Neuroanesthesia and Intensive Care

Inhaled prostacyclin (PGI$_2$) is an effective addition to the treatment of pulmonary hypertension and hypoxia in the operating room and intensive care unit

[L'inhalation de prostacycline (PGI$_2$) est un traitement complémentaire efficace de l'hypertension pulmonaire et de l'hypoxie observées en salle d'opération et à l'unité des soins intensifs]

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Purpose: There is a growing interest in the intraoperative and intensive care use of inhaled epoprostenol (PGI$_2$) for the treatment of pulmonary hypertension (PHT) and hypoxia of cardiac or non-cardiac origin. We report our experience with this form of therapy.

Methods: A retrospective chart review of all patients who received inhaled PGI$_2$ over a one-year period was undertaken. Demographic, hemodynamic, oxygenation status, mode of administration, side effects, duration of hospital stay, and mortality were noted.

Results: Thirty-five patients, of which 33 (92%) were in the intensive care unit, received inhaled PGI$_2$. Of the 27 patients whose pulmonary artery pressure (PAP) was monitored, a significant decrease in mean PAP from 34.8 ± 11.8 mmHg to 32.1 ± 11.8 mmHg was observed within one hour after the start of therapy (P=0.0017). Selective pulmonary vasodilatation occurred in 77.8% of the patients. Thirty-three patients had arterial blood gases before and after therapy. There was an improvement in the PaO$_2$/FiO$_2$ ratio in 88% of these with a 175% improvement on average. The ratio of PaO$_2$/FiO$_2$ improved from 108 ± 8 to 138 ± 105 (P=0.001). Six patients (17%) presented hypotension, two had subsequent pneumothorax, one had bronchospasm and in one patient PGI$_2$ inhalation was stopped because of increasing peak pulmonary pressures from the secondary flow coming from the nebulizer. Mortality of the cohort was 54%.

Conclusion: Inhaled PGI$_2$ can be useful in the treatment of patients with PHT and severe hypoxia. It can however be associated with systemic side effects.

Objectif : *Il y a un intérêt croissant pour l'utilisation de l'époprosténol (PGI$_2$) inhalé comme traitement de l'hypertension pulmonaire (HTP) et de l'hypoxie d'origine cardiaque ou non survenant en salle d'opération ou aux soins intensifs. Nous rendons compte de notre expérience avec cette forme de thérapie.*

Méthode : *On a procédé à l'examen rétrospectif de tous les dossiers des patients qui ont reçu de la PGI$_2$ par inhalation au cours d'une année. Les données démographiques et hémodynamiques, l'état de l'oxygénation, le mode d'administration, les effets secondaires, la durée du séjour hospitalier et la mortalité ont été enregistrés.*

Résultats : *Trente-cinq patients, dont 33 (92 %) étaient à l'unité des soins intensifs, ont reçu de la PGI$_2$ par inhalation. Chez 27 patients dont on a surveillé la tension artérielle pulmonaire (TAP), une baisse significative de la TAP moyenne a été observée passant de 34,8 ± 11,8 mmHg à 32,1 ± 11,8 mmHg pendant la première heure de la thérapie (P = 0,0017). La vasodilatation pulmonaire sélective est survenue chez 77,8 % des patients. Trente-trois patients ont eu une gazométrie du sang artériel avant et après la thérapie. Une amélioration du ratio PaO$_2$/FiO$_2$ a été notée chez 88 % d'entre eux et une amélioration de 175 % en moyenne. Le ratio PaO$_2$/FiO$_2$ s'est amélioré, de 108 ± 8 à 138 ± 105 (P = 0,001). Six patients (17 %) ont présenté de l'hypotension, deux ont eu un pneumothorax subséquent, un a souffert de bronchospasme et chez un autre patient l'inhalation de PGI$_2$ a été stoppée à la suite de la hausse des pics de pressions pulmonaires provenant du flux secondaire du nébuliseur. La mortalité a été de 54 % dans cette cohorte.*

Conclusion : *La PGI$_2$ inhalée peut être utile comme traitement de patients atteints d'HTP et d'hypoxie sévère. Il peut toutefois provoquer des effets secondaires systémiques.*

PROSTACYCLIN (PGI$_2$, epoprostenol) is an endogenously produced prostaglandin.[1] It is formed by the cyclo-oxygenase pathway of arachidonic acid metabolism. At physiologic pH, it is spontaneously hydrolyzed to 6-keto-prostaglandin-F1$_\alpha$ (6-ketoPGF1$_\alpha$)[2] and has a half-life of two to three minutes. Over the years, it has been used for many indications including long-term management of PHT. When given systemically, its use is limited by adverse effects including systemic hypotension and worsening of intrapulmonary shunt.[3] Administration by inhalation has been used to improve its pulmonary selectivity. Hence, it reduces pulmonary hypertension (PHT) and improves oxygenation by matching perfusion and ventilation of lung units.[4]

With approval of our Research and Ethics Committee, we present our one-year experience with nebulized PGI$_2$, including its utilization in the intensive care unit (ICU) and the operating room (OR).

Methods

We reviewed the medical charts of all patients who received off-protocol nebulized PGI$_2$ from December 1999 to November 2000 in two different hospitals (Notre-Dame Hospital of the Centre Hospitalier de l'Université de Montréal (CHUM) and the Montreal Heart Institute). Demographic data obtained included age, sex and medical history of the patients. We also noted medical conditions that warranted the administration of PGI$_2$, previous or concurrent inhaled nitric oxide (NO) administration, location of use (OR or ICU), method of administration (continuous or bolus) and total dose given. Acute respiratory distress syndrome (ARDS) was defined according to the American European Consensus Conference on ARDS.[5] PHT was defined as systolic pulmonary artery pressure superior to 30 mmHg or mean pulmonary artery pressure (MPAP) above 25 mmHg. We noted the response of inhaled PGI$_2$ on the systemic arterial pressure (SAP) and the pulmonary artery pressure (PAP) or central venous pressure (CVP) if no PAP monitoring was installed. We calculated the MPAP and the mean SAP (MSAP) by adding the diastolic pressure to the third of pulse pressure. To better evaluate the selective action of PGI$_2$ on pulmonary hemodynamics, we calculated the ratio of MSAP over MPAP. Gas exchange variables (ratio of arterial partial oxygen pressure to fraction of inspired oxygen (PaO$_2$/FiO$_2$) or arterial oxygen saturation (SaO$_2$) if no arterial blood gases (ABG) were available) were recorded. The pulmonary and systemic hemodynamics as well as gas exchange variables were noted before

and after the first dose of medication as well as after the best response achieved during treatment. A positive response to PGI$_2$ was defined as a 10% decrease in MPAP or an increase in PaO$_2$/FiO$_2$ >10%.[6] Finally, we noted side effects, length of stay in the hospital and mortality. Patient charts were reviewed until discharge. Those in which the method of administration or the side effects were unexpected, will be described in more detail.

PGI$_2$ (Flolan, Glaxo Wellcome Inc, Mississauga, ON, Canada) was given as epoprostenol salt 1.5 mg dissolved in 100 mL of sterile glycine buffer diluent for a concentration of 15 µg·mL^{-1}. The drug is administered through a conventional in-line nebulizer kit (Ref 8901, Salter Labs, Arvin, CA, USA) with an oxygen flow of 6 L·min^{-1} connected to the inspiratory limb of the ventilator. For continuous administration, the bag containing the drug is attached to an ice pack and delivered directly in the nebulizer through a volumetric pump.

Statistical analysis

Paired Student's t tests were used to evaluate changes in hemodynamic and oxygenation variables. To determine independent predictors of death, we used unpaired Student' t tests to compare means and chi-square tests for proportions. $P < 0.05$ was considered statistically significant.

Results

A total of 37 charts were reviewed. Two were excluded because of insufficient information. Of the 35 remaining patients, 21 (60%) of them were male and 14 (40%) were female. The average age was 56.8 ± 16.5 yr. Inhaled PGI$_2$ was administered to 27 patients (77.1%) for hypoxemia and to eight patients (22.9%) for PHT of various etiologies (Table). Most of the patients were treated in the ICU with only two of them treated in the OR. One was treated both in the ICU and the OR. Twenty-two patients (62.9%) received boluses only (60–120 µg) and four patients (11.4%) were treated with continuous inhalation only (60–210 µg·hr^{-1}). Nine patients (25.7%) received a combination of the two. One patient received direct intratracheal boluses without prior nebulization (60 and 105 µg). One patient was treated before intubation with nebulization via face mask. Nine (25.7%) had NO administration before PGI$_2$ administration. Inhaled PGI$_2$ was added when NO was ineffective and the measures were recorded without any changes in the NO concentration.

Twenty-seven patients (77.8%) were monitored with a PAP catheter while six (17%) had CVP moni-

TABLE

Age	Sex	NO	Main diagnosis	Indication	Improvement? PAP	PO$_2$/FIO$_2$	Hospital length of stay (days)	Mortality
53	F	N	Post-MI VSD	hypoxemia	Y	Y	3	Y
45	F	N	Pickwick	PHT	Y	Y	351	N
69	M	N	ARDS	hypoxemia	Y	Y	26	Y
49	M	N	COPD	hypoxemia	na	Y	35	N
66	F	N	PHT (no specified cause)	PHT	Y	Y	55	Y
74	F	N	ARDS	hypoxemia	na	Y	7	Y
79	F	N	Massive PE, RV insuff.	PHT	Y	N	189	N
37	M	N	Mitro-aortic insuff.	PHT	Y	na	98	N
68	M	Y	ARDS	hypoxemia	Y	Y	13	Y
46	M	Y	Pulmonary edema post CABG	hypoxemia	Y	Y	9	Y
73	M	N	Massive PE	hypoxemia	Y	na	18	Y
54	M	Y	Lung transplant	hypoxemia	N	Y	21	N
66	M	N	Pulmonary edema	hypoxemia	Y	Y	13	Y
61	F	Y	PHT (no specified cause)	hypoxemia; PHT	N	Y	1	Y
49	F	N	ARDS	hypoxemia	Y	Y	3	Y
77	M	N	ARDS post CABG	hypoxemia	Y	Y	9	Y
42	F	Y	ARDS	hypoxemia	Y	Y	28	Y
22	F	N	Lung transplant	hypoxemia	Y	Y	30	N
75	F	N	Cardiogenic choc	hypoxemia	Y	Y	20	Y
24	F	N	Lung transplant	hypoxemia	Y	Y	23	N
54	M	N	ARDS	hypoxemia	Y	Y	16	Y
75	M	N	Aspiration pneumonia	hypoxemia	na	Y	170	N
77	M	N	ARDS	hypoxemia	na	Y	14	Y
31	M	Y	ARDS	hypoxemia	na	Y	49	N
56	M	Y	Pulmonary edema	hypoxemia; PHT	Y	N	1	Y
51	M	N	Lung transplant	hypoxemia	Y	Y	34	N
24	M	N	ARDS	hypoxemia	na	Y	36	N
39	M	Y	Pulmonary edema	hypoxemia	na	N	>107*	N
81	F	N	ARDS	hypoxemia	Y	Y	>62*	N
61	M	N	Pneumonia	hypoxemia	na	Y	>142*	N
60	M	N	ARDS, lung transplant	hypoxemia	Y	Y	21	Y
61	F	N	Postop cardiac surgery	PHT	Y	Y	16	N
68	M	Y	Postop cardiac surgery	PHT	Y	Y	94	Y
55	F	N	Postop cardiac surgery	PHT	Y	Y	18	N
67	M	N	Postop cardiac surgery	PHT	Y	N	17	Y

NO=nitric oxide, PAP=pulmonary artery pressure, PO$_2$=partial pressure of oxygen, FIO$_2$=inspired fraction of oxygen, ARDS=adult respiratory distress syndrome, PHT=pulmonary hypertension, MI=myocardial infarction, VSD=ventricular septal defect, COPD=chronic obstruction pulmonary disease, PE=pulmonary embolism, RV=right ventricular, Postop=postoperative, CABG=coronary artery bypass grafting.

*=Patients still hospitalized at time of evaluation.

toring only. The remaining two patients (6%) had no invasive hemodynamic monitoring. Of the 27 patients whose PAP was monitored, there was a statistically significant decrease in MPAP from before the start of therapy to the first measurement from 34.8 ± 11.8 mmHg to 32.1 ± 11.8 mmHg (P=0.0017) and to the best response 27.5 ± 11.1 mmHg (P <0.0001). Twenty-five (93%) of these patients showed a decrease in MPAP after inhaled PGI$_2$ administration. Twenty-one patients (77.8%) had lowered their MPAP within one hour with a 22% decrease in MPAP on average. The ratio of MSAP to MPAP increased from 2.33 ± 0.87 to 2.53 ± 1.05 (P=0.01) after initial treatment

and to 2.86 ± 1.22 (P=0.003) after the best response was noted. The ratio increased in 77.8% of patients. Of the six patients who had only CVP monitoring, there was an initial lowering from 13.4 ± 5.2 mmHg to 11.6 ± 4.4 mmHg (P=0.15) and further to 7.2 ± 5.1 mmHg (P=0.008).

Thirty-three patients (94.3%) had ABG analyzed before and after inhaled PGI$_2$ administration. The ratio of PaO$_2$/FIO$_2$ improved from 108 ± 81 to 138 ± 105 (P=0.001) initially and to 224 ± 134 (P 0.0001) after best improvement. In total, 87.9% of these patients improved their PaO$_2$/FIO$_2$ ratio with a 174.7% improvement on average observed in respon-

ders. Two patients did not have ABG either before or after treatment. One was a patient treated in the OR who had a SaO_2 of 100% before and after treatment with a FiO_2 of 50% and the other was treated in the ICU and improved his SaO_2 from 95 to 100% with a FiO_2 of 70%.

Six patients (17%) presented hypotension, two had subsequent pneumothoraces, one had bronchospasm and in one patient PGI_2 inhalation was stopped because of increasing peak pulmonary pressures from the secondary flow coming from the nebulizer. Nineteen patients died. On average, the patients who died were older than those who survived (49.35 ± 19.2 yr *vs* 63.2 ± 10.7 yr, *P*=0.02).

Discussion

In December 1999, inhalation of PGI_2 or epoprostenol was added to our therapeutic armamentarium for treatment of PHT and severe hypoxemia of various etiologies. We believe our experience represents the largest published case series of consecutive patients receiving inhaled PGI_2 in the OR and in the ICU. The results presented confirm that this medication can improve oxygenation in patients suffering from hypoxemia in acute pulmonary edema of cardiac or non-cardiac origin, pneumonia, after lung transplant, and in one patient after pulmonary artery thrombectomy following massive pulmonary embolism. It also helped reduce PHT in patients suffering from ARDS, Pickwick's syndrome, massive pulmonary embolism, and after cardiac surgery. Although 92.6% of patients monitored responded with decreasing MPAP, this was associated with an increase in MAP/MPAP in only 74.1% of these, which suggests pulmonary selectivity in most, but not all, cases. It was ineffective in improving oxygenation in four patients including one who had pulmonary edema of neurogenic origin with superimposed pneumonia, one who had pulmonary edema of cardiac origin, one who suffered from massive pulmonary embolism and one who presented with PHT after cardiac surgery with no concomitant hypoxemia. In two patients, PGI_2 had no effect on pulmonary hemodynamics. One had lung transplantation and did not have PHT and the other had pulmonary edema of cardiac origin and superimposed pneumonia as well as severe PHT secondary to pulmonary fibrosis and CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal motility disorder, Sclerodactyly and Telangiescasia of scleroderma). Recently, Domenighetti suggested that patients with ARDS of pulmonary origin (primary ARDS) will tend to have no response to PGI_2 as opposed to those with ARDS from an extrapulmonary origin (secondary ARDS).[6] They observed that the computed tomo-

graphic appearance of patients with primary ARDS showed more extensive consolidation. Their study however was limited to 15 patients. Also, Walmrath *et al.* noted that patients with underlying pulmonary fibrosis complicated by pneumonia tended to have a diminished response to inhaled PGI_2 compared with those having pneumonia without underlying pulmonary pathology.[7]

Prostacyclin is known to be a powerful vasodilator through an increase in intracellular cyclic adenosine monophosphate (cAMP). When given systemically, it can have adverse effects such as hypotension and worsening of intrapulmonary shunt. Recently, it has been given by inhalation after nebulization both in animals and humans and this has been shown to increase pulmonary selectivity. PGI_2 is not inactivated in the lung like other prostaglandins but is spontaneously hydrolyzed at physiologic pH to an inactive metabolite, 6-ketoPGF1$_\alpha$. Therefore, when given by inhalation, it tends to be absorbed locally in ventilated areas and is inactivated by the time it reaches the systemic circulation in significant amounts. Many animal models[7–13] of hypoxemia and PHT and human studies have confirmed that inhaled PGI_2 can improve oxygenation and decrease PHT in many subjects including those suffering from ARDS and PHT of various causes.

Case series are predominant in the literature on PGI_2. Pappert *et al.*[14] suggested that side effects and toxicity should be studied more extensively. One of our patients had bronchospasm on two occasions after receiving inhaled prostacyclin. She had a history of CREST syndrome, PHT secondary to lung fibrosis, coronary artery disease, hypertension and diabetes but was not a known asthmatic. A study by Hardy *et al.*[15] demonstrated that PGI_2 could exhibit both bronchoconstrictor and antibronchoconstrictor properties when inhaled. They demonstrated that, in asthmatics, inhaled PGI_2 can prevent metacholine or PGD_2 induced bronchospasm. On the other hand, small airway resistance as measured by forced expiratory volume in one second (FEV_1) and maximum expiratory flow at 30% vital capacity (V_{max30}) was increased while larger airway resistance, measured by specific airway conductance remained unchanged. They hypothesized that pulmonary vasodilation could enhance the clearance of inhaled bronchoconstrictors while causing engorgement of small airways, thereby increasing resistance. On the other hand, Burghuber did not observe any changes in pulmonary function tests in normal volunteers receiving inhaled PGI_2.[16]

Six patients had hypotension after treatment with inhaled PGI_2. It is noteworthy that these patients were suffering from hypotension before the start of therapy. There was a patient with postmyocardial infarction per-

sisting ventricular septal defect who had an intra-aortic balloon pump, a postoperative cardiac surgical patient on vasoactive support, a patient who had dilated cardiomyopathy and suspected septic shock and two patients with septic shock. Hypotension has rarely been encountered after inhaled PGI_2 as opposed to *iv* PGI_2 treatment.[17] It is possible that ventricular dysfunction in these patients was associated with an improvement in cardiac output through a reduction in afterload, which has been reported with PGI_2. Such a reduction in afterload could be associated with a fall in blood pressure but not in cardiac output. This is what we observed in one patient who had hypotension while receiving direct intratracheal boluses. The hypotension was associated with a 25% increase in cardiac index. It is also possible that with direct intratracheal administration or with relatively large nebulized doses that systemic absorption occurred because PGI_2 is not inactivated by pulmonary epithelium. This "spillover" into the systemic circulation has been described.[18]

Inhaled NO has received a fair amount of interest in the last few years as a treatment of ARDS and PHT because of its ability to provoke selective pulmonary vasodilation.[19] Its effect remains localized because it is inactivated by hemoglobin as soon as it reaches the circulation. It may, however, have toxic metabolites and can cause methemoglobinemia, especially when given at high concentrations for a long period of time and necessitates specialized and costly equipment to administer. Prostacyclin, on the other hand, has no known toxic metabolites and very few side effects. It can be administered easily by simple nebulization with minimal extra equipment, which is interesting for utilization in the OR. A full 24-hr of treatment, is estimated to cost $115.00 CDN. Several studies have compared NO and PGI_2. Some authors have observed a better reduction in PAP with inhaled PGI_2[17,20,21] while some show no significant difference between the two agents.[18,22] Improvement in oxygenation sometimes appears to be better with NO,[20] or with inhaled PGI_2.[23] Others showed no differences between the two agents.[22] It should be noted that in all these studies, the administration of inhaled PGI_2 was not controlled or randomized and that the doses used are not necessarily equipotent to NO.

Our study has several limitations. First, it is a retrospective study. Second, patients had very different pathologies bringing about the use of inhaled prostacyclin. This may explain why some responded sooner than others and why others required escalating doses of prostacyclin, becoming somewhat resistant to the drug. Some authors have reported inhaled PGI_2 to be associated with *in vitro* hemostatic disturbances[16,23]

but this remains controversial. We did not explore this aspect. In addition, we could not determine the aerosol fraction that was deposited in the lung. This has been estimated to be less than 5% in mechanically ventilated patients.[24,25]

In summary, inhaled prostacyclin is a useful and affordable addition to anesthesiologists and intensivists in the treatment of PHT and hypoxia of various origins. Systemic absorption can occur despite administration by the inhaled route. Further studies are required to determine dose-responsiveness, optimal condition of utilization and impact on survival.

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