Effects of diadenosine tetraphosphate on systemic and regional hemodynamics in dogs

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Abstract

Purpose. Diadenosine tetraphosphate (AP₄A) produces vasodilation and hypotension. If AP₄A is to be employed clinically, its influence on systemic and regional hemodynamics needs to be investigated. In this study, we observed systemic and regional hemodynamics during reduction of mean arterial pressure (MAP) induced by AP₄A in dogs.

Methods. Nineteen mongrel dogs were allocated to three groups: those given physiological saline (vehicle group) and dogs in which MAP was decreased either by 8% (8% group) or by 30% (30% group) by infusion of AP₄A. Systemic hemodynamics and microsphere-determined regional blood flow to vital organs were assessed before and during AP₄A infusion.

Results. In the 8% group, cardiac output (CO) increased, and systemic vascular resistance (SVR) decreased during AP₄A infusion. Although regional blood flow to myocardium and portal organs increased, hepatic blood flow decreased. In the 30% group, heart rate and SVR decreased, and stroke volume index increased without change in CO. Regional blood flow to myocardium, kidneys, and portal organs increased. In both groups, cerebral blood flow remained unchanged.

Conclusion. During the decrease in MAP induced by AP₄A, there were increases in regional blood flow distributed to the myocardium, kidneys, and portal organs, without change in the blood supply to the brain. This finding suggests that AP₄A may be clinically useful for reducing blood pressure without compromising blood flow to vital organs.

Key words: Diadenosine tetraphosphate, Regional blood flow, Microsphere method

Introduction

Diadenosine tetraphosphate (AP₄A) is a bioactive substance that is stored in the dense granules found in human platelets [1] and in chromaffin granules [2]. It has a potent vasodilating action [3]. When continuously administered to dogs under enflurane anesthesia, AP₄A decreased mean arterial pressure (MAP) in a dose-dependent manner [4]. This effect was due to its vasodilating action on resistance vessels and occurred despite increased cardiac output (CO), with no change in heart rate (HR) when MAP was decreased by up to 40% [4]. However, to our knowledge, there are no reported investigations of the comparative changes in regional hemodynamics when MAP is reduced by varying degrees by AP₄A infusion. In the present study, therefore, in order to assess the possibility of clinical application, we examined regional hemodynamics during mild (target decrease in MAP of 8%) and moderate (target decrease in MAP of 30%) reduction in MAP induced by AP₄A.

Methods

Animals

Approval for the study was granted by the University Animal Care Committee, and we studied 19 mongrel dogs, weighing 10–14 kg. After induction with intravenous thiopental 20 mg·kg⁻¹, anesthesia was maintained with oxygen/nitrous oxide (FIO₂ 0.4) and enflurane (1.5%). After muscle relaxation was achieved with pancuronium, ventilation was adjusted, using a mechanical ventilator, to maintain normocapnia (PaCO₂ 35–41 mmHg). Lactated Ringer’s solution was infused at a rate of 5 ml·kg⁻¹·h⁻¹, and the rectal temperature was maintained at about 37°C. Both femoral arteries were catheterized, for blood pressure measurement and arterial blood gas analysis, and both femoral veins were
cannulated, for the administration of AP₄A and insertion of a 7-Fr balloon-tipped thermodilution pulmonary artery catheter. Another catheter was inserted from the right common carotid artery into the left ventricle for the injection of radionuclide-labeled microspheres.

**Experimental protocol**

The experimental animals were allocated to three groups: (1) those given physiological saline (vehicle group, n = 6), (2) dogs in which MAP was decreased by 8% of the pre-AP₄A value by low-dose AP₄A administration (25–30 µg·kg⁻¹·min⁻¹; 8% group, n = 6), and (3) dogs in which MAP was decreased by 30% of the pre-AP₄A value by higher-dose AP₄A administration (80–140 µg·kg⁻¹·min⁻¹; 30% group, n = 7). AP₄A was dissolved in physiological saline. Pre-AP₄A values for MAP, systolic arterial pressure (SAP), HR central venous pressure (CVP), CO, and arterial blood gas tensions were determined under steady state conditions. Then cardiac index (CI), stroke volume index (SI), and systemic vascular resistance (SVR) were calculated by the formula for body surface area [5]. Hemodynamic measurement, the first microspheres bolus was administered via the left ventricular catheter, and then AP₄A or physiological saline was administered intravenously with an infusion pump. Each episode of decreased MAP was maintained for 30 min. At this point, the individual hemodynamic parameters were determined again and a second microspheres bolus was given. The microspheres used were ⁴⁶Sc- or ⁸⁵Sr-labeled spherical granules, 15 µm in diameter (185 MBq/g, New England Nuclear, Boston, MA, USA). Approximately 4 × 10⁶ granules per dose were diluted with 5 ml of physiological saline and injected over a 30-s period into the left ventricle. After the second administration of microspheres, the animals were killed by exsanguination. Various organs and tissues, including brain, heart, liver, kidneys, adrenal glands, pancreas, stomach, duodenum, small intestine, large intestine, skeletal muscle (4% of body weight), and skin (500 cm²), were then extracted. The extracted organ weight was measured and the radioactivity was determined with a Universal Gamma-Counter (JSM-R 17-3871; Aloka, Tokyo, Japan).

**Calculation of percent distribution of CO to organs, and organ blood flow**

The ratio of the γ-ray level for a given organ to the total γ-ray dose administered by way of the microspheres was determined. Then, the percentage of CO distributed to a given organ and the blood flow per 100 g of tissue were calculated with the equations below:

\[ \text{Percentage of CO to a given organ (\%)} = \frac{\gamma\text{-ray level in organ} \times 100}{\text{total } \gamma\text{-ray dose given}} \times 100\% \]

\[ \text{Blood flow per 100 g of tissue (ml·min}^{-1} \cdot \text{100 g}^{-1}) = \frac{\text{CO} \times \text{percentage of CO to that organ}}{100/\text{organ weight (g)}} \]

The stomach, duodenum, small and large intestines, spleen, and pancreas were grouped together as “the portal organs”. The total weight of the skin was calculated according to the formula for body surface area [5]. The skeletal muscle sample used was taken as 4% of the body weight.

**Statistical analysis**

The experimental data values were expressed as means ± SEM. A paired Student’s t-test was used for comparison within each group. Statistical comparison among groups was performed by analysis of variance. P values <0.05 were considered statistically significant.

**Results**

**Vehicle group**

No significant change was observed in arterial blood gas tensions (Table 1), hemodynamic variables (Table 2), regional blood flow (Table 3), or percent blood flow (distribution of CO) to each organ tested (Table 4).

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**Table 1. Effects of diadenosine tetraphosphate (AP₄A) on arterial blood gas tensions**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Vehicle</th>
<th>8% group</th>
<th>AP₄A</th>
<th>Control</th>
<th>AP₄A</th>
<th>30% group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>38.2 ± 0.7</td>
<td>38.9 ± 0.8</td>
<td>37.5 ± 0.8</td>
<td>37.0 ± 0.7</td>
<td>38.6 ± 0.5</td>
<td>38.0 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>265.3 ± 5.9</td>
<td>265.3 ± 6.5</td>
<td>268.5 ± 10.2</td>
<td>268.5 ± 22.8</td>
<td>272.1 ± 6.1</td>
<td>270.6 ± 7.6</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.38 ± 0.01</td>
<td>7.37 ± 0.01</td>
<td>7.38 ± 0.01</td>
<td>7.38 ± 0.01</td>
<td>7.36 ± 0.01</td>
<td>7.37 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>BE (mEq/l)</td>
<td>-1.3 ± 0.5</td>
<td>-1.6 ± 0.3</td>
<td>-1.4 ± 0.5</td>
<td>-1.8 ± 0.4</td>
<td>-1.6 ± 0.3</td>
<td>-1.6 ± 0.3</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as means ± SEM. BE: Base excess; PaCO₂, arterial carbon dioxide tension; PaO₂, arterial oxygen tension.