Cardiohemodynamic Effects of Nipradilol (K-351) in the Dog: Comparison with Propranolol, Nadolol and Prazosin

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Accepted May 17, 1986

Abstract—The cardiohemodynamic effects of nipradilol (K-351) were studied in comparison with those of propranolol, nadolol and prazosin in anesthetized, open-chest dogs. All drugs were administered intravenously. Nipradilol produced dose-dependent decreases in systemic blood pressure (BP), heart rate (HR), venous return (VR) and cardiac output (COP), but virtually no change in right atrial pressure (RAP). Propranolol decreased HR, tended to decrease VR and COP and increased RAP, but produced no change in systemic BP. Nadolol also decreased HR, VR and COP and increased RAP, but did not change systemic BP. Prazosin decreased systemic BP, VR and COP and tended to decrease RAP, but scarcely affected HR. After propranolol or nadolol, nipradilol failed to reduce HR, but still produced definite decreases in systemic BP, VR and COP and a slight decrease in RAP. After prazosin, nipradilol still produced decreases in systemic BP, HR, VR and COP. These results suggest that nipradilol decreases VR and COP mainly by increasing venous capacitance through direct venodilator action and in part by increasing resistance to VR through beta-adrenoceptor blockade. This effect also appears to be responsible for its hypotensive effect.

Nipradilol (K-351) is a unique beta-adrenoceptor blocking agent because it possesses a nitroxy group in its chemical structure (1). The nitroxy group was incorporated into the chemical structure with the aim of making the compound possess a nitroglycerin-like action in addition to a beta-adrenoceptor blocking action (1). In the treatment of patients with angina pectoris, hypertension or both, such a beta-adrenoceptor blocking agent would be superior to hitherto known beta-adrenoceptor blocking agents that block beta-adrenoceptors alone. This is because increases in coronary arterial resistance and total peripheral resistance by beta-adrenoceptor blocking agents, particularly seen in the acute phase, are their main drawbacks. If the drug reduces the preload as nitroglycerin does, this property is also favorable as an antianginal agent. Nipradilol has been shown to be only about 2 times as potent as propranolol in producing a non-selective beta-adrenoceptor blocking effect in isolated guinea-pig atria and trachea (1). Nevertheless, nipradilol, unlike propranolol, produces a definite hypotensive effect in spontaneously hypertensive and DOCA hypertensive rats after acute oral administration, suggesting that it possesses some types of vasodilator action (1, 2). The direct relaxant action of nipradilol on vascular smooth muscle has been demonstrated in isolated arteries and veins (1, 3). However, these findings are unable to settle the question of whether the hypotensive and vascular relaxant action of nipradilol can be ascribed to its nitroglycerin-like action. The following findings are highly suggestive of the nitroglycerin-like action of nipradilol. Unlike propranolol, nipradilol decreased left ventricular end-diastolic pressure (LVEDP) in anesthetized dogs (4). This is remarkable in view of the fact that nipradilol has a certain degree of negative inotropic and non-specific membrane stabilizing actions (1, 5). Nipradilol...
also decreased central venous pressure previously raised with dihydroergotamine in pithed rats, suggesting the reduced venous return (VR) through its dilator effect on capacitance vessels (6). However, so far no experimental data are available about whether nipradilol really produces a reduction of VR and consequently a reduction of cardiac output (COP). The present study was carried out to elucidate whether nipradilol mimics nitroglycerin or other nitrates in cardiohemodynamic effects particularly in its effects on VR and right atrial pressure (RAP) in anesthetized, open-chest dogs. The effects of propranolol, nadolol and prazosin were also investigated in order to estimate the possible contribution of alpha- or beta-adrenoceptor blocking action to the cardiohemodynamic effects of nipradilol, because nipradilol has also been shown to possess a weak alpha-adrenoceptor blocking action (1).

Materials and Methods

Experiments were performed on young mongrel dogs of both sexes weighing 7 to 11 kg which were free from filarial infection. The preparation was essentially the same as had been used by Kokubun et al. (7) and Imai et al. (8). The animals were anesthetized with sodium pentobarbital initially at a dose of 30 mg/kg, i.v., and hourly at a maintenance dose of 4 to 5 mg/kg, i.v. Under artificial respiration with room air in a tidal volume of 20 ml/kg at a rate of 18 breaths/min by the use of a dog respirator (Harvard Apparatus, Model 607), the chest was opened by mid-sternal incision. The azygos vein was ligated and both phrenic nerves were cut. The heart was kept in position by the pericardial cradle. Non-cannulating probes of a 2-channel electromagnetic flowmeter (Nihon Kohden, MF-27) were fitted to the superior and inferior vena cavae to measure the mean blood flow through the two vessels. The mean blood flow through the pulmonary trunk was also measured with another non-cannulating probe of a 1-channel electromagnetic flowmeter (Nihon Kohden, MFV-1200). The mean right atrial pressure was measured with a pressure transducer (Nihon Kohden, LPU-0.1). The zero base line reference for the RAP was set equal to the level of the tricuspid valve. These 4 variables were recorded on a 4-channel rectilinear recorder (Watanabe Sokki, Linear Corder Mark 3). The systemic blood pressure was measured at the femoral artery with a pressure transducer (Statham, P-50). The heart rate was measured with a cardiotachometer (Sanei, type 2140) which was triggered by the R wave of lead II electrocardiograms. These two variables were recorded on a 6-channel rectilinear recorder (Sanei, 8S). The zero flow level in each probe was simultaneously determined at the end of the experiment when the cardiac arrest was abruptly produced by a rapid injection of saturated KCl solution.

The drugs used were as follows: Nipradilol (Kowa), (+)-propranolol hydrochloride (Kowa), (±)-nadolol (Squibb) and prazosin hydrochloride (Pfizer Taito). Nipradilol and nadolol were dissolved in 0.1 N HCl to give a concentration of 30 mg/ml, and propranolol was dissolved in 0.9% saline at a concentration of 10 mg/ml. These drug solutions were diluted with 0.9% saline to the desired concentrations. Prazosin was dissolved in distilled water to give a concentration of 0.5 mg/ml and then diluted with distilled water. All the drugs were injected into the femoral vein in doses of 1, 2, 7, 20, 70, 200 and 700 µg/kg at 10 min intervals. These doses correspond to the cumulative doses of 1, 3, 10, 30, 100, 300 and 1000 µg/kg, respectively. Doses of drugs refer to their bases.

Values of changes in cardiohemodynamic variables used for construction of dose-response curves refer to those just before administration of the next dose.

Statistical significance of difference between mean values was evaluated by Student's paired t-test. A P value of less than 0.05 was considered to be significant.

Results

Control values of 9 cardiohemodynamic variables: The control values of 9 cardiohemodynamic variables in 20 dogs are presented in Table 1. The pulmonary arterial blood flow (PAF) which represents the total COP was within a range from 600 to 1000 ml/min. The blood flow through the inferior
Table 1. Control values of cardiohemodynamic variables in 20 dogs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>129±20</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>84±15</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>99±16</td>
</tr>
<tr>
<td>PAF (ml/min)</td>
<td>733±136</td>
</tr>
<tr>
<td>IVCF (ml/min)</td>
<td>519±106</td>
</tr>
<tr>
<td>SVCF (ml/min)</td>
<td>208±62</td>
</tr>
<tr>
<td>VR (ml/min)</td>
<td>727±133</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>21±5</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>137±19</td>
</tr>
</tbody>
</table>

Body weight was 9.4±1.1 (mean±S.D.) kg. SBP, DBP and MBP: systolic, diastolic and mean blood pressure, respectively; PAF, IVCF and SVCF: blood flow through the pulmonary artery, inferior vena cava and superior vena cava, respectively; VR: venous return; RAP: right atrial pressure; HR: heart rate.

Fig. 1. Cardiohemodynamic effects of nipradilol in an anesthetized, open-chest dog. SBP: systemic blood pressure; PAF, IVCF and SVCF: blood flow through the pulmonary artery, inferior vena cava and superior vena cava, respectively; VR: venous return; RAP: right atrial pressure; HR: heart rate.

Effects of nipradilol on cardiohemodynamics: The effects of cumulative intravenous injections of nipradilol (1–1000 μg/kg) were studied in 5 dogs. A typical experiment is shown in Fig. 1, and changes in cardiohemodynamic variables are summarized in Fig. 2. Nipradilol significantly decreased the SBP in doses of 10–1000 μg/kg in a dose-dependent manner. In doses larger than 30...
μg/kg, the DBP and MBP also decreased; however, the decrease was more pronounced in SBP than in DBP or MBP, at 1000 μg/kg the decrease was 59±14 mmHg in SBP as against 26±10 mmHg and 37±11 mmHg in DBP and MBP, respectively. With doses of 10–1000 μg/kg, the PAF significantly decreased after a slight and transient increase. At the largest dose (1000 μg/kg), the PAF decreased down to about 56% of the control values. The IVCF decreased in doses larger than 30 μg/kg, but the SVCF remained virtually unchanged in all the doses except for 1000 μg/kg. The changes in VR are very similar to those in the PAF; at a dose of 1000 μg/kg, the VR decreased by 338±59 ml/min. The RAP tended to increase in relatively small doses, and no further increase occurred with increasing doses. However, these changes in RAP were not statistically significant. The HR decreased in a dose-dependent manner in doses of 3–1000 μg/kg.

Effects of propranolol on cardiohemodynamics: The effects of propranolol (1–1000 μg/kg, i.v.), a non-selective beta-adrenoceptor blocking agent, were examined in 5 dogs, and data are summarized in Fig. 3. Propranolol had virtually no effects on the SBP, DBP and MBP. The PAF tended to decrease with increasing doses, but decreases were not statistically significant except for the largest dose (1000 μg/kg). There also were small decreases in IVCF and VR, although these changes were not statistically significant. The decrease in VR produced by 1000 μg/kg of propranolol was 100±64 ml/min, which was much smaller than that produced by the same dose of nipradilol. The SVCF did not change in all the doses examined. Unlike nipradilol, propranolol caused a dose-dependent increase in RAP; with a dose of 1000 μg/kg, the RAP increased by 8.8±2.4 mmH2O. The HR decreased in a dose-dependent manner in doses of 3–1000 μg/kg.

Effects of nadolol on cardiohemodynamics: The effects of nadolol (1–1000 μg/kg, i.v.), a non-selective beta-adrenoceptor blocking agent which lacks a direct cardio-depressant action (9), were studied in 5 dogs, and results are summarized in Fig. 4. Nadolol did not change the SBP, DBP and MBP in all the doses examined. The PAF and IVCF decreased moderately in doses of 3–1000 μg/kg, and the SVCF decreased in doses of 30 and 100 μg/kg. The VR decreased in doses of 1–1000 μg/kg, but even at the largest dose, the decrease remained only by

**Fig. 2.** Dose-response curves to nipradilol for changes in cardiohemodynamic variables. Abbreviations are the same as in Table 1. Data points represent means±S.E. of 5 dogs. *P<0.05, **P<0.01 against the respective control values.
140±21 ml/min, which was considerably smaller than that produced by nipradilol. Despite lack of a direct cardiodepressant action, nadolol produced a significant increase in RAP in doses of 3 and 10 μg/kg. The HR decreased in a dose-dependent manner in doses of 1–100 μg/kg, and the decrease attained to the maximum with 100 μg/kg.

Effects of prazosin on cardiohemodynamics: The effects of prazosin (1–1000 μg/kg, i.v.), a selective alpha1-adrenoceptor blocking agent, were examined in 5 dogs, and data are summarized in Fig. 5. Prazosin in doses of 1–100 μg/kg produced dose-dependent decreases in SBP, DBP and MBP. The hypotensive effect attained to the maximum with a dose of 100 μg/kg, and no further decrease in blood pressure occurred

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Fig. 3. Dose-response curves to propranolol for changes in cardiohemodynamic variables. Abbreviations are the same as in Table 1. Values are means±S.E. of 5 dogs. *P<0.05, **P<0.01 against the respective control values.

Fig. 4. Dose-response curves to nadolol for changes in cardiohemodynamic variables. Abbreviations are the same as in Table 1. Values are means±S.E. of 5 dogs. *P<0.05, **P<0.01 against the respective control values.
even with increasing doses up to 1000 μg/kg. The IVCF and VR decreased moderately in doses of 3–1000 μg/kg, and at the largest dose (1000 μg/kg), the VR decreased by 126±36 ml/min, although these variables increased transiently after dosing. The PAF and SVCF behaved similarly to the IVCF and VR. The RAP tended to decrease in doses of 3–1000 μg/kg, but the changes were not statistically significant. The HR remained unchanged in all the doses examined.

Comparison of the effects of nipradilol, propranolol, nadolol and prazosin on the relation between the VR and RAP: Since the RAP is one of the determinants of the VR, the correlation between changes in RAP and those in VR was examined. In Fig. 6, changes in RAP caused by the drugs are plotted against those in VR. Nipradilol markedly decreased the VR, but caused virtually no change in RAP; and as a result, there was no significant correlation between the VR and RAP (r=0.057). Propranolol produced a slight decrease in VR which was accompanied by a marked increase in RAP. Consequently, there was a negative correlation between the VR and RAP (r=-0.483, P<0.05). Nadolol also decreased the VR and increased the RAP, but there was no statistically significant correlation between the VR and RAP (r=-0.062). Prazosin caused simultaneous decreases in VR and RAP, although these changes were rather small and statistically insignificant. Thus, there was a positive correlation between the VR and RAP (r=0.756, P<0.001).

Effects of propranolol, nadolol and prazosin on cardiohemodynamic changes produced by nipradilol: The effects of propranolol, nadolol and prazosin on changes in cardiohemodynamic variables produced by nipradilol were further investigated to look into possible involvements of beta- and/or alpha-adrenoceptor blocking activities in the effects of nipradilol. Figure 7 shows the effect of propranolol (1 mg/kg, i.v.), nadolol (1 mg/kg, i.v.) or prazosin (1 mg/kg, i.v.) on changes in SBP, DBP, MBP and HR caused by nipradilol. After propranolol, nadolol or prazosin, nipradilol still produced a dose-dependent hypotensive effect in doses of 10–1000 μg/kg; however, the decrease in SBP produced by 300 μg/kg of nipradilol was slightly attenuated after prazosin. The bradycardia produced by nipradilol was nearly abolished by propranolol or nadolol, whereas prazosin failed to affect the bradycardic effect of nipradilol. Figure 8 illustrates the effects of propranolol, nadolol and prazosin on the changes in PAF, IVCF, SVCF, VR and RAP produced by nipradilol.

Fig. 5. Dose-response curves to prazosin for changes in cardiohemodynamic variables. Abbreviations are the same as in Table 1. Values are means±S.E. of 5 dogs. *P<0.05, **P<0.01 against the respective control values.
The decreases in PAF, IVCF and VR produced by nipradilol were scarcely affected by propranolol or nadolol. After prazosin, nipradilol still caused definite decreases in PAF, IVCF and VR; however, the decreases in IVCF caused by large doses (300 and 1000 μg/kg) of nipradilol were somewhat attenuated by prazosin. Although nipradilol per se was without effect on the RAP, it did cause a significant decrease in RAP after beta-adrenoceptor blockade with propranolol or nadolol. In contrast, after prazosin, the RAP was slightly increased by nipradilol.

Discussion

In the present experiments, nipradilol produced decreases in BP, HR and PAF which is equivalent to the COP, but failed to change the RAP. These results are largely consistant with those obtained by previous workers from anesthetized dogs (4); in their experiments, nipradilol decreased the BP, HR, mean aortic flow and LVEDP. The principal finding of the present experiments was a profound decrease in VR by nipradilol which had not been directly demonstrated so far, although circumstantial evidence has suggested it.

From the comparative study, it became evident that nipradilol differed from current beta-adrenoceptor blocking agents like propranolol and nadolol in the following respects: Firstly, nipradilol produced an immediate and marked decrease in BP, whereas propranolol and nadolol did not. Secondly, nipradilol caused a striking decrease in VR which was much greater than those produced by propranolol and nadolol: e.g., at 1 mg/kg the decrease in VR by nipradilol was about 46% as against only about 14% and 19% by propranolol and nadolol, respectively. Thirdly, nipradilol did not change the RAP which is one of indices of contractility of the heart, whereas propranolol and even nadolol which has no direct cardiodepressant action (9) increased the RAP significantly.

It has been widely accepted that as an acute effect, beta-adrenoceptor blocking agents decrease the COP in man. Experiments on anesthetized dogs (10, 11) have demonstrated that the decrease in COP by
beta-adrenoceptor blocking agents is due to the decreased VR. This decrease has been ascribed to an increase in transhepatic venous resistance due to beta-adrenoceptor blockade (10). In the present experiments, too, the two beta-adrenoceptor blocking agents nadolol and nipradilol definitely reduced the VR, and propranolol also tended to do so. Thus, the decrease in VR by these agents would be attributed at least in part to the beta-adrenoceptor blockade per se. However, the decrease in VR produced by nipradilol was greater than those produced by the other beta-adrenoceptor blocking

Fig. 7. Effects of propranolol, nadolol and prazosin on changes in systolic (SBP), diastolic (DBP), mean blood pressure (MBP) and heart rate (HR) produced by nipradilol. Open circles, control; solid circles, after propranolol (1 mg/kg, i.v.); open triangles, after nadolol (1 mg/kg, i.v.); solid triangles, after prazosin (1 mg/kg, i.v.). Values are means±S.E. of 5 dogs. *P<0.05, **P<0.01 against control group (unpaired t-test.)

Fig. 8. Effects of propranolol, nadolol and prazosin on changes in blood flow through the pulmonary artery (PAF), inferior vena cava (IVCF), superior vena cava (SVCF), venous return (VR) and right atrial pressure (RAP) produced by nipradilol. Otherwise, the same as in Fig. 7.
agents. Therefore, additional mechanisms must be involved in the greater decrease in VR produced by nipradilol.

It has been shown that, although weak, nipradilol possesses an alpha-adrenoceptor blocking action (1). Therefore, a possible involvement of this mechanism should be argued. In the present experiments, the alpha-adrenoceptor blocking agent, prazosin decreased the VR. The observed decrease in VR by prazosin may be attributable to venodilatation resulting from alpha-adrenoceptor blockade, i.e., an increase in venous capacitance. Indeed, prazosin has been reported to dilate more effectively dorsal hand veins than forearm arteries in man both of which were contracted by noradrenaline (12). The extent of decrease in VR by prazosin, however, was only about 17% of the control value even with its largest dose (1 mg/kg) as against about 46% by the largest dose (1 mg/kg) of nipradilol. Moreover, in producing alpha-adrenoceptor blockade nipradilol is far less potent than prazosin (13). Thus, it is unlikely that alpha-adrenoceptor blockade by nipradilol, if any, is greatly involved in the decreased VR.

Alternatively, it is highly likely that another mechanism would be responsible for the reduction of VR by nipradilol. This supposition has become more plausible through the present findings that nipradilol definitely decreased the VR even after propranolol, nadolol or prazosin. Concomitant decreases in VR and RAP by nipradilol after beta-adrenoceptor blockade are very much similar to what has been observed with nitroglycerin (7). As described in the introduction section, nipradilol possesses the nitroxy group, and it has been reported that like nitroglycerin, nipradilol dilates preferentially large conductive coronary arteries (1). Thus, a reduction of VR by nipradilol appears in all probability to be due to its rather preferential dilator action on capacitance vessels.

Another characteristic of nipradilol was a marked hypotensive effect. Here should be argued a role of the effect of nipradilol on the arterial side in producing acute hypotension. Possible mechanisms involved in acute hypotension would be its alpha-adrenoceptor blocking (13) and direct vasodilator (1, 3, 14) actions, however nitroglycerin-like or not it may be. Uchida (4) reported a decrease in peripheral vascular resistance in anesthetized dogs with doses of 100 μg/kg or more of nipradilol. However, in the present experiments, total peripheral resistance remained practically unchanged in all the doses examined (data are not shown). Therefore, it appears that the alpha-adrenoceptor blocking and direct vasodilator actions on arterial beds may not much contribute to the hypotensive effect either. Thus, instead, the reduction in COP following a decrease in VR would be a major cause of the acute hypotensive effect of nipradilol, as suggested by previous investigators (6).

Acknowledgement: We gratefully acknowledge Kowa Co. Ltd., Tokyo for the gift of nipradilol; Squibb Japan, Inc. Tokyo for nadolol; and Pfizer Taito Co. Ltd., Tokyo for prazosin.

References
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