Potentiation of the Negative Chronotropic and Inotropic Effects of Adenosine by Dipyridamole

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The isolated right atrium of the dog was perfused with blood led from a support dog. The selective injection of dipyridamole into the sinus node artery at a dose of 1-10 μg induced a slight negative chronotropic and positive inotropic effect. The administration of 0.3-10 μg of adenosine caused a negative chronotropic and inotropic effect. The effects induced by adenosine were potentiated by a single injection or a continuous infusion of dipyridamole usually in the duration of adenosine action and frequently in the maximum decreases of the atrial rate and developed tension.

dipyridamole; adenosine; canine atrium; chronotropism; inotropism

Dipyridamole has been reported to have potentiating effects on adenosine action on the coronary arteries of the dog and the cat (Hashimoto et al. 1964; Scholtholt et al. 1965; Nott 1970; Raberger and Kraupp 1971) and on the AV conduction of the guinea-pig heart (Stafford 1966). In this study, it was attempted to study the effect of dipyridamole on the negative chronotropic and inotropic effects of adenosine, using the isolated, blood-perfused atrium preparation of the dog which originally developed by Chiba et al. in 1972.

METHODS

Seven mongrel dogs, weighing 7 to 10 kg, were anesthetized with sodium pentobarbital, 30 mg/kg. The right atrium was quickly excised and plunged into a Tyrode's solution at about 4°C. The right atrium was perfused through the sinus node artery with blood led from a heparinized support dog by the aid of a peristaltic pump (Harvard Apparatus, Model 600-1200). The atrium was suspended in the bath filled with blood at a constant temperature of 37°C. Isometric tension was measured with a force displacement transducer (Grass FTO3B). Atrial rate was measured with a tachometer which triggered by the wave of atrial electrograms. Dipyridamole (Boehringer Sohn) was administered by a microinjector (Terumo Co.) or by an infusion pump (Harvard Apparatus, Model 505-1200). The volume of injection of adenosine was 0.01 to 0.03 ml in a period of 4 sec, and its effects were compared between before and during or after dipyridamole administration.

RESULTS AND DISCUSSION

The perfusion flow rate was 3.3 ± 0.4 ml/min (mean ± s.e.) in five preparations. Spontaneous beating rate was 108 ± 5.1 beats/min (mean ± s.e.) in 7 preparations.
Adenosine at doses of 1 to 10 μg caused a dose-related decrease either in the atrial rate or in the developed tension. On the other hand, a single injection of 1 to 10 μg of dipyridamole induced a decrease in the rate and simultaneously a slight increase in the developed tension. A continuous infusion of dipyridamole at a concentration of 10–30 μg/min also produced a slight increase in the developed tension and a slight or little decrease in the atrial rate. In all 5 experiments, dipyridamole potentiated the duration of adenosine actions, i.e., the negative inotropic and chronotropic effects. Fig. 1 shows a typical potentiation of adenosine action by a continuous infusion of 30 μg/min of dipyridamole. The duration of adenosine actions at each dose level is markedly enhanced in the developed tension and rate by an infusion of dipyridamole. Fig. 2 shows a potentiation of effect of 3 μg of adenosine by a single injection of 30 μg of dipyridamole. In this time, it is demonstrated that 30 μg of dipyridamole induced a positive inotropic effect and negative chronotropic

![Fig. 1. Effect of dipyridamole on adenosine actions.](image)

(A) Effects of adenosine on the canine atrium preparation before dipyridamole treatment. (B) Effects of adenosine during an infusion of 30 μg/min of dipyridamole.

![Fig. 2. Potentiation of effect of 3 μg of adenosine by a single injection of 30 μg of dipyridamole.](image)
TABLE 1. Effect of dipyridamole on the responses to adenosine in atrial contractility and pacemaker activity

<table>
<thead>
<tr>
<th>Dose of adenosine (µg)</th>
<th>Dipyridamole treatment* (N=5)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
</tr>
<tr>
<td></td>
<td>NIE (%)</td>
</tr>
<tr>
<td>0.3-1.0</td>
<td>21±4.9</td>
</tr>
<tr>
<td>3-10</td>
<td>46±8.2</td>
</tr>
</tbody>
</table>

* i.a. single injection of 10 to 30 µg or continuous infusion of 1 to 30 µg/min.
Control atrial rate was 112±3.8 beats/min (mean±s.e.) in 5 preparations. NIE, negative inotropic effect; NCE, negative chronotropic effect.

effect and dipyridamole potentiated not only the duration but also the maximum decreases in the developed tension and rate induced by adenosine. These potentiation effects of dipyridamole continued approximately 20-40 min in 5 preparations. Summarized data are shown in Table 1.

The mode of action of this potentiation induced by dipyridamole has been explained by block of adenosine uptake, inhibition of adenosine deaminase or inhibition of phosphodiesterase (Schümann 1958; Koss et al. 1962; Pfleger and Schöndorf 1969; Kolassa et al. 1970; Hopkins 1973). However, it was also reported that dipyridamole potentiated not only adenosine but also norepinephrine, 5-HT or angiotensin in the renal circulation (Hashimoto et al. 1970). Therefore, another mechanism may be involved in addition to above mechanisms. The detail of the experiments will be reported elsewhere.

References


