Original Articles

Acute effects of nebulised epoprostenol in pulmonary hypertension due to systemic sclerosis

K. PARAMESWARAN*, I. PURCELL†, M. FARRER†, C. HOLLAND*, I. K. TAYLOR* AND N. P. KEANEY*

Departments of *Respiratory Medicine, †Cardiology and Rheumatology, Royal Sunderland Hospital, Sunderland, U.K.

Pulmonary hypertension often has a lethal outcome in systemic sclerosis and the treatment is challenging. Epoprostenol is a potent pulmonary vasodilator and its efficacy has been demonstrated when delivered by the intravenous and aerosolized routes. We report the haemodynamic and functional benefits of epoprostenol administered by inhalation to a spontaneously breathing patient with partially reversible pulmonary hypertension due to systemic sclerosis. Aerosolized epoprostenol, equivalent to the maximum tolerated intravenous dose (31.2 µg), produced a 58% fall in pulmonary vascular resistance, increased the cardiac output by 42% and improved functional performance by one MET (3.5 ml kg^-1 min^-1 of oxygen uptake) without any significant side-effects. Selective distribution of epoprostenol by the inhaled route may offer a new strategy for treatment of pulmonary hypertension.

Introduction

Pulmonary hypertension has been observed in 55–80% of patients with systemic sclerosis (1) either with or without associated parenchymal and interstitial involvement. While there is no cure for pulmonary hypertension associated with systemic sclerosis and other connective tissue diseases, several pharmacological (2) and surgical (3) approaches to treatment have been developed over the last decade which have proved beneficial in a significant proportion of patients. In particular, vasodilator therapy may produce sustained haemodynamic and symptomatic improvement in up to approximately two-thirds of patients. The most promising results have been obtained with intravenous administration of epoprostenol (3–5) and a synthetic analogue, Iloprost (6). Intravenous epoprostenol (prostacyclin) has been administered acutely to assess reversibility in pulmonary artery pressures (7) and chronically for the treatment of pulmonary hypertension (3–5), and chronic improvement in exercise capacity in patients with severe heart failure and right ventricular dysfunction (10). There is less information on the haemodynamic and functional effects of aerosolized prostacyclin (11–13). The safety and efficacy of nebulised epoprostenol (Flolan, Wellcome Laboratories, Beckenham, Kent, U.K.) has already been demonstrated in ventilated patients with adult respiratory distress syndrome (14) and in patients with severe pulmonary hypertension (15).

We report both haemodynamic and functional benefits of epoprostenol delivered by inhalation to a spontaneously breathing patient with pulmonary hypertension due to systemic sclerosis.

Case Report

A 53-year-old Nigerian woman presented in 1991 with an illness clinically and immunologically suggestive of mixed connective tissue disease associated with exertional dyspnoea. Initial investigations showed a normochromic, normocytic anaemia, ESR of 30 mm, leukopenia, positive nucleolar pattern of staining for anti-nuclear factor in a
Control Dose fell by 53% with intravenous sodium nitroprusside in PVR compared with the previous study. We used a Wright's nebuliser (Aerosol Products Ltd., London, U.K.) driven by a compressor at a calibrated flow rate of 71 min⁻¹ and 17 psi to deliver the aerosols via a face mask during tidal breathing. The output of the nebuliser was checked by the conventional weight loss method and the concomitant loss of solute by evaporation during the nebulisation was measured by using a fluoride tracer aerosol impaction method (17). The nebuliser gave an output of 120–150 ml min⁻¹, of which 67% was lost by evaporation. The effective nebulised dose was 40–50 μl min⁻¹ (33%). The respiratory pattern during tidal breathing was monitored using a spiograph and the inspiratory–expiratory ratio was calculated as 1:3. The effective amount of the drug delivered to the airways was therefore about 85 (25% of 33%) of the volume nebulised.

Doses were administered over 10 min and the volume of residue recorded. Between each administration, haemodynamic values were allowed to return to baseline. A pulse oximeter was used to monitor arterial oxygen saturation (SpO₂). FEV₁ was measured after each nebulisation using a Vitalograph dry rolling spirometer. Table 1 shows the haemodynamic effects observed together with the changes in oxygen saturation. The duration of effect varied with the dose of epoprostenol: 19 min for 50 μg, 26 min for 100 μg, 38 min for 200 μg and 39 min for 400 μg.

The patient was subsequently exercised on a treadmill according to the modified Naughton protocol (18). The work load was quantified as metabolic equivalents (MET, 1 MET = 3.5 ml kg⁻¹ min⁻¹ of oxygen uptake). The exercise started at less than 2 METs at 2 mph and zero gradient and increased by 1-0 to 1-5 METs between stages. The exercise was preceded by 2 min of warm-up and each stage lasted for 2 min. Systolic PAP at rest and post-exercise were measured from Doppler estimate of the regurgitant pressure across the tricuspid valve. At the same time the following day, epoprostenol (200 μg) was nebulised over 10 min as previously described, PAP measured and exercise

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean RAP (mm Hg)</th>
<th>Mean PAP (mm Hg)</th>
<th>Mean PAWP (mm Hg)</th>
<th>HR (bpm)</th>
<th>SBP (mean)</th>
<th>CI (1 min⁻¹ m⁻²)</th>
<th>FEV₁ (litres)</th>
<th>SaO₂ (%)</th>
<th>PVR (dyne s⁻¹ cm⁻⁵)</th>
<th>SVR (dyne s⁻¹ cm⁻⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (diluent) 50 μg</td>
<td>11 58/27 (41)</td>
<td>8 57/24 (35)</td>
<td>8 54/21 (41)</td>
<td>9 57/28 (38)</td>
<td>12 60 (67)</td>
<td>12 69 (67)</td>
<td>127/70 (89)</td>
<td>3.53</td>
<td>93</td>
<td>521-6 (63%)</td>
</tr>
<tr>
<td></td>
<td>100 μg 15 76/74 (57)</td>
<td>12 69 (67)</td>
<td>127/70 (89)</td>
<td>9 57/28 (38)</td>
<td>12 69 (67)</td>
<td>127/70 (89)</td>
<td>3.57</td>
<td>99</td>
<td>64 (54%)</td>
<td>1728 (24%)</td>
</tr>
<tr>
<td></td>
<td>200 μg 8 57/28 (36)</td>
<td>12 71 (67)</td>
<td>126/64 (85)</td>
<td>8 54/21 (41)</td>
<td>12 71 (67)</td>
<td>126/64 (85)</td>
<td>3.57</td>
<td>99</td>
<td>588 (58%)</td>
<td>1616 (29%)</td>
</tr>
<tr>
<td></td>
<td>400 μg 8 54/21 (41)</td>
<td>12 71 (67)</td>
<td>126/64 (85)</td>
<td>8 54/21 (41)</td>
<td>12 71 (67)</td>
<td>126/64 (85)</td>
<td>3.57</td>
<td>99</td>
<td>588 (58%)</td>
<td>1616 (29%)</td>
</tr>
</tbody>
</table>


In October 1994 she developed right-sided heart failure. She was treated with frusemide 40 mg, nifedipine 5 mg twice daily and prednisolone 10 mg once daily. An invasive haemodynamic study was performed using a triple lumen thermodilution Swan-Ganz catheter to record the following pressures (systolic/diastolic, mean) (mm Hg): right atrial pressure (RAP) 12/2, 8; pulmonary arterial pressure (PAP) 66/36, 46; femoral arterial pressure (FAP) 126/165, 86; mean pulmonary artery wedge pressure (PAWP) 10, cardiac index (CI) 2.9 l min⁻¹ m⁻². Pulmonary vascular resistance (PVR) was calculated to be 992 dyne s⁻¹ cm⁻⁵ and pulmonary vascular resistance (PVR) was calculated to be 992 dyne s⁻¹ cm⁻⁵ and fell by 53% with intravenous sodium nitroprusside (2.5 ng kg⁻¹ min⁻¹). Intravenous epoprostenol lowered pulmonary vascular resistance (PVR) in a dose-dependent manner, by 39% at 4, 48% at 8 and 57% at 12 ng kg⁻¹ min⁻¹ (representing a total dose of 31.2 pg). The beneficial effect of sodium nitroprusside was accompanied by a symptomatic fall in FAP (to 89/45, 58) whereas epoprostenol only caused a 13% fall in mean FAP, but there was unpleasant flushing, nausea, and abdominal cramps at doses of 8 and 12 ng kg⁻¹ min⁻¹.

The patient was then commenced on nifedipine 40 mg four times a day for 2 months and then the dose was reduced to 10 mg four times a day. Subsequently, in June 1995, the efficacy of epoprostenol made up in a vehicle of glycine and NaCl (pH 10.5) and driven by a compressor at a calibrated flow rate of 71 min⁻¹ and 17 psi to deliver the aerosols via a face mask during tidal breathing. The output of the nebuliser was checked by the conventional weight loss method and the concomitant loss of solute by evaporation during the nebulisation was measured by using a fluoride tracer aerosol impaction method (17). The nebuliser gave an output of 120–150 μl min⁻¹, of which 67% was lost by evaporation. The effective nebulised dose was 40–50 μl min⁻¹ (33%). The respiratory pattern during tidal breathing was monitored using a spiograph and the inspiratory–expiratory ratio was calculated as 1:3. The effective amount of the drug delivered to the airways was therefore about 85 (25% of 33%) of the volume nebulised.

In October 1994 she developed right-sided heart failure. She was treated with frusemide 40 mg, nifedipine 5 mg twice daily and prednisolone 10 mg once daily. An invasive haemodynamic study was performed using a triple lumen thermodilution Swan-Ganz catheter to record the following pressures (systolic/diastolic, mean) (mm Hg): right atrial pressure (RAP) 12/2, 8; pulmonary arterial pressure (PAP) 66/36, 46; femoral arterial pressure (FAP) 126/165, 86; mean pulmonary artery wedge pressure (PAWP) 10, cardiac index (CI) 2.9 l min⁻¹ m⁻². Pulmonary vascular resistance (PVR) was calculated to be 992 dyne s⁻¹ cm⁻⁵ and fell by 53% with intravenous sodium nitroprusside (2.5 ng kg⁻¹ min⁻¹). Intravenous epoprostenol lowered pulmonary vascular resistance (PVR) in a dose-dependent manner, by 39% at 4, 48% at 8 and 57% at 12 ng kg⁻¹ min⁻¹ (representing a total dose of 31.2 μg). The beneficial effect of sodium nitroprusside was accompanied by a symptomatic fall in FAP (to 89/45, 58) whereas epoprostenol only caused a 13% fall in mean FAP, but there was unpleasant flushing, nausea, and abdominal cramps at doses of 8 and 12 ng kg⁻¹ min⁻¹.

The patient was then commenced on nifedipine 40 mg four times a day for 2 months and then the dose was reduced to 10 mg four times a day. Subsequently, in June 1995, the efficacy of epoprostenol made up in a vehicle of glycine and NaCl (pH 10.5) and delivered by a jet nebuliser was studied. Baseline haemodynamics were measured as before and demonstrated a 15% rise in systolic PAP, 9% rise in mean PAP and a 41% rise in PVR compared with the previous study. We used a Wright's nebuliser (Aerosol Products Ltd., London, U.K.) driven by a compressor at a calibrated flow rate of 71 min⁻¹ and 17 psi to deliver the aerosols via a face mask during tidal breathing. The output of the nebuliser was checked by the conventional weight loss method and the concomitant loss of solute by evaporation during the nebulisation was measured by using a fluoride tracer aerosol impaction method (17). The nebuliser gave an output of 120–150 μl min⁻¹, of which 67% was lost by evaporation. The effective nebulised dose was 40–50 μl min⁻¹ (33%). The respiratory pattern during tidal breathing was monitored using a spiograph and the inspiratory–expiratory ratio was calculated as 1:3. The effective amount of the drug delivered to the airways was therefore about 85 (25% of 33%) of the volume nebulised.

Doses were administered over 10 min and the volume of residue recorded. Between each administration, haemodynamic values were allowed to return to baseline. A pulse oximeter was used to monitor arterial oxygen saturation (SpO₂). FEV₁ was measured after each nebulisation using a Vitalograph dry rolling spirometer. Table 1 shows the haemodynamic effects observed together with the changes in oxygen saturation. The duration of effect varied with the dose of epoprostenol: 19 min for 50 μg, 26 min for 100 μg, 38 min for 200 μg and 39 min for 400 μg.

The patient was subsequently exercised on a treadmill according to the modified Naughton protocol (18). The work load was quantified as metabolic equivalents (MET, 1 MET = 3.5 ml kg⁻¹ min⁻¹ of oxygen uptake). The exercise started at less than 2 METs at 2 mph and zero gradient and increased by 1-0 to 1-5 METs between stages. The exercise was preceded by 2 min of warm-up and each stage lasted for 2 min. Systolic PAP at rest and post-exercise were measured from Doppler estimate of the regurgitant pressure across the tricuspid valve. At the same time the following day, epoprostenol (200 μg) was nebulised over 10 min as previously described, PAP measured and exercise
Table 2. Response to exercise at baseline and 8 min after 10 min of nebulisation of 200 µg epoprostenol

<table>
<thead>
<tr>
<th>Level of exercise (mph, % gradient)</th>
<th>Baseline</th>
<th>After nebulisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of exercise</td>
<td>2, 14% 11 min, 24 s</td>
<td>2, 17% 12 min, 25 s</td>
</tr>
<tr>
<td>METs</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>HR</td>
<td>147</td>
<td>149</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>110</td>
<td>130</td>
</tr>
<tr>
<td>Δ Systolic PAP (mm Hg)</td>
<td>+47</td>
<td>+63</td>
</tr>
<tr>
<td>Δ SpO₂ (%)</td>
<td>-4</td>
<td>-4</td>
</tr>
</tbody>
</table>

was commenced 8 min after the nebulisation was complete. Table 2 shows the changes in exercise tolerance, heart rate, blood pressure and SpO₂, and PAP before and after the nebulisation.

Discussion

This case report highlights several interesting aspects of clinical features and treatment of pulmonary hypertension with systemic sclerosis. We have shown that nebulised epoprostenol is safe and effective in improving haemodynamics in systemic sclerosis and can be employed as a screening method for assessment of reversibility in pulmonary haemodynamics. Secondly, we have demonstrated that it can be delivered to spontaneously breathing patients, thereby making it an alternate method of long-term administration of this drug. Thirdly, we have demonstrated objectively an improvement in the functional performance following aerosolised administration of the drug.

In this study, the maximum improvements in PAP and PVR were observed with 100 µg of nebulised epoprostenol, whereas the maximum improvements in CI and SpO₂ were observed with 400 µg which was the highest dose of nebulised epoprostenol (effective airway dose of 32 µg). This was roughly equivalent to the maximum tolerated intravenous dose (31.2 µg) and produced a 58% fall in pulmonary vascular resistance and increased cardiac output by 42% without causing any systemic symptoms, although a dose-dependent fall in FEV₁ was observed. These observations are comparable to previously reported results (11). In addition to producing acute lowering of pulmonary artery pressure and resistance, 200 µg of epoprostenol (effective airway dose of 16 µg) caused an increase in exercise tolerance by one MET, 8 min after completion of nebulisation. Although this is only a modest improvement in exercise performance and the study was not placebo-controlled, this observation could have important clinical implication in the management of pulmonary hypertension.

The duration of effect increased with the dose of epoprostenol. The vasodilatation persisted twice as long after 400 µg of nebulised epoprostenol (39 min) compared to 50 µg (19 min). Local deposition of epoprostenol will increase with higher doses of the drug and persistence of the higher local concentration produces longer lasting vasodilator effects. This is further exemplified by the observation that the oxygen saturation improved progressively throughout the study, exhibiting a dose-related increment which did not return to baseline by the time the next dose was administered.

In summary, this case demonstrates that inhaled epoprostenol delivered to a spontaneously breathing patient with progressive pulmonary hypertension due to systemic sclerosis was safe and produced clinically significant pulmonary vasodilatation, an improvement in effort tolerance and a sustained increase in arterial oxygenation presumably by improving V/Q mismatch. These data and the observation that the inhaled route of administration avoided the side-effects associated with the intravenous use indicate that aerosolized epoprostenol can be safely and effectively used as a screening agent for assessing reversibility of pulmonary hypertension and that further acute and chronic studies are required.

References