead space (22).

Aerosols of $PGE_1$ with a mean particle size of 2 to 3 $\mu$m were generated with a jet nebulizer (miniHeart, Westmed Inc., Lakewood, CO). The nebulizer was connected to the inspiratory limb of the ventilator (Fig. 1). During the inhalation period, the ventilator flow was adapted according to the additional flow of the nebulizer to maintain alveolar ventilation and

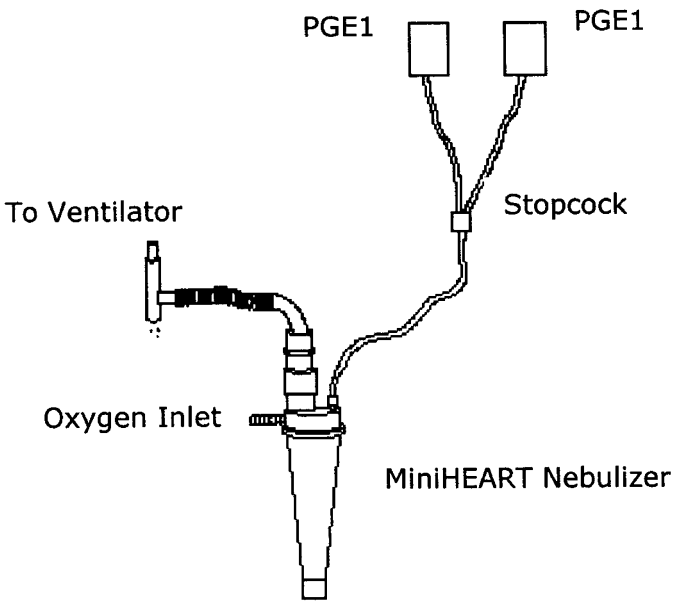


**Figure 1.** Aerosols of $PGE_1$ were generated with a jet nebulizer (miniHeart, Westmed Inc) connected to the inspiratory limb of the ventilator. Different doses of $IPGE_1$ for nebulization were delivered by syringe pumps through a stopcock to the nebulizer chamber.

inspired oxygen concentration. Baseline conditions were assessed by aerosolization of normal saline (2 mL/h) for 15 min before the first dose of aerosolized $PGE_1$ (25 ng/kg/min).

***Monitoring during administration of aerosolized $PGE_1$.*** Hemodynamic parameters and gas exchange (arterial blood gas) were assessed before $PGE_1$ administration, after each dose change and 60 min after withdrawal of the final dose. Blood counts, serum electrolytes and liver enzymes were obtained before and 24 h after concluding the study. The infants were monitored clinically for hyperthermia, hypotension, dysrhythmias, signs of bleeding, and seizures.

***Outcome variables.*** The primary outcome variable was the change in $P_aO_2$ from baseline after 30 min exposure to aerosolized $PGE_1$ and at end of $IPGE_1$ administration. To determine this, an arterial blood gas analysis was performed after 30 min of exposure to each dose of $IPGE_1$. A response was defined as an increase in $P_aO_2 \geq 25$ (full), 10–25 (partial) or $<10$ (none) mm Hg. Secondary outcome variables included change in oxygenation index, need for nitric oxide and/or ECMO, mortality, and duration of mechanical ventilation, oxygen therapy, and hospitalization.

***Exit Criteria.*** Infants in both groups exited the study if there was an acute drop in pulse oximeter saturation of >10% for which no mechanical cause could be identified. Additionally, infants in Group I exited the study if the OI exceeded 35 for more than 30 min during the study in the absence of mechanical cause for the worsening oxygenation. Infants in Group II awaiting ECMO, exited when ECMO was available.

***Statistical Analyses.*** We estimated a sample size of 17 to determine minimum difference in $P_aO_2$ before and after $IPGE_1$ of 25 mm Hg, a SD of 30 mm Hg, assuming a power of 90, and alpha of 0.05 (2-tailed). The sample was increased to 20 to account for infants exiting the study.

Statistical analysis was done using an intention-to-treat analysis. We evaluated categorical variables using $\chi^2$ tests. Continuous variables were compared with paired or independent samples *t* tests and ANOVA. Longitudinal data were analyzed using the mixed procedure in SAS. Significance level was set at 0.05.

## RESULTS

### Baseline Characteristics

Twenty infants were enrolled in the trial; 13 in Group I and 7 in Group II. The baseline maternal, perinatal, and postnatal characteristics are summarized (Table 1). Air leaks were present in three (15%), pulmonary hemorrhage in two (10%), and seizures in two infants (10%) before enrollment.

Cardio-respiratory variables at enrollment are summarized (Table 2). All infants in Group I had at least one OI ≥25, 10 had at least 2 such OIs. Although all infants had an echocardiogram at some point in the acute course of their illness, 85% ($n = 17$) had an echocardiogram before enrollment; of these, 82.4% had evidence of pulmonary hypertension (right-to-left or bidirectional shunting, systemic or supra-systemic right ventricular pressure or a diagnosis by the cardiologist of pulmonary hypertension).

**Table 1.** *Baseline characteristics*

| | Group I ($n = 13$) | Group II ($n = 7$) |
|---|---|---|
| Maternal | | |
| Age (years) | 26.2 ± 7.6 | 27.6 ± 6.5 |
| Positive GBS* status (%) | 5 (38.5) | 2 (28.6) |
| Fetal distress† present (%) | 5 (41.7) | 1 (20) |
| Meconium stained amniotic fluid (%) | 4 (30.8) | 4 (57.1) |
| Cesarean delivery (%) | 6 (46.2) | 3 (42.9) |
| Baby | | |
| Birth weight (g) | 3005 ± 588 | 3280 ± 582 |
| Gestational age (wk) | 37.2 ± 2.2 | 38.3 ± 2.8 |
| Male sex (%) | 7 (53.8) | 5 (71.4) |
| Race (%) | | |
| Black | 8 (61.5) | 6 (85.7) |
| White | 3 (23.1) | 1 (14.3) |
| Out born | 8 (61.5) | 7 (100) |
| 1-Minute Apgar‡ score <3 (%) | 3 (23.1) | 1 (16.7) |
| 5-Minute Apgar score <3 (%) | 0 (0) | 0 (0) |
| Delivery room resuscitation | 10 (76.9) | 4 (57.1) |

Plus-minus values are mean ± SD.

* GBS Group B streptococcus.

† Data for fetal distress are based on 17 infants, 12 in Group I, 5 in Group II.

‡ Data for 1-Minute Apgar is based on 19 infants, 13 in Group I and 6 in Group II.

**Table 2.** *Cardio-respiratory Variables at Enrollment*

| | Group I ($n = 13$) | Group II ($n = 7$) |
|---|---|---|
| Primary diagnosis (%) | | |
| Aspiration syndrome | 5 (38.5) | 4 (57.1) |
| RDS | 4 (30.8) | 1 (14.3) |
| Idiopathic PPHN | 2 (15.4) | 1 (14.3) |
| Suspect pulmonary hypoplasia | 2 (15.4) | 0 (0) |
| Pneumonia/sepsis | 0 (0) | 1 (14.3) |
| Systolic blood pressure (mm Hg) | 66.5 ± 12.9 | 80.4 ± 13.6 |
| First qualifying arterial-blood gas value | | |
| Oxygenation index (OI) | 29.8 ± 4.9 | 44.1 ± 5.1§ |
| Mean airway pressure (cm of water) | 15.4 ± 4.4 | 19.3 ± 3.2* |
| $FiO_2$ (mm Hg) | 1.0 ± 0.0 | 1.0 ± 0.0 |
| $P_aO_2$ (mm Hg) | 51.9 ± 10.4 | 44.1 ± 9.7 |
| Alveolar-arterial oxygen gradient (mm Hg) | 618.1 ± 19.8 | 624.6 ± 21.2 |
| Age at admission - hr (Median) | 9.7 | 9.8 |
| Age at enrollment - hr (Median) | 24.2 | 12.7 |
| Median time, enrollment to $IPGE_1$ initiation (min) | 19 | 25 |

Plus-minus values are mean ± SD.

$FiO_2$ denotes fraction of inspired oxygen, and $P_aO_2$ partial pressure of arterial oxygen.

* $p < 0.1$, § $p < 0.001$.

Conventional therapy before enrollment included volume resuscitation (100%), sedation/analgesia (100%), vasopressors (95%), steroids for hypotension (40%), surfactant (60%), neuromuscular blockade (45%), and i.v. $PGE_1$ (5%). Twenty-five percent of the infants had respiratory alkalosis (defined as pH >7.45 at enrollment). Ninety percent of the infants had a trial of high frequency oscillatory ventilation before enrollment; however, only 55% were on an oscillatory ventilator at the time of enrollment.

### Primary Outcome: Change in $P_aO_2$ from Baseline

Fig. 2 is the flow diagram of enrolled subjects whose clinical descriptions are shown in Table 3.

***Group I.*** Two infants in Group I met exit criteria before receiving $IPGE_1$. Three infants met exit criteria during the study. Eight infants completed the study and had a full response to $IPGE_1$. At the end of the study, there was a significant increase in $P_aO_2$ (63.0 ± 62.3, $p = 0.024$), decrease in OI (13.0 ± 8.8, $p = 0.004$) and decrease in alveolar-arterial oxygen gradient (58.3 ± 65.2, $p = 0.039$).

***Group II.*** All infants in this group had demonstrated a lack of response to INO. Five received INO during transport from birth hospital to the referral center. Duration of INO therapy before enrollment was 6.1 h (median) (range 1.5 to 91 h). One infant exited the study without receiving $IPGE_1$ and two infants exited during the study as ECMO was available. Four infants in Group II completed the $IPGE_1$ study. One infant improved before receiving $IPGE_1$. This infant demonstrated an additional full response to $IPGE_1$. The mean± SD increase in $P_aO_2$ (39.8 ± 62.1), decrease in OI (7.6 ± 13.4) and alveolar-arterial oxygen gradient (39.3 ± 66.6), was not statistically significant compared with baseline ($p > 0.05$ for all) in these four infants.

### Dose Response Effect

Among the eight subjects completing the study in Group I, a full response was observed in 50% after a dose of 50 ng/kg/min, and in 87.5% after a dose of 150 ng/kg/min. One patient (12.5%) had a partial response in the escalation phase, but showed a complete response during the weaning phase (Fig. 3). At the end of the weaning phase, five infants *sustained* a full response.

In the four patients in Group II completing the $IPGE_1$ study, a full response was observed in 25% after a dose of 50 ng/kg/min, in 50% after a dose of 150 ng/kg/min, and in 75% after a dose of 300 ng/kg/min (Fig. 3). At the end of the weaning phase, the three infants with a full response *sustained* it.

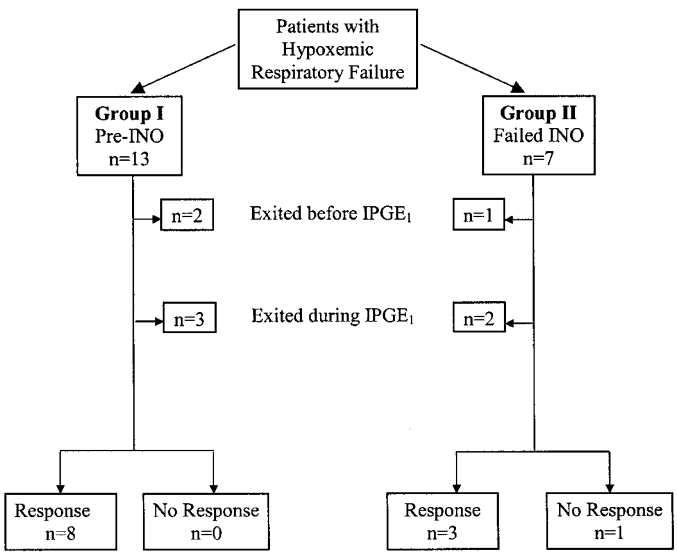


**Figure 2.** Flow diagram of enrolled patients.

Analysis using Mixed Models (SAS) (Fig. 3) revealed a significant association of $IPGE_1$ dose and $P_aO_2$ during the escalation phase in Group I ($\beta = 11.4$, SE = 3.5, $p = 0.009$) but not during weaning. In Group II, no association was observed either in the escalation phase or during weaning. A more complex model adjusting for time on $IPGE_1$ and $IPGE_1$ dose revealed a significant effect of both dose ($\beta = 7.1$, SE = 2.4, $p = 0.02$) and time ($\beta = 6.2$, SE = 1.1, $p < 0.0001$) for Group I and only a significant effect of time ($\beta = 2.7$, SE = 1.3, $p = 0.0461$) but not dose ($\beta = 6.5$, SE = 19.8, $p = 0.8$) for Group II.

### Secondary Outcomes

***Need for INO or ECMO.*** Nine of the 13 infants in Group I (69.2%) received INO and 6 (46.2%) eventually were placed on ECMO. All infants in Group I who did not respond to $IPGE_1$ ($n = 5$) also failed to respond to INO and all qualified for ECMO. Fifty percent ($n = 4$) of the infants with full response to $IPGE_1$ in Group I continued to improve without need for INO or ECMO. The median time from the discontinuation of $IPGE_1$ to initiation of INO in the four patients who did not sustain a response was 8.2 h (range 0.3 to 30 h). Of these, two did not respond to INO and were placed on ECMO 13.5 and 75 h after conclusion of the $IPGE_1$ study. Four of the seven infants in Group II (57.1%) were placed on ECMO.

***Mortality.*** Three infants in Group I (23.1%) and 1 infant in Group II (14.3%) died before hospital discharge or 120 d of life (Table 4). Causes of death included fulminant sepsis ($n = 1$) and pulmonary hypoplasia ($n = 3$).

***Results of cranial imaging studies.*** A cranial ultrasound was obtained in all patients during the acute phase of the illness. It was obtained before enrollment in 9 of 13 (69.2%) infants in Group I and 6/7 (85.7%) infants in Group II. Abnormal findings included cerebral edema, ventriculomegaly, Grade I IVH, and periventricular echogenicity. Abnormal findings in the initial sonogram obtained within 24 h after the $IPGE_1$ study ($n = 5$) included Grade I IVH. No new findings or progression was observed in patients who had a sonogram both before enrollment and after the $IPGE_1$ study in the acute phase. Cranial imaging findings before discharge or death included hydrocephalus ($n = 1$), stable ventriculomegaly ($n = 7$), extra-axial fluid ($n = 10$), infarction ($n = 1$) and periventricular leukomalacia ($n = 2$).

***Toxicity/adverse effects.*** Inhaled $PGE_1$ was not discontinued in any infant because of adverse effects. No episodes of exacerbation of hypotension, hyperthermia, dysrhythmias, or bleeding tendency were observed. Paired *t* tests did not reveal significant differences in temperature, systolic blood pressure or heart rate at baseline and end of $IPGE_1$ administration in either group. Results of blood counts and serum chemistries obtained before and 24 h after study conclusion are presented in Table 4. The hematocrit, total leukocyte count and aspartate aminotransferase were lower after $IPGE_1$ whereas blood urea nitrogen was higher; however all values were within normal limits and the differences were not clinically significant. Seizures and ventriculomegaly were documented in two infants before enrollment in study. No new onset seizures were doc-

**Table 3.** *Description of Patients*

| Pulmonary diagnosis | Response to $IPGE_1$ | $IPGE_1$ - No. of doses* | Maximal support† | Comments | Cranial imaging before discharge/death | Age at discharge/death (days) | Survival status‡ |
|---|---|---|---|---|---|---|---|
| Group I | | | | | | | |
| Idiopathic | Full | Complete | HFOV | — | | 16.2 | S |
| RDS | Full | Complete | CMV | — | | 16.4 | S |
| RDS | Full | Complete | HFOV | — | | 10 | S |
| RDS | Full | Complete | CMV | Intractable hypoglycemia, seizures | Normal | 37.2 | S |
| Idiopathic | Full | Complete | INO | Down's syndrome | | 17.6 | S |
| Aspiration | Full | Complete | INO | — | | 13.8 | S |
| Aspiration | Full | Complete | ECMO | — | VM, EAF | 34.6 | S |
| Aspiration | Full | Complete | ECMO | — | VM, EAF | 31.5 | S |
| Hypoplasia | Exit | 1 Dose | ECMO | Hydrops | PVL, EAFz | 31.9 | D (Sepsis, pulmonary hypoplasia) |
| Aspiration | Exit | 1 Dose | ECMO | — | EAF | 22.2 | S |
| Aspiration | Exit | 2 Doses | ECMO | Deterioration from mechanical cause | EAF | 26 | S |
| Hypoplasia | Exit | No $PGE_1$ | INO | Deteriorated during placement of urinary catheter, IPCKD, not candidate for ECMO | | 2.7 | D (IPCKD, Pulmonary hypoplasia) |
| RDS | Exit | No $PGE_1$ | ECMO | Rapidly progressive course, died during cannulation for ECMO 10 h later | | 5.1 | D (Pseudomonas sepsis, HMD) |
| Group II | | | | | | | |
| Idiopathic | Full | Complete | INO | Skeletal dysplasia, reservoir placed for HC | HC, EAF | 115.2 | D (Pulmonary hypoplasia) |
| RDS | Full | Complete | INO | $P_aO_2$ improved after enrollment but before $IPGE_1$ | | 19.1 | S |
| Aspiration | Full | Complete | INO | — | VM, EAF | 89.6 | S |
| Pneumonia | Partial | Complete | ECMO | — | VM, EAF | 54.2 | S |
| Aspiration | Exit | 4 Doses | ECMO | On intravenous $PGE_1$ prior to study<br>Study Stopped as ECMO team ready | INFARCT, PVL, VM, EAF | 29.3 | S |
| Aspiration | Exit | 3 Doses | ECMO | Study stopped as ECMO team ready | VM | 30.6 | S |
| Aspiration | Exit | No $PGE_1$ | ECMO | $P_aO_2$ deteriorated after enrollment but before starting $IPGE_1$ | VM, EAF | 22.7 | S |

GA, gestational age; VM, stable ventriculomegaly; EAF, extra-axial fluid; PVL, periventricular leukomalacia; HC, hydrocephalus; IPCKD, infantile polycystic kidney disease.

* The study design included 8 doses of IPGE1–4 in the escalation phase and 4 in the weaning phase. "Complete" refers to a patient completing both the escalation and weaning phase of the study. "No $PGE_1$" indicates a patient who exited the study prior to receiving any $IPGE_1$. For babies exiting during the study, the number of doses administered is indicated.

† Babies with hypoxemic respiratory failure receive CMV initially, followed by trial of HFOV, INO, and ECMO, generally in that order.

‡ S, survived; D, died; significant autopsy findings given in parentheses for infants who died.

umented in any of the patients within 1 wk after enrollment. Mild ventriculomegaly was documented in babies who had undergone ECMO and is probably not attributable to the use of $IPGE_1$ in these infants.

## DISCUSSION

The results of this phase I-II study suggest that $IPGE_1$ is a safe selective pulmonary vasodilator in hypoxemic respiratory failure at the concentrations and durations used in the trial. No evidence of tolerance, rebound pulmonary hypertension between doses and after cessation of $IPGE_1$ or systemic side effects was detected.

Although a few studies have reported on the use of aerosolized $PGI_2$ in newborns with hypoxemic respiratory failure, there are no reports on the use of $IPGE_1$ in this population. De Jaegere *et al.* (20) reported improved oxygenation without adverse systemic effects in 4 preterm infants following endotracheal instillation of $PGI_2$. Similar benefits were reported by Soditt *et al.* in a preterm newborn with pulmonary hypertension (21). Aerosolized $PGI_2$ was associated with improvement in oxygenation in two term infants with persistent pulmonary hypertension and one infant with congenital heart disease (22,24). Sustained improvement in oxygenation was also reported by Kelly *et al.* in three of four term infants who had failed to respond to INO following administration of $IPGI_2$ and milrinone (23). Milrinone has been shown to amplify the pulmonary vasodilatory response to inhaled $PGI_2$ (33).

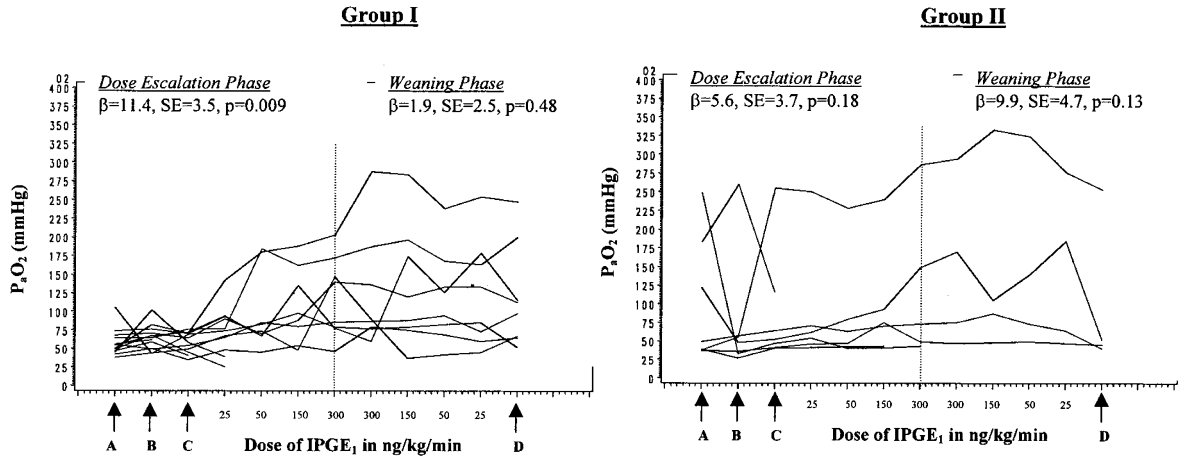


**Figure 3.** The *x* axis represents the dose of $IPGE_1$ in ng/kg/min. The data points represent oxygenation at the end of each dose. *A* and *B* represent oxygenation in two arterial blood gases immediately before enrollment. *C* represents oxygenation at the end of nebulized normal saline. *D* represents oxygenation 1 h after discontinuing $IPGE_1$. The hatched vertical line demarcates the escalation and weaning phases. The individual lines represent the subject-specific $P_aO_2$ profiles over time. In Group I, there is significant increase in $P_aO_2$ with increasing $IPGE_1$ dose in the escalation phase; the response is sustained in the weaning phase in the group as a whole. In Group II, there is no association between the $IPGE_1$ dose and $P_aO_2$ response in either the escalation or weaning phase. The between subjects variability is more marked in Group II compared with Group I.

**Table 4.** *Adverse Effects*

| | Before $IPGE_1$ Mean (SD) | After $IPGE_1$ Mean (SD) | *p* |
|---|---|---|---|
| Alanine aminotransferase* | 26.3 (10.2) | 25.3 (14.1) | NS |
| Aspartate aminotransferase* | 74.7 (65.6) | 47.2 (29.4) | 0.04 |
| Alkaline phosphatase* | 193.4 (272.5) | 93.6 (54.9) | NS |
| Bilirubin† | 4.6 (2.9) | 5.3 (4.3) | NS |
| Blood urea nitrogen† | 7 (3.3) | 9.9 (5.5) | 0.011 |
| Creatinine† | 0.7 (0.18) | 0.7 (0.23) | NS |
| Hematocrit (%) | 46.8 (6.4) | 40.1 (6.6) | 0.001 |
| Platelets‡ | 219.3 (116.7) | 187 (77.5) | NS |
| Total leukocyte count‡ | 16.2 (6.8) | 12.6 (6.4) | 0.039 |

* U/L.
† (mg/dL).
‡ $10^3/mm^3$.

A clinically significant improvement in oxygenation was observed in the patients in Group I when $IPGE_1$ was given for 3 h. This improvement was sustained during the weaning phase in this group. The magnitude of the improvement in oxygenation in this group is comparable to that reported previously for INO (1,2,34). In Group II, at least one infant had already received i.v. $PGE_1$ at the referring hospital. This may have interfered with the selective pulmonary action of $IPGE_1$. Three infants in this group did show a full response to $IPGE_1$ and never qualified for ECMO. This provides credence to the speculation that INO and $IPGE_1$ may have additive effects because of activation of different cellular mechanisms (32). The improvement in $P_aO_2$ was observed earlier and at lower $IPGE_1$ dose in Group I patients compared with Group II patients. Previous studies have referred to the benefits of earlier institution of therapy for hypoxemic respiratory failure (1,35). The improvement in $P_aO_2$ was predicted by both dose and time in study for Group I but only by time in study for Group II. It is possible that a greater number of patients might have responded and sustained the response had the $IPGE_1$ been administered for longer.

This study was designed to find a safe and effective dose of inhaled $PGE_1$ and found that a dose of 150 to 300 ng/kg/min may be used safely and effectively in neonates with hypoxemic respiratory failure. The sample size is relatively small and heterogeneous without a placebo control group, not atypical for clinical phase 1 and phase 2 drug trials and can only detect large differences. The drug was administered for a short duration (3 h) and the efficacy and safety of a longer drug inhalation remains to be evaluated. This study describes for the first time the use of inhaled $PGE_1$ in neonates with hypoxemic respiratory failure and suggests further placebo controlled randomized studies to establish efficacy and safety of this drug in this neonatal population.

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