DIFFERENCES AMONG DIPYRIDAMOLE, CARBOCHROMEN AND LIDOFLAZINE IN RESPONSES OF THE CORONARY AND THE RENAL ARTERIES

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Received for publication June 29, 1972

Chemical compounds which are used as coronary vasodilators in the clinic may be divided into specific and non-specific groups. Dipyridamole (1), carbochromen (2) and lidoflazine (3) belong to the former, while nitroglycerin and papaverine derivatives are typical drugs belonging to the latter.

Since Bretschneider (4) discovered in 1962 that dipyridamole potentiated hypotensive response to adenosine, extensive studies have been published as to the effect of dipyridamole on adenosine metabolism. Miura et al. (5) observed a marked potentiation of adenosine induced coronary vasodilation after dipyridamole treatment. On the other hand, Hashimoto et al. (6) described that dipyridamole induced a vasoconstriction in the renal artery similar to the effects of AMP or adenosine. Sakai et al. (7) found that in the renal artery dipyridamole potentiated vasoconstrictor response not only to adenosine and AMP but also to norepinephrine. Recently, the authors (8) confirmed a potentiation of coronary vasodilator response to norepinephrine after dipyridamole treatment. In this paper, the effects of dipyridamole, carbochromen and lidoflazine on the renal and the coronary vessels have been compared. A constant volume perfusion was arranged and the change in perfusion pressure was recorded.

Drug solution, 0.1 ml was injected intra-arterially in a period of 10 sec. The continuous administration of drug solution was performed using a Harvard infusion pump (Model 600/900). Dipyridamole was infused at a rate of 0.01 and 0.1 μg/min and carbochromen or lidoflazine was infused at the rate of 0.1 and 1.0 μg/min.

METHODS

Arrangement for coronary perfusion (Fig. 1)

Langendorff's dog heart preparations with ventricular fibrillation were perfused with arterial blood of a donor dog by the cross-circulation technique. Sixty-eight adult mongrel dogs of both sexes were used in thirty-four experiments. Recipient dogs, 7 to 10 kg of body wt., were anesthetized with sodium pentobarbital, 30 mg/kg i.v. Donor dogs, over 18 kg of body wt. were anesthetized with morphine, 10 mg/kg and 1 g/kg of urethane s.c. Sodium heparin, 500 U/kg was initially given and 200 U/kg added at 2 hr intervals.
The perfusion pressure was kept at 100 mm Hg throughout the experiment and was monitored using an electromanometer (Nihon Kohden RP-2). Changes in the coronary blood flow were measured using an electromagnetic flowmeter (Nihon Kohden MF-2).

**Arrangement for the perfusion of the kidney (Fig. 2)**

Six mongrel dogs of both sexes, weighing 11 to 13 kg were used. Animals were anes-

![Diagram of the modified Langendorff's dog heart preparation](image1)

**Fig. 1.** Diagram of the modified Langendorff's dog heart preparation. EF, electromagnetic flow-meter; EM, electric manometer; DSP, Dale-Schuster pump; TS, thermostat; PR, pneumatic resistance; Rv, blood reservoir (venous side); Ra, blood reservoir (arterial side); AC, air cushion; Ca, carotid artery; Jv, jugular vein; PT, pulmonary trunk and A, aorta.

![Diagram for constant flow perfusion of the renal artery with blood from the femoral artery](image2)

**Fig. 2.** Diagram for constant flow perfusion of the renal artery with blood from the femoral artery. EF, electromagnetic flow-meter; PP, manometer for perfusion pressure and SP, manometer for blood pressure.
The left renal artery was cannulated and perfused with the animal's own blood led from the femoral artery by a Sigma-motor pump.

RESULTS

1) Effects of dipyridamole, carbochromen and lidoflazine on the coronary blood flow

Typical responses to dipyridamole, carbochromen and lidoflazine in the canine heart are illustrated in Fig. 3. Dipyridamole, carbochromen and lidoflazine induced potent and long-lasting coronary vasodilatation. The threshold dose of dipyridamole was approx. 10 μg, and the effect of 1 mg continued for approx. 30 min. The threshold dose of carbochromen was 100 μg, and carbochromen had initial and transient vasoconstriction followed by long-lasting vasodilatation. The effect of 1 mg lasted for approx. 30 min. The threshold dose of lidoflazine was 10 μg. It caused a rapid increase in coronary blood flow to a maximum value and then gradually recovered to the initial level. The effect of 1 mg lasted for approx. 30 min. The initial increase was mainly attributed to tartaric acid, 1.0 ml of 0.1 N, in which lidoflazine is dissolved, because tartaric acid itself does transiently increase the coronary flow.

2) Effects of carbochromen and lidoflazine on the renal blood flow

A typical experiment is shown in Fig. 4. Dipyridamole increased the renal vascular resistance as reported previously (6). Carbochromen also increased an increase of the renal arterial resistance in 5 of 6 experiments, when administered into the renal artery. There was no change in one case. Lidoflazine, however, produced a slight initial dilation followed by vasoconstriction in 3 cases out of 6 while in other cases vasodilatation was ob-

![Fig. 3. Coronary vascular responses to 1 mg of dipyridamole, carbochromen and lidoflazine.](image-url)
Fig. 4. Renal vascular responses to dipyridamole, carbochromen and lidoflazine.

Fig. 5. Responses produced by adenosine were potentiated by infusion of 0.01 μg/min and 0.1 μg/min and 0.1 μg/min of dipyridamole. P.P., perfusion pressure; C.F., coronary flow.

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3) Effects of dipyridamole, carbochromen and lidoflazine on the adenosine-induced dilatation of the coronary artery in the fibrillating heart

Figs. 5, 6 and 7 show effects of dipyridamole, carbochromen and lidoflazine on the adenosine-induced vasodilatation respectively. The vasodilator action of adenosine was served. Tartaric acid, a solvent of lidoflazine, had no effect on the renal artery.
FIG. 6. Responses by adenosine (Ade) were potentiated by infusion of 0.1 μg/min but not potentiated by a rate of 1.0 μg/min of carbochromen. P.P., perfusion pressure and C.F., coronary flow.

markedly increased, 69±11% by infusion of dipyridamole at a rate of 0.01 μg/min, while this increase rather diminished to about one half, 34±6%, when the infusion rate of dipyridamole was increased up to 0.1 μg/min. Adenosine-induced coronary dilator response was potentiated by carbochromen infusion at a rate of 0.1 μg/min in 40±9%. Potentiation was not observed, however when the rate of carbochromen infusion was increased to 1 μg/min. Lidoflazine potentiated adenosine-induced coronary vasodilation in the similar grade at a rate of either 0.1 or 1 μg/min. Results are summarized in Table 1.

Fig. 7. Coronary vascular response to adenosine was potentiated at both infusion of 0.1 μg/min and 1.0 μg/min of lidoflazine. P.P., perfusion pressure and C.F., coronary flow.
4) Effects of dipyridamole, carbochromen and lidoflazine on norepinephrine-induced coronary vasodilatation in fibrillating hearts

A typical experiment is shown in Fig. 8. Dipyridamole potentiated norepinephrine-induced coronary vasodilatation in 4 out of 6 experiments, but carbochromen and lidoflazine did not.

**Table 1.** Effects of dipyridamole, carbochromen and lidoflazine on the coronary vasodilator action of adenosine, 10 µg, in the fibrillating heart.

| Drug       | Dose of infusion (µg/min) | No. of expts. | Initial flow rate (ml/min mean±S.E.) | Increase in % (mean±S.E.) |
|------------|---------------------------|---------------|-------------------------------------|--------------------------|
| Dipyridamole | 0.01                      | 4             | 69±11                               | 67±9                     |
|            | 0.1                       | 4             | 34±6                                 |                          |
| Carbochromen | 0.1                       | 4             | 40±9                                 | 53±10                    |
|            | 1.0                       | 4             | 5±8                                  |                          |
| Lidoflazine | 0.1—1.0                   | 8             | 33±15                                | 50±8                     |

**Table 2.** Effects of dipyridamole, carbochromen and lidoflazine on the coronary vasodilator action of norepinephrine, 1 µg, in the fibrillating heart.

| Drug       | Dose (µg) | No. of expts. | Increase in % (mean±S.E.) |
|------------|-----------|---------------|--------------------------|
| Dipyridamole | 10        | 6             | 21±6                     |
| Carbochromen | 100       | 6             | 1±7                      |
| Lidoflazine  | 10        | 6             | 8±10                     |

**Fig. 8.** Potentiation of norepinephrine-induced coronary vasodilation by dipyridamole but not by carbochromen and lidoflazine.
DISCUSSION

Dipyridamole, carbochromen and lidoflazine induced selective vasodilatation in the coronary circulation when given intravenously. Although the chemical constitutional formulas are quite different, some common features were observed in peripheral vascular responses. When selectively administered, a long-lasting vasodilatation was induced in the coronary artery, while the dilatation in the mesenteric and the femoral arteries was weak and transient. Vasoconstriction was observed in the renal artery.

Bretschneider (4) reported that dipyridamole potentiated adenosine-induced hypotension in vivo, and Hashimoto et al. (6) observed that adenosine and AMP caused vasodilatation in the coronary, the mesenteric and the femoral arteries, while vasoconstriction resulted in the renal artery. If adenosine or AMP is considered as a common metabolite of adenine nucleotides in these organs, vascular responses induced by these coronary dilators could be explained on the basis of interaction with adenosine or AMP, as these compounds potentiate vascular responses of adenosine or AMP. These compounds could then be termed "specific coronary vasodilators".

Berne and his co-workers (9-11) detected degradation products of adenosine in the venous blood following a brief interruption in the coronary circulation, thus suggesting that adenosine plays a key role of coronary circulation as a mediator. Gerlach and Deuticke (12) observed that a significant amount of adenosine accumulated in the ischemic myocardium after dipyridamole. Miura et al. (5) reported that selective administration of dipyridamole into the coronary artery augmented both adenosine-induced vasodilation and reactive hyperemia. Afonso et al. (13) reported that a certain potentiation of adenosine-induced coronary vasodilatation was also observed with lidoflazine treatment.

In the present experiments, adequate doses of carbochromen and lidoflazine also potentiated adenosine-induced vasodilation in the coronary artery. Previously, the dilator action of dipyridamole was ascribed to inhibition of the disappearance of adenosine from the blood (14) and the rate of disappearance from dog whole blood after administration of dipyridamole was due to a permeability decreasing action on the platelet membranes (15). Potent long-lasting coronary vasodilation and potentiation of adenosine-induced coronary vasodilation, and induction of renal vasoconstriction are common with dipyridamole, carbochromen and lidoflazine but there are differences in responses as follows: 1) Lidoflazine reduces the rate of disappearance of adenosine from the blood by the same mechanism as that of dipyridamole, while carbochromen has no effect(15). 2) Dipyridamole potentiates not only the effect of adenosine but also coronary dilation induced by norepinephrine, while carbochromen and lidoflazine only potentiate the adenosine-induced coronary dilation. 3) The potentiation of vascular response to adenosine is inversely reduced by increasing doses of dipyridamole and carbochromen but not with increasing doses of lidoflazine. 4) The renal artery responds to dipyridamole and carbochromen by vasoconstriction, but to lido-
flazine with only initial vasoconstriction followed by vasodilation and sometimes with vasodilation only.

Previously Yasuda et al. (16) observed the potentiation of adenosine-induced vasoconstriction in the renal circulation with a lower dose of dipyridamole but such potentiation was not observed with a larger dose. These observations hardly explain the hypothesis mentioned above, in which the probable mechanism of the coronary dilation is ascribed to the activity preventing disappearance of adenosine from whole blood by reducing adenosine permeability of the tissue cell membrane. Shahab and Wollenberger (17), however, proved the release of norepinephrine by temporal occlusion of the coronary artery suggesting a mediator action of catecholamine in the coronary circulation. Recently, a definite interaction between adenosine and catecholamine has been demonstrated (18). It is hence presumed that the mechanism of these coronary vasodilators is based on prevention of the disappearance of adenosine, modified in different ways at the effector site of the vascular smooth muscle according to the direct effect. "Specific" coronary vasodilators are differentiated from others by the specificity of activity on inhibition of deamination of adenosine (13, 15), but can be more reasonably classified by the qualitative difference among responses of the peripheral circulation especially in the renal vasoconstriction, as other coronary vasodilators also dilate the renal artery.

SUMMARY

The vascular responses of the coronary and the renal arteries to dipyridamole, carbochromen and lidoflazine were studied using Langendorff's isolated heart preparations and blood perfused kidney preparations of dogs. Common character of these specific coronary vasodilators was a potent long-lasting coronary vasodilatation, while the renal vasculature was constricted. The adenosine-induced coronary vasodilatation was potentiated by these drugs, which reached a maximum and then became less with increasing doses. Dipyridamole also potentiated the norepinephrine-induced coronary vasodilatation while the other two compounds did not potentiate norepinephrine at all. The above observations can hardly be explained only by inhibition of disappearance of adenosine from the blood. The authors suggest that this principal mechanism is modified by direct effect of these drugs on the vascular smooth muscle, which in turn characterizes the different responses.

Addendum: It has recently been suggested that carbochromen metabolite induced dipyridamole-like action preventing disappearance of adenosine in the whole blood after carbochromen is hydrolysed (Dr. Shoichi Imai: personal communication).

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