Enhancement of Coronary Vasodilator Action of Adenosine Triphosphate by Dipyridamole

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ABSTRACT

It has been reported that previously administered dipyridamole intensifies the coronary vasodilator action of adenosine compounds. In the present study, a combination of dipyridamole and ATP at doses that alone are ineffective was examined for its effect on the coronary sinus blood flow. In 10 anesthetized dogs, heart rate, arterial blood pressure, cardiac output, and coronary sinus blood flow were measured before and during a 20-min constant-rate infusion of (a) ATP alone, 1 mg/min; (b) a combination of ATP, 1 mg/min, and dipyridamole, 0.005 mg/kg/min; and (c) dipyridamole alone, 0.005 mg/kg/min. Coronary sinus flow was measured by a newly developed thermodilution flowmeter. Consistently during the infusion of ATP or dipyridamole alone no changes in the measured parameters occurred, whereas during infusion of the combination a very marked and sustained elevation (+493%) of coronary flow occurred, associated with a moderate increase in cardiac rate (+37%) and output (+42%) and a decrease in arterial blood pressure (−17%). In 7 other dogs, coronary vasodilator responses to ATP were determined before and 1 hour after a single 10-mg dose of dipyridamole. After dipyridamole, the coronary vasodilator action of ATP increased 5- to 100-fold. In a third group of 3 dogs, dipyridamole did not enhance the coronary vasodilator effects of nitroglycerin, bradykinin, or acetylcholine.

ADDITIONAL KEY WORDS

coronary vasodilation
anesthetized dogs

Dipyridamole,1 2,6-bis (diethanolamino)-4,8-dipiperidino-pyrimido-(5,4-d) pyrimidine, is a well known coronary vasodilator. Besides this immediate action, prior administration of dipyridamole greatly intensifies the coronary vasodilator effect of adenosine (1); however, no specific data concerning this interesting action is available. In this study coronary and systemic effects of the concurrent administration of adenosine 5-triphosphate (ATP) and dipyridamole are reported. In addition, the effect of prior administration of dipyridamole on ATP-induced coronary vasodilation was quantified. ATP was used since previous work (2) and preliminary trials have shown no differences in the coronary vasodilator effects of ATP and adenosine when administered in equimolar doses; ATP is dephosphorylated to adenosine blood (3). Other types of coronary vasodilators were also examined for possible potentiation by dipyridamole.

Methods

Three groups of dogs were studied. The objective in the first group was to evaluate the coronary vasodilator response to combinations of ATP and dipyridamole in doses which alone are ineffective. Ten healthy fasting mongrel dogs (dogs 1-10) were used. Their weights, in the order of their assigned numbers, were 20.4, 22.2, 18.0, 18.6, 23.6, 18.2, 18.0, 26.3, 17.2, and 23.7 kg. Anesthesia was produced by 3 mg/kg of morphine sulfate subcutaneously followed in 1 hour by intravenous administration of allobarbital, 12.5

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1Persantin, as the intravenous form, was supplied through the courtesy of Dr. Paul A. Kennedy, Jr., Geigy Pharmaceuticals, Ardsley, New York.
mg/kg, urethane, 50 mg/kg, monoethylurea, 50 mg/kg, and sodium pentobarbital 8 mg/kg. Cardiac output, femoral arterial blood pressure, cardiac rate, and coronary sinus blood flow were measured in these animals. Cardiac output was determined by the dye dilution technique and coronary sinus flow was measured by a thermodilution flowmeter intended for intravascular use

(4). Briefly, its working principle is that heat produced electrically by a resistance wire coil is uniformly distributed in the blood stream by the stirring action of a rotating blade, and the temperature change is measured downstream by a thermistor; blood flow is inversely proportional to the temperature change. Two cardiac catheters were placed in the right atrium, one for the infusion of drugs and the other for the injection of indocyanine green for dye dilution curves. The thermodilution flowmeter was inserted through the jugular vein and placed in the coronary sinus, under fluoroscopic control. Cardiac rate was measured from electrocardiographic records. Femoral arterial blood pressure was recorded from a Statham strain gauge connected to a percutaneously inserted Courmand needle. Mean arterial pressure was obtained by electrical stimulation. Coronary sinus blood flow, arterial pressure, and electrocardiograms were recorded on a direct writing Sanborn Polyviso. Dye dilution curves were obtained with a Gilson dye tracer model DTL and Macropolygraph. Left ventricular work was calculated from mean arterial blood pressure and cardiac output. To eliminate coronary flow changes associated with changes in heart rate, in dogs 1, 2, 7 and 8 (Fig. 2), rate was maintained constant by electrical stimulation of the right atrium via a catheter with a bipolar electrode coiled against the atrial wall. The experiment was performed in three parts: (a) Femoral arterial blood pressure, cardiac rate, and coronary sinus blood flow were measured continuously before and during a 20-min rate infusion of ATP in saline delivered through the right atrium catheter. Doses used were 1 mg/min in 8 dogs and 2 mg/min in 2 dogs. Cardiac output was determined before and at 10 min after the start of the infusion. (b) The same parameters were measured as mentioned above, before and during a continuous 20-min infusion of a mixture of dipyridamole and ATP. The doses were 0.005 mg/kg/min of dipyridamole and 1 mg/min of ATP. (c) After this infusion and when coronary sinus flow had returned to the control level, the same parameters measured previously were redetermined before and during a 20-min infusion of dipyridamole alone. Eight dogs received 0.005 mg/kg/min and the 2 dogs which had previously received 2 mg/min of ATP were given 0.01 mg/kg/min. Doses of dipyridamole and ATP were selected on the basis of preliminary experimentation which indicated these doses to be ineffective. Since dipyridamole would be expected to influence the action of ATP, infusion of ATP always preceded the infusions containing dipyridamole.

In the second group of seven dogs, the objective was to quantify the enhancement of the coronary vasodilator action of ATP produced by dipyridamole. The animals were anesthetized in the same manner as those in the first group. In the first part of the experiment the coronary vasodilator responses to effective doses of ATP given as continuous infusions into the right atrium were determined. Then a single intravenous dose of 10 mg of dipyridamole was injected, and 1 hour later coronary vasodilator responses to effective ATP infusions were redetermined.

In the third group, three dogs were studied to determine if the enhancing effect of dipyridamole extends to other types of coronary vasodilators such as nitroglycerin, bradykinin, and acetylcholine. These animals were anesthetized as the previous ones. First, coronary vasodilator responses to single intravenous injections of nitroglycerin, bradykinin, and acetylcholine were determined. Each agent was used in two doses: one chosen to produce a small increase in coronary flow and the other twice this amount. Then, the responses were redetermined for the same doses as used earlier, 40 min after the intravenous administration of 10 mg of dipyridamole. The dogs weighed 20, 23.5 and 19 kg. Doses used in the first dog were 75 and 37.5 μg of nitroglycerin, 5 and 2.5 μg of bradykinin and 25 and 12.5 μg of acetylcholine. The other two dogs received double these doses. The sequence of administration of these agents was at random.

All dogs were heparinized with 500 units of heparin/kg given intravenously at the beginning of the experiment.

Results

A typical coronary sinus flow tracing in a dog of the first group, whose heart rate was paced, is shown in Figure 1. During infusions of ATP or dipyridamole alone, there was no appreciable change in coronary flow or pressure, but during infusion of the mixture of the two, there was a striking and sustained increase in flow accompanied by a decrease in arterial pressure. Since the coronary flow changes were of particular interest in this study, values of coronary sinus flow for individual dogs were plotted before and during
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Figure 1

Coronary sinus blood flow (CF) and blood pressure (BP) in a 20.4-kg dog, whose heart was paced, before (A), during the first 10 min (B), and at the end of 20 min of continuous infusion (C) of 1 mg/min of ATP (I); 1 mg/min ATP with 0.1 mg/min of dipyridamole (II) and 0.1 mg/min of dipyridamole alone (III). Arrows show time infusions started. There were no appreciable changes in coronary flow in I and III, but a great increase in II.

The infusion of ATP alone, ATP with dipyridamole, and dipyridamole alone. These results are presented in Figure 2. No significant or consistent changes in flow were observed during the infusions of either substance alone, except in the 2 dogs (9 and 10) that received double doses of dipyridamole; in these dogs a small increase in flow occurred at the end of the infusion. In marked contrast, during infusion of ATP with dipyridamole, every dog responded with a dramatic increase in flow which was maintained throughout the infusion. In all dogs, values of coronary sinus flow, arterial pressure, cardiac output and heart rate (unpaced dogs only) measured at 10 min after the start of each infusion were compared to those obtained before the start of the infusion and analyzed statistically. Results shown in Table 1 indicate that no significant changes occurred in coronary flow, pressure, output, and rate during the infusion of ATP or dipyridamole alone. During infusion of the two combined, a very large and statistically significant increase (+493%) in coronary sinus flow occurred, associated with a much smaller but significant increase in cardiac output (+42%), a moderate increase in heart rate (+37%), and a decrease in mean femoral arterial blood pressure (-17%). Ventricular work increased 26%, however, this change did not reach statistical significance (P < 0.1).

A representative recording of coronary sinus blood flow in a dog from the second group is illustrated in Figure 3. Before administration of dipyridamole, infusions of
7.6 and 15.3 mg/min of ATP raised the coronary blood flow from 27 ml/min to 39 and 134 ml/min respectively. One hour after the single dose of 10 mg of dipyridamole, an infusion of 0.76 mg/min of ATP raised coronary flow to 92 ml/min, which is intermediate in magnitude between the levels obtained before dipyridamole with doses of ATP ten and twenty times larger. Thus, in this dog, dipyridamole enhanced the coronary vasodilator action of ATP by ten to twenty times. In Table 2 coronary vasodilator responses of ATP before and 1 hour after dipyridamole are given for each dog. In all seven dogs sensitivity to ATP increased after dipyridamole, the increase varying from 5 to over 100 times. Ten to 15 min after dipyridamole alone, coronary flow was significantly elevated (average +135%) and returned to control level within 1 hour.

In the three dogs which received nitroglycerin, bradykinin, and acetylcholine, increases in coronary blood flow produced by each dose of each agent were measured. Increases in flow obtained before dipyridamole were comparable to the respective ones after dipyridamole. Coronary vasodilation was not enhanced.

**Discussion**

Results of experiments in this study demonstrate that the coronary vasodilator action

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**Table 1**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>ATP Control</th>
<th>ATP Study</th>
<th>ATP + Dipyridamole</th>
<th>Dipyridamole</th>
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<tr>
<td>Cardiac output (liter/min)</td>
<td>1.603</td>
<td>1.603</td>
<td>1.869</td>
<td>2.008</td>
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<tr>
<td>% Change</td>
<td>-5.9</td>
<td>+41.7</td>
<td>+0.8</td>
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<tr>
<td>Cardiac output</td>
<td>1.704</td>
<td>1.704</td>
<td>1.992</td>
<td></td>
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<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>112</td>
<td>114</td>
<td>115</td>
<td>102</td>
</tr>
<tr>
<td>% Change</td>
<td>+1.2</td>
<td>-16.6</td>
<td>-4.1</td>
<td></td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.001</td>
<td>0.1</td>
</tr>
<tr>
<td>Coronary sinus blood flow (ml/min)</td>
<td>84</td>
<td>84</td>
<td>84</td>
<td>85</td>
</tr>
<tr>
<td>% Change</td>
<td>0.0</td>
<td>+492.9</td>
<td>+8.8</td>
<td></td>
</tr>
<tr>
<td>Coronary sinus blood flow (ml/min)</td>
<td>84</td>
<td>84</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>82</td>
<td>82</td>
<td>88</td>
<td>84</td>
</tr>
<tr>
<td>% Change</td>
<td>+9.0</td>
<td>+37.4</td>
<td>+14.2</td>
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</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>89</td>
<td>89</td>
<td>121</td>
<td>98</td>
</tr>
<tr>
<td>% Change</td>
<td>0.1</td>
<td>0.02</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>
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FIGURE 3

I: A, control recordings; B, response to 7.6 mg/min of ATP; C, response to 15.3 mg/min ATP; D, response to intravenous injection of dipyridamole (arrow shows time of injection). II: A, 3 min after injection of dipyridamole; B, 20 min after injection, and C, 1 hour after injection. Infusion of 0.76 mg/min ATP began at arrow.

TABLE 2
Coronary Sinus Blood Flow during ATP Infusions

<table>
<thead>
<tr>
<th>Dog</th>
<th>Weight (kg)</th>
<th>Control CF ml/min</th>
<th>Before dipyridamole ATP mg/min</th>
<th>1 Hour after dipyridamole ATP mg/min</th>
<th>Increased sensitivity to ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 91 3.8 7.5 15.3</td>
<td>0.076 0.19 0.38 0.76</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19.0</td>
<td>30.0</td>
<td>42.5 166.0</td>
<td>100.0</td>
<td>&lt;10x</td>
</tr>
<tr>
<td>2</td>
<td>24.5</td>
<td>52.7</td>
<td>148.0 280.0</td>
<td>154.0</td>
<td>&lt;10x</td>
</tr>
<tr>
<td>3</td>
<td>16.0</td>
<td>17.5</td>
<td>17.5</td>
<td>54.0</td>
<td>&gt;100x</td>
</tr>
<tr>
<td>4</td>
<td>18.1</td>
<td>27.0</td>
<td>39.0 134.0</td>
<td>92.0</td>
<td>&gt;20x</td>
</tr>
<tr>
<td>5</td>
<td>19.0</td>
<td>69.2</td>
<td>100.0 156.0</td>
<td>187.0</td>
<td>&gt;40x</td>
</tr>
<tr>
<td>6</td>
<td>23.7</td>
<td>39.2</td>
<td>80.0 253.0</td>
<td>258.0</td>
<td>40x</td>
</tr>
<tr>
<td>7</td>
<td>17.2</td>
<td>33.2</td>
<td>50.0 288.0</td>
<td>275.0</td>
<td>40x</td>
</tr>
</tbody>
</table>

of ATP is greatly enhanced by prior or concurrent administration of dipyridamole. These findings are in accordance with the observation of Bretschneider et al. (1) of intensification of the effect of intravenous adenosine after dipyridamole. On the basis of recent biochemical studies (3, 5, 6), it is likely that the intensification of adenosine action is due to an adenosine-sparing effect of dipyridamole in blood and possibly at cellular levels. It was shown in their studies that dipyridamole effectively prevents the disappearance

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of adenosine added to whole blood. The mechanism of this protection was attributed to a reduction in the permeability of the red blood cell membrane to adenosine, thus avoiding its destruction by the intracellular adenosine deaminase. The combined effects of ATP and dipyridamole can be classified as supra-additive, since in the first group of dogs no appreciable changes in flow were observed during the infusions of ATP or dipyridamole alone.

It should be emphasized that coronary sinus blood flow measured in this study refers to the flow at the cross section of the coronary sinus where the thermistor is located and includes only the coronary venous drainage up to this location. In this study it is important to note that the changes in cardiac output during the infusion of the combination of ATP and dipyridamole are relatively small (+41.7%) when compared to the exceedingly great increase in coronary blood flow. Such an enormous increase in coronary flow cannot be attributed to the small changes in left ventricular work and cardiac rate. Considering that about half of the increase in cardiac output can be accounted for by the increase in the measured coronary flow, which is only a part of the total coronary blood flow, it is reasonable to believe that the combination of ATP and dipyridamole has a selective action on the coronary vascular bed, although adjustments in the vascular beds at the peripheral level have not been ruled out. In view of the great increase of coronary flow by the combinations of ATP and dipyridamole it is suspected that they may be acting at the level of myocardial microcirculation as well as at the coronary arterial level. Concomitant sampling of coronary sinus blood for arteriovenous differences would be desirable to assess alterations in myocardial metabolism; however, such sampling was not technically feasible in this study. Although the combination of ATP and dipyridamole seems to have a selective coronary vasodilator action, additional knowledge is necessary before its use can be suggested in clinical situations.

References
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