Cardiovascular Effect of [3, 4-dihydro-8-(2-Hydroxy-3-Isopropylaminopropoxy)-3-Nitrato-2H-1-Benzopyran] (K 351)

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SUMMARY

Cardiovascular effect of a new compound, K 351, was examined in anesthetized dogs. Intravenous injections of 100 $\mu\text{g/Kg}$ or over of K 351 caused a fall in systemic blood pressure, reduced peripheral vascular resistance, left ventricular enddiastolic pressure, max dP/dt and V_{max} , and increased time constant T and PQ interval. Heart rate was reduced with 1 $\mu\text{g/Kg}$ K 351. The magnitudes of the changes in heart rate, T and PQ interval were not different between K 351 and propranolol groups, while those in max dP/dt and V_{max} caused by K 351 were larger than those induced by the same doses of propranolol. It is suggested that K 351 suppressed left ventricular contractility, sinus node activity and atrioventricular conduction through its β -receptor blocking action and reduced peripheral vascular resistance and left ventricular enddiastolic pressure through its vasodilating action.

Additional Indexing Words:

K 351 β -blocking action Vasodilating action Intrinsic
adrenoceptor Venous return Left ventricular function

THREE, 3, 4-dihydro-8-(2-hydroxy-3-isopropylaminopropoxy)-3-nitrato-2H-1-benzopyran (K 351) was found by Uchida and his coworkers during search for antihypertensive agents of a new type. Although its antihypertensive effect was proved in spontaneously hypertensive rats (SHR), DOCA/saline rats, and in Goldblatt rats,¹⁾ cardiovascular action of the agent is not well known. Therefore, I examined the effect of intravenous injections of the agent on cardiovascular systems in anesthetized dogs.

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MATERIALS AND METHODS

Fourteen mongrel dogs were anesthetized with intravenous pentobarbital sodium (35 mg/Kg). The trachea was intubated for positive pressure respiration with air. The fourth rib on the left side was removed. After pericardiotomy, a catheter-tip manometer (Miller, TCB-100) was introduced through a pulmonary vein into the left ventricle for measurement of left ventricular pressure. The first derivative of the ventricular pressure, dP/dt , was obtained by a unit (Nihonkoden, EQ-600G). A magnetic flowmeter was placed at the left circumflex coronary artery to monitor coronary blood flow. Another flowmeter was placed at the aortic root to monitor aortic blood flow. Monopolar electrodes were placed on four limbs for recording electrocardiogram (the second limb lead). A catheter was introduced in retrograde fashion through the left subclavian artery into the aortic arch for measurement of systemic blood pressure. Heart rate was obtained by a pulse-integrator triggered by R wave of electrocardiogram. Heart rate, pressures, flows, and electrocardiogram were recorded on a pen-recorder (Saneisokki, S-50). At the same time, electrocardiogram, left ventricular pressure and dP/dt were recorded on a photo-recorder (Nihonkoden, 2933) and they were used for calculation of $\max dP/dt$, $V_{\max}^{2)}$ and the first index of left ventricular relaxation, time constant T .³⁾

K 351 and propranolol were dissolved in distilled water and were injected intravenously. In 7 dogs, K 351 was injected at an interval of 15 min by increasing the dose stepwise since the peak changes in flows and pressures appeared within 15 min in a preliminary study. Also, propranolol was injected at an interval of 15 min in another group of 7 dogs. The peak changes in heart rate, pressures, flows, $\max dP/dt$, $V_{\max}$, and T were compared with the control values and between K 351 and propranolol groups.

RESULTS

Fig. 1 shows the effect of intravenous injection of 100 $\mu\text{g/Kg}$ of K 351 on systemic and left ventricular pressures, aortic and coronary flows, electrocardiogram and heart rate observed in a preliminary experiment. Following the injection, heart rate and pressures were reduced. Aortic blood flow increased transiently and then returned to the control level, or decreased. Coronary blood flow usually decreased and did not show any increase. Heart rate was reduced with 1 $\mu\text{g/Kg}$ K 351. However, the threshold dose for reduction of heart rate and the magnitude of heart rate reduction were not different between K 351 and propranolol (Fig. 2). Systemic blood pressure was low-

Fig. 1. From top channel: aortic blood flow (AoF), systemic blood pressure (SBP), coronary blood flow (CBF), electrocardiogram (ECG), left ventricular pressure (LVP), and heart rate (HR). K 351 was injected at arrow.

Fig. 2. Effects of K 351 and propranolol on HR and mean SBP. The values are shown as mean $\pm$ SE. C=control value. Open circles=K 351. Solid circles=propranolol. † and ††: $p < 0.05$ and < 0.01 respectively, when compared with the control values. # and ##: $p < 0.05$ and < 0.01 respectively, when compared between K 351 and propranolol groups.

ered with 100 $\mu\text{g/Kg}$ or over of K 351 while no significant reduction in systemic blood pressure was induced by propranolol with doses below 500 $\mu\text{g/Kg}$ (cumulative dose 611 $\mu\text{g/Kg}$) (Fig. 2). Aortic blood flow at the peak fall in systemic blood pressure, was reduced with 10 $\mu\text{g/Kg}$ (cumulative dose, 11 $\mu\text{g/Kg}$) K 351. Similarly, the flow was also reduced with 500 $\mu\text{g/Kg}$ propranolol (Fig. 3). Peripheral vascular resistance was reduced with 100 $\mu\text{g/Kg}$ (cumulative dose, 111 $\mu\text{g/Kg}$) or over of K 351. Differing from K 351, propranolol could not reduce the peripheral vascular resistance (Fig. 3). Coronary blood flow was reduced by K 351. The magnitude of the flow reduction induced

Fig. 3. Effects of K 351 and propranolol on mean AoF and peripheral vascular resistance (PVR).

Fig. 4. Effects of K 351 and propranolol on CBF and coronary vascular resistance (CVR).

by K 351 was larger than that caused by the same dose of propranolol. However, coronary vascular resistance was not increased by K 351 (Fig. 4).

Figs. 5 and 6 show the changes in left ventricular pressure and dP/dt caused respectively by K 351 and propranolol. Left ventricular enddiastolic pressure was reduced with 100 μg/Kg (cumulative dose, 111 μg/Kg) or over of K 351, and it was also elevated with the same dose of propranolol. The time-constant T which is an indicator of left ventricular relaxation, was increased by both K 351 and propranolol, indicating that relaxation was suppressed by these agents (Fig. 7). The magnitudes of the reductions in max dP/dt caused by K 351 were larger than those caused by the same doses of propranolol (Fig. 8). PQ interval of the electrocardiogram was increased by K 351, but the magnitude of the increase was not different between K 351 and propranolol groups. QT was interval little influenced by K 351 (Fig. 9).

Fig. 5. Effect of 500 $\mu\text{g/Kg}$ K 351 on left ventricular pressure and dP/dt. Upper half: before K 351. Lower half: after K 351.

Fig. 6. Effect of propranolol on left ventricular pressure and dP/dt. Upper half: before propranolol. Lower half: after 500 $\mu\text{g/Kg}$ propranolol.

DISCUSSION

In this study, K 351 reduced systemic and left ventricular enddiastolic pressures, while propranolol increased left ventricular enddiastolic pressure and did not cause a fall in systemic blood pressure except when a large dose

Fig. 7. Effects of K 351 and propranolol on left ventricular enddiastolic pressure (LVEDP) and time constant T.

Fig. 8. Effects of K 351 and propranolol on max dP/dt and V_{max} .

Fig. 9. Effects of K 351 and propranolol on PQ and QT_c intervals.

was used. These were the essential differences between K 351 and propranolol.

K 351 relaxed while propranolol did not relax vascular smooth muscles

in vitro.⁴⁾ Therefore, the difference in the actions on vascular smooth muscles may have caused the different effects on systemic and left ventricular end-diastolic pressures. The relaxing action of K 351 on vascular smooth muscles was lost when the radical of ONO_2 was replaced by OH, indicating that ONO_2 is essential for the vasodilating action of K 351 in a preliminary study. A decrease in peripheral vascular resistance and a rapid fall in systemic blood pressure induced by K 351 can be attributed to the vasodilating action in which ONO_2 plays an important role. Kuriyama suggested that the vaso-depressor action of K 351 is partly attributable to its inhibitory action on intrajunctional adrenoceptor (α_3 -receptor).⁵⁾ K 351 caused a decrease in heart rate, suppressed max dP/dt and V_{max} , and increased PQ interval. Since the agent has β -receptor blocking action and since the action remains even after ONO_2 was replaced by OH,⁴⁾ these changes can be attributed to its β -receptor blocking action.

Despite a decrease in heart rate and reductions in V_{max} and an increase in time constant T which otherwise can result in elevation of left ventricular enddiastolic pressure, K 351 caused a fall in left ventricular enddiastolic pressure. Such a change was not produced by propranolol. It is supposed that the decreased peripheral vascular resistance and decreased venous return⁴⁾ counterated the negative chronotropic and inotropic actions of K 351, leading to a decreased enddiastolic pressure.

In the failing heart, a rise in left ventricular enddiastolic pressure plays an important role in production of pulmonary congestion, and therefore treatment is generally directed to lower the enddiastolic pressure. Since the majority of β -receptor blocking agents have negative inotropic action, they tend to aggravate congestive heart failure, by reducing left ventricular contractility and elevating left ventricular enddiastolic pressure.⁶⁾ Although K 351 has negative inotropic action as in case of propranolol, it reduced left ventricular enddiastolic pressure. Therefore, it is promising that congestive heart failure can less be aggravated by K 351.

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