Comparison of the Effects of Adenosine and Nifedipine in Pulmonary Hypertension

BRUCE J. SCHRADE, PHARM.D., SHMUEL INBAR, MD, LISA KAUFMANN, RN, ROBERT E. VESTAL, MD,* STUART RICH, MD

Chicago, Illinois; Boise, Idaho; Seattle, Washington

The hemodynamic effects of intravenously administered adenosine, a potent vasodilator, were examined in 15 patients with pulmonary hypertension. All patients were given adenosine, 50 μg/kg per min, increased by 50 μg/kg per min at 2 min intervals to a maximum of 500 μg/kg per min or until the development of untoward side effects. The patients were then given oral nifedipine, 30 mg every hour, until a ≥20% decrease in pulmonary vascular resistance or systemic hypertension occurred.

The administration of maximal doses of adenosine, 256 ± 45 μg/kg per min, produced a 24.6% reduction in pulmonary artery pressure (p ≠ NS), a 37% decrease in pulmonary vascular resistance (p < 0.001) and a 57% increase in cardiac index (p < 0.001). The administration of maximally effective doses of nifedipine (91 ± 36 mg) produced a 15% reduction in the mean pulmonary artery pressure (p < 0.05), a 24% decrease in pulmonary vascular resistance (p < 0.01) and an 8% increase in cardiac index (p ≠ NS).

Thus, adenosine is an effective vasodilator in patients with pulmonary hypertension and can be used for safe and rapid assessment of vasodilator reserve in these patients. The ability of adenosine to reduce pulmonary vascular resistance by 37%, and its effectiveness in patients in whom nifedipine was not, suggests that the pursuit of an oral analogue of adenosine as a therapeutic agent is warranted.

Methods

Study patients. Fifteen consecutive patients referred to the University of Illinois Hospital for evaluation of pulmonary hypertension between July 1989 and August 1990 were enrolled in the study. Eleven patients had primary pulmonary hypertension, two had cirrhosis of the liver and two had collagen vascular disease. The study protocol was reviewed and approved by the University of Illinois Institutional Review Board on January 6, 1989. The study group comprised 13 women and 2 men (mean age 34 ± 10.5 years). All patients had a thorough evaluation to identify the cause of their pulmonary hypertension; the studies included a chest radiograph, lung scan, pulmonary function testing, echocardiography and cardiac catheterization, according to the protocol of the National Institutes of Health Primary Pulmonary Hypertension Registry (8).

All patients underwent a diagnostic right heart catheterization, after an overnight fast, to assess hemodynamic variables. All medications except digoxin and diuretic agents were discontinued at least 2 weeks before the study. A 7F

Adenosine, an intermediate product in the metabolism of adenosine triphosphate, has been shown to be a potent vasodilator through actions on specific vascular receptors (1). Adenosine produces coronary vasodilation, decreases systemic vascular resistance and causes relaxation of smooth muscles, including pulmonary arteries, in vitro (2-4). The continuous intravenous administration of adenosine to normal healthy subjects has been shown to decrease systemic vascular resistance and causes relaxation of smooth muscles, including pulmonary arteries, in vitro (2-4).

Adenosine is a stable compound with a favorable safety profile and a very short serum half-life that makes it a desirable agent to test vasodilator reserve in pulmonary hypertension (5). This study was designed to assess the acute hemodynamic effects of maximally tolerated doses of adenosine on the pulmonary and systemic circulation in patients with pulmonary hypertension and to compare these effects with those of a calcium channel blocking agent also titrated to maximal effectiveness (6,7). In addition, we tested whether the response to adenosine predicted the response to calcium channel blockers.
Table 1. Hemodynamic Effects of Adenosine and Nifedipine in 15 Patients With Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean Pulmonary Artery Pressure (mm Hg)</th>
<th>Cardiac Output (L/min)</th>
<th>Pulmonary Vascular Resistance (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>AD</td>
<td>AD</td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>62</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>56</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>71</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>80</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>53</td>
<td>41</td>
<td>69</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>55</td>
<td>54</td>
<td>58</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>60</td>
<td>64</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>48</td>
<td>73</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>13</td>
<td>43</td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td>14</td>
<td>65</td>
<td>66</td>
<td>59</td>
</tr>
<tr>
<td>15</td>
<td>35</td>
<td>30</td>
<td>48</td>
</tr>
<tr>
<td>Mean</td>
<td>56.13</td>
<td>54.73</td>
<td>60.3</td>
</tr>
<tr>
<td>SD</td>
<td>15.34</td>
<td>15.16</td>
<td>17.92</td>
</tr>
</tbody>
</table>

*p values compare values after adenosine with baseline values and values after nifedipine with values after the second baseline. AD = after adenosine; B = baseline; AD2 = second baseline; N = after nifedipine.

Swan-Ganz catheter was placed in the pulmonary artery and a small Teflon catheter was placed in the femoral artery to monitor systemic arterial pressures. Cardiac output was determined by the thermodilution technique. Systemic and pulmonary artery pressures were measured with values for pulmonary vascular resistance and systemic vascular resistance was calculated by standard formulas.

Administration administration. After baseline hemodynamic measurements were obtained, adenosine was administered into an antecubital vein as a continuous infusion. The measurements were obtained, adenosine was administered in six patients, pulmonary and systemic pressures and oxygen saturation in the systemic and pulmonary arteries were measured at each increase in adenosine dose.

Nifedipine administration. After adenosine administration, the patients were transferred to the coronary care unit where they were acclimated over the next 2 to 4 h. During this time systemic and pulmonary pressures as well as cardiac output were measured periodically until stable values were obtained, and then hourly thereafter. The protocol for nifedipine administration has been described in detail (7).

Briefly, nifedipine, 20 mg every hour, was administered until one of the following occurred: a 30% reduction in pulmonary vascular resistance that did not decrease further with additional dosing, systemic hypotension, a total dose of 200 mg of nifedipine or intolerable adverse effects that required discontinuation of the drug.

Statistical methods. The mean values ± SD were computed for all variables measured. Comparisons between control and treated states were made with a Student's t test for unpaired data. A one-way analysis of variance was used to compare the two drug effects. The Pearson product correlation coefficient was used to examine the differences between the two treatments.

Results

Baseline hemodynamic findings (Tables 1 and 2). All 15 patients included in the study had pulmonary hypertension manifested by markedly elevated mean pulmonary artery pressure (56 ± 16 mm Hg) and pulmonary vascular resistance (14 ± 7 U) as well as a reduced cardiac index (2 ± 0.6 liters/min/m²).

Adenosine effects (Tables 1 and 2). Adenosine dosing was limited by the occurrence of drug-induced side effects in each case. The administration of maximal doses of adenosine (256 ± 46 μg/kg per min, range 200 to 350) resulted in a 2.4% reduction in mean pulmonary artery pressure (p = NS) and a 37% decrease in pulmonary vascular resistance (p < 0.001). Adenosine increased cardiac index by 37% (p < 0.001) and increased heart rate by 13% (44 to 94 beats/min) (p < 0.05), resulting in an increase in stroke volume index (26 to 35 ml/beat per m²) (p < 0.01). In addition, systemic vascular resistance decreased by 4% (p < 0.001), whereas systolic blood pressure decreased by only 6.8% (p < 0.01). Adenosine also resulted in a 4%
increase in systemic oxygen saturation, a 27% increase in systemic PO2, and a 22% increase in pulmonary oxygen saturation (p < 0.0001).

The reported side effects were shortness of breath (n = 7), abdominal discomfort or nausea (n = 6), chest pressure (n = 4), headache (n = 3) and numbness or tingling of the extremities (n = 3). Some of the patients experienced more than one side effect. All side effects abated within 30 s of the discontinuation of the adenosine infusion. No adverse effect was prolonged; therefore, no patient's hospital stay was extended because of adenosine administration. No arrhythmias were noted during any adenosine infusion.

To examine the possibility that titrating the adenosine to the onset of side effects might overshoot the maximal pharmacologic effect, a subset of six patients had systemic and pulmonary artery pressures and oxygen saturation recorded at each dosing increment. In all six patients the arteriovenous oxygen saturation difference narrowed with each dose increment, reflecting an increased cardiac output with each successive dose. In all six patients, pulmonary vascular resistance either remained the same or decreased with successive doses.

Nifedipine effects (Tables 1 and 2). The administration of maximally effective doses of nifedipine (91 ± 36 mg, range 40 to 160) resulted in a 15% reduction in mean pulmonary artery pressure (p < 0.05) and a 24% decrease in pulmonary vascular resistance (p < 0.01). Nifedipine increased cardiac index by 8% (p = NS) and heart rate by 13% (p = NS), resulting in a slight 8% increase in stroke volume index from 26 ± 13 to 38 ± 13 ml/m2/min (p = NS). Nifedipine also caused systemic vascular resistance to decrease by 23% (p = NS) and systolic blood pressure to decrease by 14% (p < 0.05).

Side effects that limited nifedipine dosing included, systemic hypotension (two patients), severe nausea and vomiting (one patient) and lack of further hemodynamic effect on pulmonary resistance with the next dose (seven patients).

Three patients who did not have a 20% reduction in pulmonary vascular resistance with adenosine also did not respond to nifedipine. However, six patients who did not respond to nifedipine responded to adenosine with a 34% to 48% decrease in pulmonary vascular resistance. In addition, two patients who had limited tolerance to nifedipine because of systemic hypotension had a decrease in pulmonary vascular resistance with adenosine of 23% and 46%, respectively.

Comparative effects of adenosine and nifedipine. Nifedipine resulted in a 13% reduction in pulmonary artery pressure in contrast to a 1% decrease with adenosine (p = NS). Cardiac output increased by 26% with adenosine versus 18% with nifedipine (p < 0.05). Thus, adenosine resulted in a greater decrease in pulmonary vascular resistance (37%) than did nifedipine (24%) (p < 0.0001). (Fig. 1). The reduction in pulmonary vascular resistance induced by adenosine was associated primarily with an increase in cardiac output, whereas that induced by nifedipine was associated with both a decrease in pulmonary artery pressure and an increase in cardiac output. There was a significant correlation (r = 0.71, p = 0.01) between the reduction in pulmonary vascular resistance that resulted from adenosine administration with that achieved with nifedipine (Fig. 2). There was no correlation between the increase in cardiac index (r = -0.20, p = NS) or the reduction in pulmonary artery pressure (r = 0.47, p = NS) achieved with adenosine and that achieved with nifedipine.
Figure 1. Selective effects of adenosine and nifedipine on mean pulmonary artery pressure (PAP), cardiac output (CO) and pulmonary vascular resistance (PVR). It appears that the two agents lower pulmonary vascular resistance by slightly different mechanisms.

Discussion

Adenosine for testing in pulmonary hypertension. Adenosine is an endogenous nucleoside that has a variety of pharmacologic effects, including modulation of platelet function and vasodilation (2,3,9). The vasodilator effects have been examined in various vascular beds in normal volunteers (2,4,10). Adenosine administration produces a stepwise increase in coronary blood flow with increasing incremental dosing (2). Bush et al. (3) reported that adenosine infusion at a constant dose of 70 μg/kg per min resulted in an increase in pulmonary blood flow of 0.52 ± 6.08 ml/min/m² and a decrease in systemic vascular resistance of 357 ± 44 dynes-s-cm⁻⁵ without inducing reflex tachycardia. These effects, coupled with the short half-life of adenosine, are desirable properties for a vasodilator for testing in pulmonary hypertension. The mechanism that produces these effects is considered to be secondary to stimulation of endothelial cell and vascular smooth muscle receptors of the A₁ type, which induce vascular smooth muscle relaxation by increasing cyclic adenosine monophosphate (1).

The availability of a safe, easily administered test drug for rapid determination of pulmonary vasoreactivity would be a valuable investigative adjunct. Adenosine can induce hemodynamic changes within seconds and can be eliminated, along with untoward side effects, in seconds. The ideal predictive agent would induce a hemodynamic response that would correlate with the response to oral vasodilators such as calcium antagonists. Prostacyclin has been used as an acute testing agent, but maximal effectiveness is almost always limited by systemic hypotension. The response to prostacyclin, however, appears to predict the response to calcium channel blockers (11–13).

In the present study, adenosine decreased pulmonary vascular resistance by >20% in 12 of 15 patients tested. The three patients who did not respond to adenosine also did not respond to nifedipine. There were six patients who did not respond to nifedipine although they responded to adenosine, and two patients had limited tolerance to nifedipine because of hypotension, whereas they had a decrease in pulmonary vascular resistance of 23% and 48%, respectively. These findings suggest that adenosine has broader vasodilator abilities than does nifedipine in pulmonary hypertension, and that perhaps other classes of drugs should be tested in patients who respond to adenosine but not nifedipine. Because no patient treated with adenosine had systemic hypotension, even though pulmonary vascular resistance was reduced, and because the effects of adenosine can be assessed in minutes during the catheterization procedure, this drug is a very attractive test agent. The testing of the maximal physiologic effectiveness of the calcium channel blockers requires invasive hemodynamic monitoring for a period of hours.

Mechanism of drug action. Adenosine and nifedipine appear to cause vasodilation by different mechanisms, as exemplified by their differing hemodynamic effects. Adenosine improves hemodynamic status primarily by increasing cardiac output and decreasing pulmonary vascular resistance. This overall increase in cardiac output would account for the increase in the pulmonary capillary wedge pressure and right atrial pressure due to adenosine. Nifedipine administration resulted in a nonsignificant increase in cardiac output; hence, it had no significant effect on pulmonary capillary wedge pressure or right atrial pressure. However, it did cause a significant reduction in pulmonary artery pressure. These two drugs may produce mildly disparate hemodynamic responses, but adenosine is used to predict vasodilator reserve in these patients.

Our study was of a limited scope. Because of the method of preparation and dosing schedule used, we were unable to assess the effects of a long-term adenosine infusion. We also did not identify the cellular mechanisms responsible for the...
hemodynamic effects of adenosine, although they appear to differ from those of the calcium channel blockers.

Conclusions. Adenosine is an effective vasodilator in patients with pulmonary hypertension and can be used safely to quickly assess vasodilator reserve in these patients. It appears to decrease pulmonary vascular resistance primarily by increasing cardiac output. The observation that adenosine was able to reduce pulmonary vascular resistance by 37% on average, and that it was effective in patients in whom nifedipine was not, suggests that the pursuit of oral analogues of adenosine as possible therapeutic agents for the treatment of pulmonary hypertension is warranted.

References