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Notes from the Chair

by Timothy R. Myers, BS, RRT

As I embark upon my third year as your section chair, it is memorable to look back on the positive changes that our section has undergone in the past two years. Among the more notable: a new name for our section, the addition of some long-awaited credentials for the Neonatal-Pediatric Specialty Exam, and a Neonatal-Pediatric Journal Conference published in the 2003 March and April issues of RESPIRATORY CARE.

Of course, there is still more to be done. The AARC's Clinical Practice Guideline (CPG) Committee is undertaking the enormous task of reviewing and revising CPGs that are over five years old, including 6-10 related to our specialty. The committee will be in need of individuals to assist in revising these guidelines or in reviewing CPGs that have already been updated. In you have an interest in participating in this endeavor, contact me at the address or numbers found on page two.

I have recently reviewed neonatal-pediatric proposals submitted for the International Respiratory Congress to be held in Las Vegas this December. All areas of our specialty were well represented. I am personally looking forward to some exciting lectures and dynamic speakers when we meet in December.

As many of you are aware, every year the Specialty Sections honor Specialty Practitioners of the Year at the Awards Ceremony during the International Congress. Our past award winners include Justin Twitchell, Jenni Raake, Michael Tracy, Esther Taylor, and current Bulletin co-editors Kathy Deakins and Melissa Brown. I

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Section Connection

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Prostaglandin I2 as an Alternative to Inhaled Nitric Oxide

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Following the recent Food and Drug Administration approval of inhaled nitric oxide (INO) for persistent pulmonary hypertension of the newborn (PPHN), INO Therapeutics set the price for this therapy at $125 per hour. That price has forced many clinicians to reconsider their indications for administering INO and to study alternative agents that selectively decrease pulmonary artery pressure (PAP).

Because of the high cost of INO, insurance companies have either never reimbursed for it or have offered to reimburse only a small percentage, leaving hospital administrators and clinicians with an ethical dilemma: whether to treat pulmonary hypertension (PH) with INO, which might help but that is only Food and Drug Administration-approved for PPHN. A number of animal experiments, case reports, and small clinical studies investigated the hemodynamic effects of short-acting vasodilators administered via inhalation. This was an active area of research prior to the appearance and widespread testing of INO in the 1990s, but, with the increasing acceptance and use of INO, interest in other pulmonary vasodilators declined.

Prostaglandin I2

Prostaglandin I2 (PGI2) (also known as epoprostenol [brand name Flolan] inhalable prostacyclin) is a naturally-occurring compound found in endothelial cells and within the lung.[1] PGI2 is a vasodilator and the most potent inhibitor of platelet aggregation yet discovered. These properties strongly suggest that it has a role in preventing clot formation in uninjured vessels and producing vasodilation in low-resistance vascular beds such as the pulmonary circulation. These effects are mediated via binding to cell surface prostaglandin receptors and activation of adenyl cyclase.[2] PGI2 also stimulates endothelial release of nitric oxide.[3]

PGI2 is spontaneously hydrolyzed at neutral pH to its inactive metabolite, 6-keto-prostaglandin-F1, and it may also be subject to enzymatic degradation. The manufacturers of PGI2 report that its in vitro half-life in human blood at 37° C and pH 7.4 is approximately 6 min.[4] Animal studies indicate that intravenous PGI2 has a high clearance (93 mL/kg), small volume of distribution (357 mL/kg), and a short half-life (2–3 min).[2]

For nearly 20 years PGI2 has been used to treat PPHN. Other indications have included acute respiratory distress syndrome (ARDS),[5,6] peripheral vascular disease, and congestive cardiac failure, as well as after heart transplantation. Much of our information concerning the pharmacologic effects of PGI2 are derived from clinical experience with intravenous PGI2. The reported adverse reactions to intravenous PGI2 include flushing, headache, jaw pain, nausea and vomiting, anxiety, chest pain, flu-like symptoms, dizziness, abdominal pain, and bradycardia (at low doses). PGI2 is contraindicated in patients with severe left ventricular dysfunction, on the basis of a study that found a higher mortality in patients with (New York Heart Association class III and IV) heart failure given intravenous PGI2 (see page 3). Pulmonary edema has also been reported in some PPHN patients who received intravenous PGI2. Abrupt withdrawal, including interruptions in drug delivery and sudden large reductions in dose, may result in rebound PH. The manufacturers warn that the death of 1 patient with PPHN has been attributed to this phenomena. Despite the known effects of PGI2 on platelet aggregation no studies have reported a problem with bleeding, even in patients maintained on warfarin. Unlike INO, PGI2 has no known toxic effects or metabolites, and no known adverse reaction with other drugs. The effect of an overdose is reversible hypotension.

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PROSTAGLANDIN 12 AS AN ALTERNATIVE TO INHALED NITRIC OXIDE

Inhaled PGI2 is not substantially metabolized within the lung, and arterial concentrations of 6-keto-PGF1 during therapy with inhaled PGI2 are undetectable, suggesting that there is little absorption of inhaled PGI2 into the systemic circulation. Inhalation for 8 hours in healthy lambs produced no evidence of toxicity, as measured by changes in lavage fluid cell counts, protein concentrations, lactate dehydrogenase and alkaline phosphatase (nonspecific markers of cell injury), and fibronectin.[7] There was no effect on collagen-induced platelet aggregation. Impaired adenosine 5´-diphosphate (ADP)-induced platelet aggregation was noted in 1 clinical study of inhaled PGI2 with healthy volunteers and asthma patients.[8] The clinical relevance of this observation is unknown, given the lack of bleeding complications with the intravenous use of PGI2. There are conflicting reports concerning the effect of PGI2 on bronchial tone; some studies found bronchoconstriction, whereas others found bronchodilation.[9,10] Reports have suggested that PGI2 is an airway irritant when administered intratracheally. This may be related to the alkalinity (pH 10.5) of the glycine buffer in which it is dissolved. PGI2 has satisfactory stability for up to 12 hours in the appropriate buffer.

The administration of inhalable PGI2 to humans was first reported in 1978,[8] and since then a number of trials have studied its effects in animal models and various clinical settings. The studies described below suffered from various handicaps, including small numbers of enrolled patients and the fact that most of the studies examined only the short-term response to a bolus of inhaled PGI2 rather than the response to sustained treatment, which is a more relevant model of the clinical situation in which selective pulmonary vasodilation is required.

Animal Studies

In one of the earliest studies on inhaled PGI2, Welte et al11[1] demonstrated that inhaled PGI2 inhibits hypoxic pulmonary vasoconstriction in dogs, without decreasing systemic arterial pressure (SAP).

Pulmonary Hypertension

Mikhail et al[12] compared increasing doses of inhaled PGI2 (15–50 ng/kg/min, administered via face mask) to INO and intravenous PGI2, with 12 PH patients (7 with PPHN and 5 secondary to causes such as thromboembolism and ischemic cardiomyopathy). Inhaled PGI2 produced the greatest decrease in pulmonary vascular resistance (PVR) (38%), without any effect on SAP. Interestingly, there was no detectable dose response over the 15–50 ng/kg/min dose range, suggesting that a maximum response had been attained at the lowest dose tested.

Olschewski et al[13] compared INO (10–28 ppm), inhaled PGI2, and inhaled iloprost (the stable analogue of PGI2) with 4 PPHN patients and 2 patients suffering severe PH secondary to connective tissue disease. All 3 agents produced comparable selective pulmonary vasodilation, but inhaled PGI2 improved oxygenation more than INO.

Webb et al[14] described the emergency use of inhaled PGI2 in the management of a cyanosed hypotensive patient with severe PH caused by acute on chronic pulmonary thromboembolism. A high dose of PGI2 (200 ng/kg/min) decreased mean PAP from a high of 59 mm Hg to 53 mm Hg at 24 hours, and increased the P_{aO_2}/F_{IO_2} ratio from a low of 66 to 225. This high dose of inhaled PGI2 decreased mean SAP from 79 to 71 mm Hg.

Haraldson et al[15] compared the short-term response to INO (40 ppm) and inhaled PGI2 (20–30 μg) with 10 PH patients (PVR > 200 dyn·s·cm^{-5}) awaiting heart transplantation. INO and PGI2 selectively decreased PAP and PVR to a similar extent. Inhaled PGI2 caused an 11% increase in cardiac output. Both INO and PGI2 increased pulmonary artery occlusion pressures, and some patients developed pulmonary congestion during inhalation of either PGI2 or INO. The Haraldson et al study[15] highlights the fact that inhaled pulmonary vasodilators should be used with extreme caution, if at all, in patients with severe left ventricular dysfunction. PGI2-induced increase in cardiac output has been observed by others[16] and was observed in an in vitro study.[17]

After Cardiac Surgery

Haraldson et al[18] studied the short-term effects of inhaled PGI2 at 3 concentrations (2.5, 5.0, and 10 μg/mL) with 9 postoperative patients (2 heart-transplantation and 7 coronary artery bypass graft) suffering elevated PVR (> 200 dyn·s·cm^{-5}). Mean PAP and PVR significantly decreased with 5 and 10 μg/mL PGI2, with no decrease in SAP.

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Acute Respiratory Distress Syndrome

The use of intravenous PGI2 for ARDS is limited by its propensity to cause systemic hypotension and increase pulmonary venous admixture.[5,6] In contrast, inhaled PGI2 causes selective pulmonary vasodilation almost identical to that produced by INO. In a 1993 study, Walmrath et al[19] administered inhaled PGI2 (17–50 ng/kg/min) to 3 ARDS patients. Mean PAP decreased in all patients (from a mean of 40 mm Hg down to 32 mm Hg), which was associated with a P_{aO_2}/F_{IO_2} increase from 120 to 173. Van Heerden et al[20] also showed that inhaled PGI2 at 50 ng/kg/min produced pulmonary and systemic effects comparable to INO at 10 ppm. In one of the larger reported studies, Walmrath et al[21] compared the effects of the lowest doses of INO and inhaled PGI2 that produced the maximum P_{aO_2} increase in 16 ARDS patients. The INO dose range that produced the maximum P_{aO_2} increase was 2–40 ppm, whereas the comparable dose range for inhaled PGI2 was 1.5–34 ng/kg/min (mean 7.5 ng/kg/min). Both agents produced comparable increases in P_{aO_2}, whereas inhaled PGI2 reduced PVR more. Neither agent decreased SAP. Some patients were given the agents for ≥ 48 hours, demonstrating that inhaled PGI2 provides sustained oxygenation improvement and selective pulmonary vasodilation. Interestingly, 1 study with 16 patients suffering PH and septic shock found that, in contrast to INO, inhaled PGI2 improved splanchnic oxygenation, suggesting that some PGI2 may enter the systemic circulation.[22]

Pediatric Patients

Bindl et al[23] reported the effects of inhaled PGI2 in 2 neonates suffering PH. Inhaled PGI2 (20–28 ng/kg/min) significantly decreased the alveolar-arterial oxygen difference and was associated with a modest decrease in PAP but no decrease in SAP. Pappert et al[24] compared the effects of INO (0.1–10 ppm) and inhaled PGI2 (2–20 ng/kg/min) in 3 children suffering ARDS. Neither agent produced an impressive or consistent reduction in PAP. The authors noted that the maximum increase in the P_{aO_2}/F_{IO_2} ratio did not necessarily occur at the inhaled PGI2 dose that most decreased PAP.

Zwissler et al[25] recently reported on a 4-kg infant who had total anomalous pulmonary venous drainage and developed severe PH and acute right ventricular failure after surgical correction, despite the administration of enoximone and intravenous PGI2. Inhaled PGI2 (50 ng/kg/min) decreased systolic PAP from 60 to 50 mm Hg and increased SAP. Inhaled PGI2 was administered for a total of 13 hours. Attempts to terminate treatment were associated with a rapid increase in PAP and decreases in P_{aO_2} (from 259 down to 65 mm Hg).

De Jaegere et al[26] studied the effects of a 50 ng/kg bolus of PGI2 administered down the endotracheal tube to 4 hypoxic preterm neonates suffering PPHN. PGI2 increased the P_{aO_2}/F_{IO_2} ratio from a mean of 47 up to 218, with no change in SAP. In 1 infant, inhaled PGI2 was continuously nebulized at a rate of 50 ng/kg/min for 12 hours, with no evidence of either tolerance or systemic effects.

Use of Inhalable Prostacyclin at University of Virginia Children's Medical Center

Our experience has been similar to those described above. Table 1 illustrates the effectiveness of inhaled prostacyclin in a diverse pediatric population. All patients were started on 50 ng/kg/h and weaned (if they stayed on for longer than 30 min) in a fashion similar to INO (50 → 25 → 12.5 → 6 → 3 → 1 → off).

TABLE 1. EFFECTS OF INHALED PROSTACYCLIN IN 3 PATIENTS

Patient	PAP (% Δ)	PVRI (% Δ)	CI (% Δ)	SVRI (% Δ)
1	↓17	↓15	↑6	NA
2	↓7	↓21	↑12	↑3*
3	↓19	↓30	↑17	NA

PAP = pulmonary artery pressure
%Δ = percent change
PVRI = pulmonary vascular resistance index
* Difference not significant
CI = cardiac index
SVRI = systemic vascular resistance index
NA = data not available

The patients listed in Table 1 were:

Patient 1: A 5-month-old male with a history of totally anomalous pulmonary venous return and suprasystemic PAP due to late restenosis after neonatal repair; inhalable prostacyclin administered in the catheterization laboratory.

Patient 2: A 25-year-old male with tetralogy of Fallot and pulmonary atresia with suprasystemic PAP; inhalable prostacyclin administered in the catheterization laboratory.

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NOTES FROM THE CHAIR

am looking for volunteers for the Section Recognition Committee, which will aide in the selection of our 2003 winner. If you'd like to serve on the committee, contact me using the information on page two. I also encourage all members to start brainstorming names of worthy candidates. (See "Section Connection" in this Bulletin for a link to the nomination form on the AARC web site.)

We will also be electing a new chair-elect this year. The ballot will be mailed to all section members in late summer/early fall. The winner will serve as chair-elect for 2004 and assume the chair position from 2005 through 2007. If the section maintains at least 1,000 members through December 31 of this year, our new chair will also hold a seat on the AARC Board of Directors. ◆

Letter to the Editor

Dear Bulletin Editor,

I am pleased that in your "Notes from the Co-Editor" you passed on the information concerning the new name and acronym for the neonatal-pediatric specialty credential. However, I would like to take issue with the last part of the announcement, "The whole section owes a debt of thanks to former section chair, Peter Betit, RRT, who worked diligently with the NBRC to acquire a credential…"

Not to take any amount of gratitude away from Mr. Betit, I do think it is only fair to point out that others are owed this amount of gratitude as well. The entire Neonatal-Pediatric Specialty Exam Committee worked diligently on this complex issue to overcome opposition and numerous other hurdles. The chairperson of the committee, and the actual individual responsible for introducing the resolution to the board, is another former section chair, Sherry Barnhart, RRT. The others on this committee along with Mr. Betit are Jackie Long-Goding, RRT, James Cairo, RRT, Tim Opt'Holt, RRT, and Barbara Wilson, RRT.

ALL of these individuals deserve our gratitude in working toward, and achieving, an acronym that allows us to recognize the credential we earned, and share our success with the public. To each of you, thank you.

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PROSTAGLANDIN 12 AS AN ALTERNATIVE TO INHALED NITRIC OXIDE

Patient 3: A 3-year-old with arteriovenous canal defect, repaired at birth, with suprasystemic PAP due to a late ventricular septal defect patch leak and moderate-to-severe mitral regurgitation. Inhalable prostacyclin administered before and after surgical repair. Inhaled prostacyclin acted in synergy with INO and was used as a single agent following repair; there was no rebound PH after 5 days of use. In sum, the PVR index was significantly reduced, from 19 ± 5.4 to 15.7 ± 4.0 woods units/m2 ($p = 0.0456$). The cardiac index increased from 3.27 ± 1.7 to 3.63 ± 1.8 L/min/m2, but that increase was not significant ($p = 0.0692$). There was no significant change in platelet aggregation following prostacyclin use.

Table 2 shows the PAP effects of inhaled prostacyclin in 3 adult patients at our hospital.

TABLE 2. EFFECTS OF INHALED PROSTACYCLIN IN 3 ADULT PATIENTS

Age (yr)	Diagnosis	Procedure	Use of Inhaled Prostacyclin	Mean PAP (%Δ)
25	Tetralogy of Fallot and pulmonary atresia	Cardiac catheterization	Cardiac catheterization	↓ 7
63	Severe mitral regurgitation	Mitral valve/aortic valve replacement	Perioperative and postoperative	↓ 40–50
35	Rheumatic mitral stenosis	Mitral valve replacement	Perioperative and postoperative	↓ 31

PAP = pulmonary artery pressure

%Δ = percent change

Similar additional patient data is forthcoming in a future report, and we believe that inhalable prostacyclin will soon be accepted as a less expensive alternative for pediatric patients suffering PH.

Inhalable Prostacyclin From the Respiratory Therapist's Perspective

Inhalable prostacyclin is not hard to mix or deliver. Most pediatric respiratory therapists are accustomed to administering continuous nebulization. Inhalable prostacyclin is, however, more labor-intensive than INO. Inhalable prostacyclin requires protection from light. PGI2 is mixed in a glycine buffer that, if not properly filtered, can cause ventilator exhalation valves to malfunction. It is a cool aerosol and we know little about its long-term effects. It is much like INO in that if stopped abruptly the patient's vital signs may become unstable if not resolved in < 6 min. This is more likely to happen with a mass-produced nebulizer than an expensive INO delivery device.

Conclusions

All available studies indicate that the clinical response to inhaled PGI2, in terms of selectively decreasing PAP without affecting SAP and/or improved oxygenation, is as good as if not better than INO. Where continuous inhalation has been used the rate of PGI2 administration is comparable to the intravenous infusion dose (1.5–50 ng/kg/min). Mikhail et al[12] were unable to detect a dose response between 15 and 50 ng/kg/min, suggesting that lower doses should be evaluated. In a dog model of hypoxic pulmonary vasoconstriction, Zwissler et al found that inhaled PGI2 as low as 0.9 ng/kg/min significantly reduced PAP.[27] The actual dose reaching the pulmonary vasculature is unknown, as only about 10% of the initial dose of a nebulized agent reaches the alveolus.[28] Distal deposition of a nebulized drug is related to particle size; to achieve distal deposition the aerosol droplets must be < 5 μm in diameter.

No studies have observed the development of tolerance with sustained inhaled PGI2 treatment, and repeated nebulized treatments have shown no evidence of deleterious rebound PH in between doses. More studies with larger patient populations are needed. However, with INO as a back-up, inhalable prostacyclin could be a logical first step in cost-effective management of PH. ◆

REFERENCES

For a complete list of references used in this article, please visit the Neonatal-Pediatric Section home page at www.aarc.org.