Adenosine as a Vasodilator in Primary Pulmonary Hypertension

John M. Morgan, MA, MRCP; David G. McCormack, MD; Mark J.D. Griffiths, MB; Clifford J. Morgan, BM, FFARCS; Peter J. Barnes, DSc, FRCP; and Timothy W. Evans, MD, PhD, MRCP

Background. The acute administration of vasodilator drugs to patients with primary pulmonary hypertension has been advocated to identify those with reversible pulmonary vasoconstriction. Unfortunately, the usefulness of the drugs currently available is limited by accompanying systemic hypotension. A vasodilator with effects confined to the pulmonary circulation would therefore be advantageous in such patients.

Methods and Results. The purine nucleoside adenosine was infused into the pulmonary artery in seven patients with primary pulmonary hypertension (baseline pulmonary vascular resistance [PVR], 442–1,295 dyne/cm/sec$^{-5}$) to determine its effect on PVR. In all patients, there was a dose-dependent and significant reduction (mean maximal percent decrease from baseline, 38.9%; $p<0.001$) in PVR mediated through a decrease in pulmonary artery pressure and an increase in cardiac output. Systemic vascular resistance (SVR) also decreased, but the ratio of PVR to SVR decreased (maximal mean percent decrease from baseline) by 10.5% ($p<0.025$), indicating that adenosine has a preferential vasodilator effect on the pulmonary circulation when administered in this manner.

Conclusions. Because of its pharmacokinetic and vasodilator properties, adenosine may have a specific role in the investigation of primary pulmonary hypertension. (Circulation 1991;84:1145–1149)

Primary pulmonary hypertension is a disease of unknown etiology characterized by severe elevations in pulmonary artery pressure leading to right ventricular hypertrophy and cor pulmonale and a high associated mortality. Histological examination of pulmonary vessels reveals a spectrum of changes, including arteriolar medial hypertrophy, intimal proliferation and fibrosis, and adventitial hypertrophy and hyperplasia. The contribution of vasoconstriction to the limitation of blood flow is highly variable. The acute administration of vasodilators in patients with primary pulmonary hypertension has therefore been advocated to identify those with reversible pulmonary vasoconstriction. Nevertheless, individual patients display an inconsistent response to the vasodilator drugs currently available, which lack actions selective to the pulmonary circulation. Modest reductions in pulmonary artery pressure are therefore almost invariably accompanied by a decrease in systemic arterial pressure. Life-threatening hypotension may result from the administration of vasodilators to patients with “irreversible” pulmonary vascular disease. A pharmacologically selective drug with effects confined to the pulmonary circulation would therefore be highly desirable to assess reversibility in these patients. The

See p 1437
TABLE 1. Baseline Data for All Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>PAP (mm Hg)</th>
<th>SAP (mm Hg)</th>
<th>CVP (mm Hg)</th>
<th>PAOP (mm Hg)</th>
<th>CO (l/min)</th>
<th>PVR (dyne sec cm⁻¹)</th>
<th>SVR (dyne sec cm⁻¹)</th>
<th>PVR-to-SVR ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>65</td>
<td>7</td>
<td>10</td>
<td>5.1</td>
<td>442</td>
<td>909</td>
<td>0.49</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>106</td>
<td>21</td>
<td>8</td>
<td>4.4</td>
<td>763</td>
<td>1,545</td>
<td>0.51</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>77</td>
<td>4</td>
<td>20</td>
<td>3.6</td>
<td>710</td>
<td>1,622</td>
<td>0.42</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>81</td>
<td>4</td>
<td>4</td>
<td>4.5</td>
<td>913</td>
<td>1,368</td>
<td>0.63</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>104</td>
<td>2</td>
<td>10</td>
<td>2.7</td>
<td>1,295</td>
<td>3,022</td>
<td>0.42</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>108</td>
<td>11</td>
<td>8</td>
<td>3.5</td>
<td>1,150</td>
<td>2,217</td>
<td>0.51</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>74</td>
<td>6</td>
<td>8</td>
<td>4.7</td>
<td>918</td>
<td>1,157</td>
<td>0.80</td>
</tr>
<tr>
<td>Mean</td>
<td>52.7</td>
<td>87.9</td>
<td>8.3</td>
<td>10.0</td>
<td>4.1</td>
<td>884.0</td>
<td>1,691.0</td>
<td>0.54</td>
</tr>
<tr>
<td>SEM</td>
<td>2.6</td>
<td>6.2</td>
<td>2.5</td>
<td>1.7</td>
<td>0.3</td>
<td>99.2</td>
<td>250.5</td>
<td>0.05</td>
</tr>
</tbody>
</table>

PAP, pulmonary artery pressure; SAP, systemic artery pressure; CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure; CO, cardiac output; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Systemic vascular resistance was calculated as SAP − CVP/CO.

Methods

Seven patients (three men; mean age, 32 years; age range, 19–56 years) with primary pulmonary hypertension were studied. In all cases, the diagnosis was based on clinical, hemodynamic, and radiographic criteria, the latter including angiographically demonstrated symmetrical peripheral pruning of the pulmonary arterial tree. All subjects gave informed consent for the study, the protocol of which was approved by the Ethical Committee of the Royal Brompton and National Heart Hospital.

Study Protocol

Patients were studied in the hospital intensive care unit while breathing inspired oxygen concentration of 60% (Ventimask) in the resting, unanesthetized postabsorptive state. Oxygen was used because several patients were hypoxemic, and an exacerbation of their hypoxemia as a result of adenosine could not be excluded. A balloon-tipped, flow-directed, pulmonary artery catheter of the thermodilution type (7.5F, Ecosse Medical Ltd., Cumbernauld, Strathclyde, UK) was introduced via the right internal jugular vein, and a radial artery was cannulated (22-gauge, Abbocath-T229, Abbott Ltd., Sligo, Ireland) to permit continuous monitoring of pulmonary and systemic blood pressures, respectively (Model 78353B, Hewlett-Packard Co., Palo Alto, Calif.). Cardiac output was measured by thermodilution (model SP1445, Gould Inc., Oxnard, Calif.) in triplicate on all occasions. Samples of arterial blood were drawn anaerobically and analyzed immediately (Corning Model 178 pH/blood gas analyzer, Corning, N.Y.).

The parameters measured were mean pulmonary artery pressure, mean systemic arterial pressure, cardiac output, mean central venous pressure, and pulmonary artery occlusion pressure.

Adenosine Infusion

All parameters were measured in triplicate before administration of adenosine (5 mg/ml diluted to 1 mg/ml in 0.9% NaCl), which was infused into the pulmonary artery at dosages of 0.001, 0.01, 0.03, and 0.05 mg/kg body wt/min for 10 minutes at each dosage increment, after which the parameters were remeasured. A final set of measurements was made 10 minutes after cessation of the infusion.

Data and Statistical Analyses

Pulmonary and systemic vascular resistances (PVR and SVR; dyne/sec/cm⁻²) were calculated by standard formulas (Table 1). Because of the spread of data, all results are shown graphically as percent change from baseline levels. Statistical analysis was performed on raw data using analysis of variance, and statistical significance was assessed using Student’s paired t test with Bonferroni’s correction for multiple comparisons. Probability values of 0.05 or less were considered significant. All data in the text are expressed as mean ± SEM values.

Results

The baseline hemodynamic data of the patients studied are summarized in Table 1. PVR decreased in a dose-dependent fashion in all patients (mean maximal decrease, 38.8% at 0.05 mg/kg/min; range, 30.7–48.8%; p<0.001; Figure 1), achieving statistical significance (p<0.001) at a dosage of 0.001 mg/kg/min. SVR also decreased in a similar manner in all patients (mean maximal decrease, 31.4% at 0.05 mg/kg/min; range, 13.2–36.4%; p<0.001; Figure 1), achieving statistical significance at a dosage of 0.03 mg/kg/min (Figure 1). By contrast, cardiac output increased in all patients, achieving statistical significance at a dosage of 0.01 mg/kg/min (mean maximal increase, 52.3% at 0.05 mg/kg/min; range, 17.7–75.0%; p<0.001; Figure 2). Mean pulmonary artery pressure decreased with adenosine in all patients, achieving statistical significance at the maximal dosage (mean decrease at 0.05 mg/kg/min, 8.3%; range, 1.9–14.5%; p<0.001; Figure 2). Mean systemic arterial pressure did not change significantly with adenosine (Figure 2). The ratio of PVR to SVR decreased significantly (mean maximal decrease at 0.05 mg/kg/min, 10.5%; range, 1.9–19.7%; p<0.025; Figure 1), achieving statistical significance at a dosage of 0.03 mg/kg/min. Pulmonary capillary
Adenosine infusion

FIGURE 1. Plots of effects of infused adenosine on (upper panel) pulmonary vascular resistance (PVR), (middle panel) systemic vascular resistance (SVR), and (lower panel) PVR-to-SVR ratio in seven patients with primary pulmonary hypertension. Values shown are mean±SEM percent change from baseline.

occlusion pressure, central venous pressure, and arterial blood gas tensions did not change significantly during the course of the study.

Discussion

The beneficial hemodynamic effects of vasodilator therapy in primary pulmonary hypertension were reported by Dresdale et al\(^1\)\(^4\) in their original description of the disease, initiating a therapeutic practice that has continued to the present day.\(^3\)\(^,\)\(^15\) In assessing the reversibility of elevated PVR in such patients, a short-acting and selective pulmonary vasodilator is required. Some authorities have suggested that prostacyclin is the drug of choice in this respect rather than conventional vasodilators such as nitroglycerin, nitroprusside, and isoproterenol,\(^16\)\(^,\)\(^17\) although the experience of others has been less favorable.\(^18\)

Our results show that adenosine acts to reduce PVR in patients with primary pulmonary hypertension. Pulmonary artery pressure decreased significantly and by more than 10% in four patients. In contrast, mean systemic blood pressure either did not
change or showed a tendency to increase. The ratio of PVR to SVR decreased significantly, indicating that intrapulmonary infusion of adenosine can achieve selectivity for the pulmonary circulation. This does not imply that adenosine has pharmacological effects specific to the pulmonary circulation; we speculate that the short half-life of the drug consequent upon its rapid metabolism (see below) was responsible for the observed effect. Adenosine has been shown to dilate carotid, coronary, and human pulmonary arteries in vitro, suggesting that it has a generalized vasodilator effect that is mediated via A2-receptors. Its precise mechanism of action remains unknown but may depend on increased intracellular concentrations of cyclic AMP. The vasodilator effect in human pulmonary vessels in vitro is not endothelium dependent, suggesting that its effects are not mediated via an endothelium-derived relaxant factor, and does not appear to vary between small (200–400 μm) and large (7–10 mm) arteries. Nevertheless, the half-life of adenosine in blood is extremely short. This suggests that the selective actions of adenosine observed in the present study are probably attributable to rapid metabolism, with decreased active drug reaching the systemic circulation.

Assessing the effect of pulmonary vasodilator agents in primary pulmonary hypertension is a matter of some controversy. Although most authorities agree that a decrease in pulmonary artery pressure accompanied by an increase in cardiac output with no change in systemic arterial pressure is the ideal hemodynamic response, this occurs in a minority of patients. Thus, in assessing the response of patients to high-dose calcium antagonists, Rich and Brundage found that approximately 30% responded in this manner. Most (50–60%) of patients displayed an isolated increase in cardiac output, similar to that shown here. Nevertheless, a reduction in PVR in excess of 20% of baseline has been accepted as indicative of a favorable response, a level that was exceeded by all of the patients in our study.

Left-sided afterload reduction increases cardiac output in disease states with elevated SVR, such as left-sided heart failure, enabling systemic arterial pressure to be maintained at acceptable levels. In contrast, if pulmonary hypertension limits cardiac performance, a vasodilator that decreased SVR but not PVR would result in the maintenance of cardiac output but a decrease in systemic arterial pressure. In the present study, adenosine had a marked effect on cardiac output in all patients, which must have been mediated primarily through a reduction in right ventricular afterload.

Adenosine-receptor agonists have been shown to reduce or prevent the positive inotropic response of isolated myocardium to adrenergic agents and may even have a negative inotropic effect. Because survival in primary pulmonary hypertension is related most directly to cardiac output, reducing PVR while increasing cardiac output (through afterload reduction) may produce benefits in addition to those resulting from a decrease in pulmonary artery pressure.

All of the patients in this study were maximally oxygenated before the start of the adenosine infusion lest any reduction in arterial pressure precipitated a decrease in Pao2. This may have had the effect of masking some vasodilator effects of the drug by obviating hypoxic pulmonary vasoconstriction. Although arterial oxygen tension was unchanged after adenosine, cardiac output (and therefore oxygen delivery) was improved, thus conferring physiological benefits.

Because this is the first reported use of the drug in this application, we were naturally cautious regarding the dosage schedule; therefore, the favorable effects of the drug may be more apparent at higher dosages.

Several studies have suggested that the acute response to a vasodilator is a useful predictor of long-term improvement. Short-term trials of vasodilator therapy therefore appear to be justified in such patients provided that a safe, effective drug is used. On the basis of the results reported here, we suggest that adenosine may prove to be such a drug. When adenosine infusion elicits a vasodilator response in individuals, use of an indwelling pulmonary catheter would allow the effects of long-term adenosine infusion on the pulmonary circulation to be assessed.

References

KEY WORDS • adenosine • pulmonary vascular resistance
Adenosine as a vasodilator in primary pulmonary hypertension.
J M Morgan, D G McCormack, M J Griffiths, C J Morgan, P J Barnes and T W Evans

Circulation. 1991;84:1145-1149
doi: 10.1161/01.CIR.84.3.1145

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/84/3/1145

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/