The Effects of Flosequinan on Hemodynamics and Oxygen Delivery in Cor Pulmonale*

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The hemodynamic effects of a new orally active vasodilator, flosequinan, were compared with placebo (single blind) over 24 h in eight patients with pulmonary hypertension secondary to severe chronic obstructive pulmonary disease. Mean pulmonary artery pressure was reduced by 5.1 (3.4, 6.7) mm Hg (mean 95 percent CI) (p<0.003) and pulmonary vascular resistance was reduced by 70 (23, 189) dynes·sec·cm⁻⁵ (p<0.013) by active drug compared with placebo. Cardiac output increased significantly with flosequinan by 0.47 (0.03, 0.91) L/min (p<0.04) and systemic oxygen delivery increased by 90 (50, 120) ml/min/m² (p<0.05). A significant reduction in systemic vascular resistance was observed, 132 (35,230) dynes·sec·cm⁻⁵ (p<0.02) but no significant changes were seen in systemic arterial blood pressure or arterial blood gas tensions. Flosequinan favorably altered pulmonary hemodynamics relative to systemic and resulted in a significant improvement in oxygen delivery. The hemodynamic and blood gas effects of this compound suggest that it is a promising vasodilator for the treatment of pulmonary hypertension.

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Pulmonary hypertension is a common complication of hypoxic chronic obstructive pulmonary disease (COPD). Long-term oxygen therapy is the only proven treatment for this condition that improves symptoms and reduces mortality. Long-term oxygen therapy has only a modest effect on pulmonary artery pressure with little other significant hemodynamic effects and it is thought to confer its therapeutic effects by improving oxygen saturation and consequently systemic oxygen delivery. Despite oxygen therapy, however, many patients continue to have symptoms of breathlessness and fatigue and have repeated episodes of cor pulmonale with associated edema and further elevation of pulmonary artery pressures.

Elevated pulmonary artery pressure (PAP) is a major factor determining the prognosis of patients with pulmonary hypertension secondary to COPD, but it is not clear if reducing PAP improves survival. A number of vasodilator drugs have been assessed in the treatment of pulmonary hypertension but there is little agreement regarding their therapeutic role. Many reports of the short-term effects of vasodilators on pulmonary artery pressure have been published but most have compared the effects of drug with baseline measurements without a placebo comparison. Most studies have concentrated on the effects of treatment on central hemodynamics and not fully assessed changes in oxygen delivery, which may be more important than pulmonary artery pressure in determining survival.

Flosequinan (7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone, BTS49465) is a new orally active direct vasodilator with balanced venous and arterial actions. The vasodilator profile of flosequinan is similar to that of sodium nitroprusside, and appears to work via cyclic guanine monophosphate (GMP). It has a half-life of 1.6 h and is converted by oxidation to an active sulfone metabolite (BTS53554) that has a half-life of 37.6 h. The hemodynamic actions of this compound were sustained over a 24-h period when given at a dose of 1.5 mg/kg. Flosequinan given orally at this dose in patients with congestive cardiac failure produced a significant increase in cardiac index (CI) (26 percent) and significant reductions in PAP (−31 percent), pulmonary vascular resistance (PVR) (−24 percent), and systemic vascular resistance (SVR) (−28 percent). Further studies have demonstrated sustained improvements in both hemodynamics and exercise tolerance in such patients treated with flosequinan 100 mg to 125 mg once daily.

The pulmonary vasodilator profile of this drug has been examined in hypoxic dogs. Flosequinan attenuated the hypoxic vasoconstrictor response to alveolar hypoxia in this model, reducing PAP by 22 percent and PVR by 36 percent. A significant improvement in systemic oxygen delivery (Do2) was also demonstrated. In view of these findings, we postulated that flosequinan might be a useful vasodilator for the treatment of acute respiratory failure in hypoxic disorders.

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treatment of pulmonary hypertension secondary to COPD. As the effects of flosequinan had not previously been studied (to our knowledge) in human subjects with pulmonary arterial hypertension, the aim of this study was to evaluate the short-term effects of flosequinan on hemodynamics and oxygen delivery in patients with pulmonary hypertension secondary to COPD.

### Material and Methods

#### Patients

We studied eight patients (five male) with COPD secondary to chronic bronchitis of at least two years' duration. All had previously been admitted to the hospital with an episode of cor pulmonale, documented peripheral edema, raised jugular venous pressure, and hypoxemia \( (\text{PaO}_2 < 7.2 \text{ kPa breathing room air}) \) at that time. Patients were clinically stable for at least four weeks at the time of the study and were receiving long-term oxygen therapy \( (>15 \text{ h day}) \) for at least six months. All were receiving diuretics and had no evidence of peripheral edema. Demographic details are shown in Table 1.

Patients with a history of myocardial infarction, impairment of left ventricular function by echocardiogram or radionuclide ventriculography, systemic hypertension, cardiac valvular disease, or current smokers were excluded. Informed consent was obtained from each patient and the study protocol was approved by the Queen's University of Belfast Ethical Committee.

#### Catheterization Study

Each patient attended the catheterization laboratory in the afternoon prior to the study and had a 7F Swan-Ganz triple lumen thermodilution catheter introduced via the subclavian vein into the pulmonary artery using the Seldinger method. Hemodynamic measurements were made with zero reference taken at the mid axillary level in the same position throughout each study. Measurements of right atrial pressure (RAP), PAP, and pulmonary capillary wedge pressure (PCWP) were made by averaging the values for at least three respiratory cycles. Cardiac output was determined by thermodilution as the mean of three consecutive measurements, all of which were within 10 percent (Marquette Electronics Inc, series 7010). Heart rate was measured continuously from an electrocardiogram and arterial blood pressure was measured by a cuff sphygmomanometer. Arterial blood gases were taken anaerobically from a radial or brachial artery and a mixed venous sample was taken from the pulmonary artery and analyzed for gas tensions, pH, and saturation (IL 492, CO-oximeter, Instrumentation Laboratories).

Derived hemodynamic parameters were calculated as follows:

\[
\text{PAP} = \text{diastolic PAP} + \frac{1}{3} (\text{systolic PAP} - \text{diastolic PAP});
\]

\[
\text{PVR} = \frac{80}{(\text{mean PAP} - \text{PCWP})/\text{CO}}; \quad \text{and SVR} = \frac{80}{(\text{mean ABP} - \text{RAP})/\text{CO}}; \quad \text{and D}_2 = \text{CaO}_2 \times \text{CI}.
\]

For each of the three study days oxygen was administered by nasal cannulae at 2 L/min from 7 PM to 7 AM except for patient 1 (Table 1) who could not tolerate breathing without oxygen and had oxygen administered continuously throughout the study. Inhaled \( \beta \)-adrenoceptor agonists and ipratropium bromide, oral diuretics, other medications (Table 1), and meal times were kept at constant times on both study days. After insertion of the Swan-Ganz catheter, patients remained in bed.

#### Protocol

At least 12 h after insertion of the Swan-Ganz catheter, base line hemodynamic parameters were recorded on three consecutive occasions 15 min apart and a venous and arterial blood sample were taken for gas analysis. Following this, at 9 AM (t = 0), a matched placebo tablet was given, orally, single blind, and hemodynamic parameters and venous blood gases were taken at 2, 4, 6, 8, and 24 h. Arterial blood samples were taken at 4, 8, and 24 h. This procedure was repeated the following day with flosequinan 100 mg being given orally at 9 AM instead of placebo.

Statistical analysis was performed using analysis of covariance (ANCOVA) with the mean of the series of three baseline measurements taken prior to drug administration on each day used as the covariate for each parameter. The profile of the hemodynamic response was compared between each 24-h period and a p value of <0.05 for the overall (mean) difference between drug and placebo for any parameter was considered to be significant. The results are expressed as the mean and SEM at t = 0, 4, and 8 h and the mean overall difference and 95 percent confidence intervals at all times were measured following placebo or flosequinan.

#### Results

There was no significant difference in the baseline values for any of the parameters studied between day 1 and 2. Flosequinan caused a significant reduction in PAP and PVR compared with placebo (Table 2). These reductions were maximal at 4 to 6 h and returned to baseline levels after 24 h (Fig 1 and 2). Significant reductions in SVR occurred following active drug (Table 2) and were again maximal at 4 to 6 h returning to baseline levels by 24 h (Fig 3). Arterial blood pressure tended to fall following flosequinan but no significant difference was demonstrated compared

<table>
<thead>
<tr>
<th>No./Age, yr/Sex</th>
<th>Weight, kg</th>
<th>FEV\textsubscript{1}, L</th>
<th>FVC, L</th>
<th>PaO\textsubscript{2}, kPa</th>
<th>PaCO\textsubscript{2}, kPa</th>
<th>pH</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/67/M</td>
<td>85</td>
<td>0.75</td>
<td>1.83</td>
<td>6.3</td>
<td>7.6</td>
<td>7.40</td>
<td>F, AL, I</td>
</tr>
<tr>
<td>2/65/F</td>
<td>73</td>
<td>0.51</td>
<td>1.21</td>
<td>6.5</td>
<td>6.7</td>
<td>7.37</td>
<td>F, AL, I</td>
</tr>
<tr>
<td>3/50/F</td>
<td>50</td>
<td>0.62</td>
<td>1.48</td>
<td>5.0</td>
<td>5.3</td>
<td>7.35</td>
<td>C, AL, I, AM</td>
</tr>
<tr>
<td>4/42/M</td>
<td>64</td>
<td>0.43</td>
<td>0.91</td>
<td>7.2</td>
<td>5.5</td>
<td>7.41</td>
<td>F, AL, I, AM</td>
</tr>
<tr>
<td>5/74/M</td>
<td>102</td>
<td>0.63</td>
<td>1.72</td>
<td>5.4</td>
<td>6.4</td>
<td>7.40</td>
<td>F, AL, I</td>
</tr>
<tr>
<td>6/63/M</td>
<td>85</td>
<td>0.93</td>
<td>1.96</td>
<td>7.0</td>
<td>6.9</td>
<td>7.48</td>
<td>F, T, I</td>
</tr>
<tr>
<td>7/67/M</td>
<td>68</td>
<td>0.66</td>
<td>1.58</td>
<td>6.0</td>
<td>5.6</td>
<td>7.32</td>
<td>C, AL, I, AM</td>
</tr>
<tr>
<td>8/63/F</td>
<td>78</td>
<td>0.92</td>
<td>1.73</td>
<td>6.3</td>
<td>8.9</td>
<td>7.40</td>
<td>F, AL</td>
</tr>
<tr>
<td>Mean 61</td>
<td>76</td>
<td>0.67</td>
<td>1.55</td>
<td>6.21</td>
<td>6.6</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>SD 10</td>
<td>16</td>
<td>0.35</td>
<td>0.74</td>
<td>1.2</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*F = furosemide; AL = albuterol; I = ipratropium bromide; T = terbutaline; Am = aminophylline; kPa = kilopascals; 1 kPa = 7.5 mm Hg.
Table 2—Hemodynamic Changes following Placebo or Flosequinan*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo t=0</th>
<th>Placebo t=4</th>
<th>Placebo t=8</th>
<th>Flosequinan t=0</th>
<th>Flosequinan t=4</th>
<th>Flosequinan t=8</th>
<th>Mean Overall Difference (95% CI)</th>
<th>p Value (ANCOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP, mm Hg</td>
<td>7.3 (0.9)</td>
<td>7.9 (0.5)</td>
<td>6.4 (1.0)</td>
<td>5.0 (0.6)</td>
<td>4.4 (0.6)</td>
<td>4.0 (1.0)</td>
<td>-1.41 (-4.03, 1.22)</td>
<td>0.24</td>
</tr>
<tr>
<td>Systolic PAP, mm Hg</td>
<td>49.8 (15.9)</td>
<td>51.3 (15.2)</td>
<td>49.8 (13.4)</td>
<td>48.4 (13.8)</td>
<td>41.9 (15.6)</td>
<td>40.6 (10.5)</td>
<td>-7.4 (-10.2, -4.7)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Diastolic PAP, mm Hg</td>
<td>25.1 (7.1)</td>
<td>26.1 (7.3)</td>
<td>24.2 (7.2)</td>
<td>21.8 (7.0)</td>
<td>19.6 (6.9)</td>
<td>18.7 (6.9)</td>
<td>-3.5 (5.9, -1.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>33.5 (0.9)</td>
<td>35.3 (10.1)</td>
<td>33.9 (8.5)</td>
<td>31.8 (9.5)</td>
<td>27.4 (8.5)</td>
<td>27.6 (10.8)</td>
<td>-5.1 (-6.7, -3.4)</td>
<td>0.0003</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>13.7 (3.6)</td>
<td>14.9 (3.2)</td>
<td>13.1 (3.2)</td>
<td>12.9 (3.1)</td>
<td>12.4 (3.1)</td>
<td>11.1 (3.0)</td>
<td>-1.5 (-3.1, 0.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>5.72 (0.5)</td>
<td>5.17 (0.5)</td>
<td>5.45 (0.4)</td>
<td>5.55 (0.3)</td>
<td>6.10 (0.4)</td>
<td>5.95 (0.5)</td>
<td>0.47 (0.03, 0.91)</td>
<td>0.04</td>
</tr>
<tr>
<td>PVR, dynes/s cm⁻³</td>
<td>256 (39)</td>
<td>306 (43)</td>
<td>307 (44)</td>
<td>247 (30)</td>
<td>189 (34)</td>
<td>203 (53)</td>
<td>-70.8 (-118.8, -22.7)</td>
<td>0.013</td>
</tr>
<tr>
<td>SVR, dynes/s cm⁻³</td>
<td>1,358 (206)</td>
<td>1,445 (256)</td>
<td>1,313 (71)</td>
<td>1,358 (136)</td>
<td>1,318 (208)</td>
<td>1,235 (174)</td>
<td>-132 (-230, -35)</td>
<td>0.02</td>
</tr>
<tr>
<td>PVR/SVR</td>
<td>0.20 (0.02)</td>
<td>0.23 (0.03)</td>
<td>0.23 (0.02)</td>
<td>0.19 (0.02)</td>
<td>0.16 (0.02)</td>
<td>0.19 (0.02)</td>
<td>-0.038 (-0.007, 0.001)</td>
<td>0.05</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>91 (11)</td>
<td>93 (11)</td>
<td>98 (12)</td>
<td>93 (10)</td>
<td>102 (12)</td>
<td>103 (12)</td>
<td>7.9 (2.2, 13.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Systolic ABP, mm Hg</td>
<td>136 (14)</td>
<td>128 (13)</td>
<td>127 (14)</td>
<td>127 (15)</td>
<td>124 (14)</td>
<td>121 (14)</td>
<td>-2.6 (-14.9, 9.4)</td>
<td>0.61</td>
</tr>
<tr>
<td>Diastolic ABP, mm Hg</td>
<td>79 (8)</td>
<td>76 (8)</td>
<td>73 (6)</td>
<td>78 (8)</td>
<td>70 (7)</td>
<td>72 (7)</td>
<td>-3.6 (-8.5, 1.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean ABP, mm Hg</td>
<td>98 (19)</td>
<td>88 (9)</td>
<td>91 (10)</td>
<td>95 (10)</td>
<td>93 (10)</td>
<td>88 (9)</td>
<td>-4.0 (-10.5, 2.5)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Results at t=0, t=4, and t=8 h are expressed as the mean and SEM. The mean overall difference and 95 percent confidence intervals between flosequinan and placebo are also given with the overall significance (p) value from the ANCOVA table. (Abbreviations as in text.)

with placebo (Fig 3). Small, though significant, increases in cardiac output and heart rate were also observed (Table 2). There were no significant differences in PCWP or RAP between flosequinan and placebo.

The partial pressure of oxygen and carbon dioxide, the arterial oxygen content, and the mixed venous oxygen saturation (Table 3) did not change significantly. A small though significant increase was observed in DO₂ (Fig 4). No significant side effects were observed following either placebo or flosequinan.

**DISCUSSION**

We have demonstrated that a single 100-mg oral dose of flosequinan has a favorable effect on resting central hemodynamics and oxygen delivery in patients with pulmonary hypertension secondary to COPD. The reduction in PAP pressure and PVR confirms flosequinan's pulmonary vasodilator profile, and these changes are similar to results obtained in a dog model of hypoxic pulmonary hypertension.16 The patients we studied had modest elevations of PAP and PVR. Other reports have shown similar values in patients with hypoxic pulmonary hypertension secondary to COPD.3,4,8 The magnitude of the hemodynamic changes in PAP observed in this study is similar to that of other vasodilator agents studied in cor pulmonale.8

In addition to the favorable effect on pulmonary hemodynamics, flosequinan significantly increased cardiac output and consequently oxygen delivery. This effect is likely to be at least as beneficial as the observed reduction in PAPs and vascular resistance.5 There was also a trend toward an improvement in mixed venous oxygen saturation, arterial oxygen tension, and arterial oxygen content. Flosequinan did not adversely affect arterial or venous blood gases which has been reported with other vasodilator agents.10,20

A significant reduction in SVR with flosequinan therapy was observed. However, the effect on the pulmonary circulation was greater than the systemic, with a 33 percent reduction in PVR compared with an 11 percent reduction in SVR. The magnitude of the fall in arterial blood pressure on flosequinan was small and no patient reported dizziness or other symptoms likely to be due to hypotension.

Many studies investigating the hemodynamics of vasodilator therapy in patients with pulmonary hypertension have been open in design and have compared the effect of active drug with a baseline level, rather than placebo.19-23 This may lead to spurious results as extraneous factors have been shown to affect central hemodynamics. Insertion of a Swan-Ganz catheter may increase cardiac output and PAP,24 meal times affect hemodynamics,25 and spontaneous diurnal variability in PAP has been demonstrated.26,27 To overcome these problems, we compared active drug with placebo given on separate days, the first study day being at least 12 h after catheterization. Meal times, concomitant medication, and oxygen therapy were standardized on both days for each patient. Although the study was single blind, we believe that the placebo compar-
Flosequinan overcomes some of the criticisms of uncontrolled studies comparing changes following intervention with baseline measurements.

FIGURE 1. Mean (SEM) pulmonary and systemic artery pressures with flosequinan (asterisks) and placebo (circles). PAP = pulmonary artery pressure; SBP = systolic blood pressure.

FIGURE 2. Mean pulmonary artery pressure (PAP) at baseline, 4, and 8 h after placebo and flosequinan 100 mg. (p<0.05 at 4 h and 8 h compared with placebo).

Flosequinan has been studied in patients with cardiac failure due to left ventricular dysfunction, where it has been shown to favorably affect hemo-

FIGURE 3. Systemic (SVR) and pulmonary vascular resistances (PVR) with flosequinan (asterisks) and placebo (circles); mean (SEM).
dynamics and improve exercise tolerance and symptom status. In patients with heart failure due to impaired left ventricular function, flosequinan (100 to 125 mg daily) improved central hemodynamics and also increased peripheral limb blood flow and exercise capacity. The improvement in maximal oxygen uptake suggests an improvement in oxygen delivery, probably as a result of improved cardiac output. In patients with pulmonary hypertension, oxygen uptake appears to be dependent on oxygen delivery and this may be due to underlying tissue hypoxia. An improvement in oxygen delivery may therefore be of therapeutic value in the treatment of such patients. The value of vasodilator therapy in patients with pulmonary hypertension due to chronic obstructive lung disease has recently been questioned. Previous studies have examined the use of β₂-adrenergic antagonists, hydralazine, nitrates, calcium antagonists, and angiotensin-converting enzyme inhibitors. However, there are few placebo-controlled, long-term studies of these vasodilators in patients to allow a definite conclusion to be made regarding short- or long-term efficacy. This is partly because an appropriate and effective drug has not been available. The short-term vasodilator profile of flosequinan with its favorable effects on PAP and oxygen delivery and greater effects on the pulmonary compared with systemic circulation make it an attractive drug for such a long-term study in patients with pulmonary hypertension due to COPD.

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Effects of Flosequinan in Cor Pulmonale (Elborn et al)

14 patients


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