Intensive Care Med (1996) 22:353–355

BRIEF REPORT

S. A. R. Webb
S. Stott
P. V. van Heerden

The use of inhaled aerosolized prostacyclin (IAP) in the treatment of pulmonary hypertension secondary to pulmonary embolism

Received: 4 October 1994
Accepted: 23 November 1995

S. A. R. Webb · S. Stott
P. V. van Heerden (✉)
Department of Intensive Care,
Sir Charles Gairdner Hospital,
Verdun St., Nedlands 6009,
Western Australia

Abstract *Objective:* To describe the use of inhaled aerosolized prostacyclin (IAP) in a patient with life-threatening pulmonary hypertension secondary to pulmonary embolism and to discuss the possible use of inhaled prostacyclin in the management of pulmonary embolism.
Design: Case report.
Setting: Intensive care unit of a university teaching hospital.
Patients: One patient with severe pulmonary hypertension secondary to acute-on-chronic pulmonary embolism.
Interventions: Conventional medical management of massive pulmonary embolism and inhaled aerosolized prostacyclin (IAP).
Measurements and results: Description of clinical course, haemodynamic data and gas exchange data.
Conclusions: We describe a patient with massive pulmonary embolism for whom the addition of IAP to his therapy appeared to result in a transient improvement in pulmonary haemodynamics and gas exchange.

Key words Inhaled prostacyclin · Pulmonay embolism · Pulmonary hypertension

Introduction

Prostacyclin (PGI_2) is known to have a vasodilator effect on both arteries and veins and as such has a powerful effect on the pulmonary vasculature, lowering pulmonary artery pressures. When given intravenously to patients with primary pulmonary hypertension, PGI_2 lowers mean pulmonary artery pressures and resistance, increases cardiac index and increases calculated oxygen delivery [1, 2].

Because of its effects on systemic resistance when given intravenously, its effectiveness as a pulmonary vasodilator has been limited. However, when given by aerosol to patients with adult respiratory distress syndrome (ARDS), there is a fall in mean pulmonary artery pressure and pulmonary vascular resistance, associated with an improvement in oxygenation [3]. This is accomplished without a deleterious fall in systemic arterial pressure [3].

We describe a case of acute pulmonary hypertension and acute right ventricular failure, secondary to pulmonary embolism, which was treated with inhaled aerosolized prostacyclin (IAP).

Case report

A 65-year-old man was admitted to the intensive care unit (ICU) after collapsing on the ward. He was unconscious, cyanosed with gasping respirations and had a blood pressure of 70/40 mmHg. Intravenous access was established, intravenous saline was administered and controlled ventilation via endotracheal tube established. He had been admitted 24 h earlier for investigation of increasing shortness of breath, which had been worsening over the preceding 2 weeks. His past history included chronic lung disease and a history of asbestos exposure. He had been a life-long smoker, but had recently stopped because of the worsening shortness of breath. It had been noted on admission that he had signs of right heart failure with a raised jugular venous pressure and oedematous ankles.

On admission to the ICU, 30 min after his collapse, he was sedated and mechanical ventilation continued. His blood pressure was 130/80 mmHg with a pulse rate of 130 beats/min. Grossly distended neck veins were noted, as were plethoric facies and conjunctival oedema. Immediately after admission he became acutely hypotensive, associated with a fall in end-tidal carbon dioxide from 30 to 11 mmHg. Intravenous boluses of adrenaline were used to restore blood pressure. A diagnosis of pulmonary embolus was made clinically and 50 mg tissue plasminogen activator (tPA) was administered intravenously. A pulmonary artery catheter was inserted, which showed pulmonary artery pressures approaching systemic pressures (Table 1).

In the 3 h following administration of tPA there was no improvement in pulmonary hypertension. At this stage, PGI_2 at 200 ng/kg per min was aerosolised continuously into the inspiratory limb of the breathing circuit on an attempt to reduce pulmonary artery pressures (Fig. 1). Prostacyclin (500 µg) was mixed with 50 ml of 0.147% sodium chloride and glycine 0.188% buffer solution and delivered continuously via an infusion pump into a jet nebulizer (Airlife Misty-Neb Nebulizer, Baxter, USA). Within 5 min of starting PGI_2 there was a sustained reduction in measured pulmonary arterial pressure from a mean of 59 mmHg to 46 mmHg with no change in systemic mean arterial pressures, which remained in the range of 75 to 80 mmHg. Over the next 4 h, in conjunction with the reduction in pulmonary artery pressures, there was an improvement in oxygenation and a fall in the calculated pulmonary vasculature resistance index (Tables 1, 2). There was no overall change in cardiac output as measured by thermodilution.

Heparin, by intravenous infusion at a rate of 1000 units per h, was started. An echocardiogram demonstrated a dilated right ventricle with tricuspid regurgitation and dilated pulmonary artery trunk. A modified ventilation : perfusion scan showed multiple perfusion defects throughout both lungs. Pulmonary angiography was not performed, as he was considered too unstable to be moved from the ICU to the radiology suite.

Over the next 24 h the patient's condition stabilised, but he required inotropic support with adrenaline at levels up to 0.3 µg/kg/min to maintain cardiac and renal function. IAP was titrated to keep pulmonary artery systolic pressures below 70 mmHg. Systemic hypotension was noted at doses of IAP over 200 ng/kg per min.

Unfortunately, his condition then suddenly deteriorated, with progressive hypotension despite high-dose adrenaline support. He developed marked sacral and ankle oedema and his right heart filling pressures increased. At this time consideration was given to performing surgical embolectomy, but before this could be done he became asystolic and resuscitation was unsuccessful.

Post-mortem examination revealed a large embolus stradding the bifurcation of the pulmonary artery with extension into the major branches of the left and right pulmonary arteries. This consisted of both fresh and organised clot.

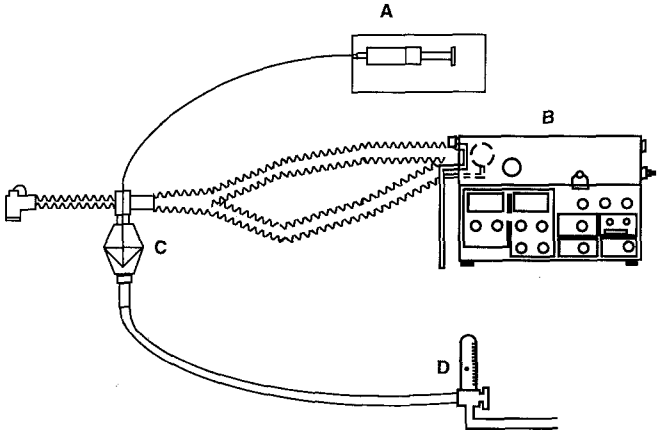

Fig. 1 **A** Prostacyclin in syringe pump. **B** Mechanical ventilator. **C** Nebuliser. **D** Oxygen gas source (6 l/min)

Table 1 Haemodynamic data prior to starting PGI_2 and at 4, 12 and 24 h during inhaled PGI_2 therapy. *PAP* pulmonary artery pressure, *CI* cardiac index, *AP* systemic arterial pressure, *PAOP* pulmonary capillary wedge pressure, *CVP* central venous pressure

	pre-PGI_2	4 h	12 h	24 h
Mean PAP (mmHg)	59	48	54	53
CI (l/min/m^2)	2.3	2.4	2	2.3
Mean AP (mmHg)	79	81	77	71
PAOP (mmHg)	18	20	21	15
CVP (mmHg)	24	22	17	17

Table 2 Gas-exchange data prior to starting PGI_2 and at 6 and 12 h during inhaled PGI_2 therapy. *FIO_2* Fractional inspired concentration of oxygen, *$PaCO_2$* arterial partial pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen

	pre-PGI_2	6 h	12 h
FIO_2	1.0	0.8	0.6
$PaCO_2$ (mmHg)	55.0	37.9	37.6
PaO_2 (mmHg)	66.2	124.8	135.2

Discussion

Acute and chronic pulmonary emboli are known causes of pulmonary hypertension [4]. Pulmonary hypertension increases right ventricular filling pressures, right ventricular stroke work and oxygen consumption and can precipitate right heart failure and death [1].

Prostacyclin is a known systemic and pulmonary vasodilator. Its use has been limited when given intravenously because of systemic hypotension. When given by inhalation, reduction in pulmonary artery pressures have been reported without significant concomitant falls in systemic pressures in both dogs [5] and humans [3]. These are reports of pulmonary hypertension as a result of hypoxic pulmonary vasoconstriction and ARDS, respectively. To our knowledge, inhaled prostacyclin has not been used before to treat pulmonary hypertension secondary to pulmonary embolism.

In acute pulmonary hypertension a reduction in pulmonary artery pressures is necessary to preserve right heart function. Any reduction in systemic pressures will cause reduction in right coronary artery blood flow as the normal gradient between aorta and right ventricle is reduced. Consequently, therapeutic interventions that can selectively reduce pulmonary artery pressures without affecting systemic pressures may improve the chance of

right ventricular recovery. Embolectomy and thrombolysis are currently used for reducing right ventricular afterload in patients with pulmonary embolic disease. However, despite thrombolysis, some patients will be left with persisting excessive right ventricular afterload.

Inhaled nitric oxide has been demonstrated to reduce pulmonary vascular resistance without adverse effects on systemic arterial pressures [6]. Administration of nitric oxide is not without difficulties. It is potentially toxic and specialised monitoring and delivery equipment are required for its administration. In our experience prostacyclin was easily administered as an aerosol into the inspiratory limb of the breathing circuit of a mechanical ventilator. However, we were not able to collect data regarding particle size or lung distribution of particles for the nebulizer system described in our case report. In addition, we do not know if the aerosol properties of this nebulizer change with continuous use. Although the determination of particle size and lung distribution is of major importance, the demonstration of physiological effects argues for effective drug delivery by this route. However, it is not possible to determine, in our case, the "real" dose of deposited IAP, nor is it possible to compare our nebulised dose with that administered by others. This is of interest, as the dose of IAP which we administered is considerably higher than previously reported doses [3]. It is possible that such differences in the administered dose reflect variations in the effectiveness of different nebuliser systems. The "gold standard" in this setting would be to determine the site of deposition of the active agent using a technique such as radiolabelling. The side-effect of most concern with prostacyclin, systemic hypotension, is easily monitored in the ICU.

The patient described had evidence of chronic pulmonary artery hypertension, which was most likely due to recurrent pulmonary emboli, as evidenced by the abnormal ventilation/perfusion scan. A further massive embolus then produced an acute rise in pulmonary artery pressures, precipitating acute right heart failure and his subsequent admission to ICU.

It must be emphasised that the potentially selective pulmonary vasodilating effects of IAP are at present experimental. Furthermore, the safety profile for inhalation of prostacyclin and its buffer solution remains to be determined. It was our clinical impression that IAP resulted in an improvement in pulmonary vascular resistance and that this improvement was maintained for approximately 24 h with the maximal response occurring 4 h after administration (Table 1). Despite the initial improvement seen with administration of IAP, the patient developed refractory right heart failure. However, we feel that this progression was probably due to the severity of the pulmonary embolism, despite thrombolysis and heparin, with a large saddle embolus being identified at post-mortem examination. We think that IAP may be of benefit in certain circumstances to lower pulmonary pressures acutely without lowering systemic pressures. We await with interest the outcome of controlled trials to assess whether our clinical impression is confirmed.

References

1. Jones DK, Higgenbottom TWJ, Wallwork J (1987) Treatment of primary pulmonary hypertension with intravenous epoprostenol (prostacyclin). Br Heart J 57:270–278
2. Rubin CJ, Mendoza J, Hood M, McGown M, Barst R, Williams WB, Diehl JH, Crow J, Lang W (1990) Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomised trial. Ann Intern Med 112:485–491
3. Walmrath D, Scheider T, Pilch J, Grimminger F, Seeger W (1993) Aerosolised prostacyclin in adult respiratory distress syndrom. Lancet 342:961–962
4. McKintyre KM Sasahara AA (1971) The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol 28:288–294
5. Welte M, Zwissler B, Habazettl H, Messmer K (1993) PGI_2 Aerosol versus nitric oxide for selective pulmonary vasodilatation in hypoxic pulmonary vasoconstriction. Eur Surg Res 25: 329–340
6. Frostell C, Fratocci MD, Wain JC, Jones R, Zapol WM (1991) Inhaled nitric oxide: a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 83:2038–2047