Br. J. Pharmac. (1984), **81**, 409–411

Nicorandil attenuates myocardial acidosis during coronary occlusion in dogs

Y. Abiko, T. Nishimura* & K. Sakai

Departments of Pharmacology and Oral Surgery*, Asahikawa Medical College, Asahikawa 078-11, Japan

1 In dogs anaesthetized with pentobarbitone, the left anterior descending coronary artery (LAD) was partially occluded. Before and 30 min after partial occlusion, the myocardial pH was 7.52–7.54 and 6.89–6.91, respectively.

2 Nicorandil (50 $\mu g\,kg^{-1}$, i.v.) increased the pH that had been reduced by partial occlusion and this effect lasted at least 60 min. Thus nicorandil attenuates ischaemic myocardial acidosis.

Introduction

N-(2-hydroethyl)nicotinamide nitrate (nicorandil) is a recently developed antianginal drug having both coronary and peripheral vasodilator effects (Uchida, *et al.*, 1978; Sakai, *et al.*, 1983). Clinical studies performed in 30 Japanese institutes have revealed that the drug decreases the number of anginal attacks and the consumption of nitroglycerine (Murao & Kimura, 1982), suggesting that nicorandil improves ischaemic changes of the myocardium. If this is so, it should attenuate myocardial acidosis during coronary occlusion. This is because coronary occlusion decreases myocardial pH (Benzing *et al.*, 1971/72; Gebert *et al.*, 1971; Ichihara *et al.*, 1979), and clinically effective antianginal drugs such as nitroglycerine and propranolol attenuate myocardial acidosis induced by partial occlusion of the coronary artery in dogs (Abiko & Sakai, 1980; Shibano & Abiko, 1983). The present study therefore was undertaken to examine whether nicorandil attenuates myocardial acidosis induced by partial occlusion of the dog coronary artery.

Methods

Twelve mongrel dogs of either sex, weighing 8 to 19 kg, were anaesthetized with sodium pentobarbitone (30 $mg\,kg^{-1}$, i.v.). Under artificial respiration, a left thoracotomy was performed and the left anterior descending coronary artery (LAD) was separated free from the adjacent tissues. An electromagnetic flow probe and a snare were placed around the LAD at the level just proximal to the first diagonal branch as described earlier (Abiko & Sakai, 1980). The LAD flow was gradually reduced by about 60% of the original flow by the use of a snare (partial occlusion) and kept constant throughout the experiment. Nicorandil was dissolved in saline to give a concentration of 100 $\mu g\,ml^{-1}$. Nicorandil (50 $\mu g\,kg^{-1}$) or saline (0.5 $ml\,kg^{-1}$) was injected into the femoral vein 30 min after partial occlusion. The myocardial pH was measured by a glass microelectrode (MI-410, Microelectrodes, Londonderry, NH, U.S.A.) inserted in the area that was expected to become ischaemic after partial occlusion. The tip (1 mm in diameter) of the pH electrode was placed about 8 mm below the surface of the ventricular wall. The electrode was calibrated with standard pH solutions (pH 6.840 and 7.384) before each experiment. Changes in myocardial pH were recorded continuously with a pen recorder via a pH meter (F-7 II, Horiba Co., Ltd. Kyoto, Japan). The heart rate was counted from the ECG (standard limb lead II) and systolic and diastolic blood pressures in the left carotid artery were recorded together with LAD flow on a polygraph (San-Ei Instrument, Tokyo, Japan). Experiments were started after a 60 min period of stabilization. Results were evaluated by Student's *t* test for paired data, and the analysis of variance for unpaired data. A *P* value of 0.05 or less was considered significant. Calculation of the mean ± s.e. value of pH and statistical analysis of pH values were made in terms of hydrogen ion concentration ($[H^+]$).

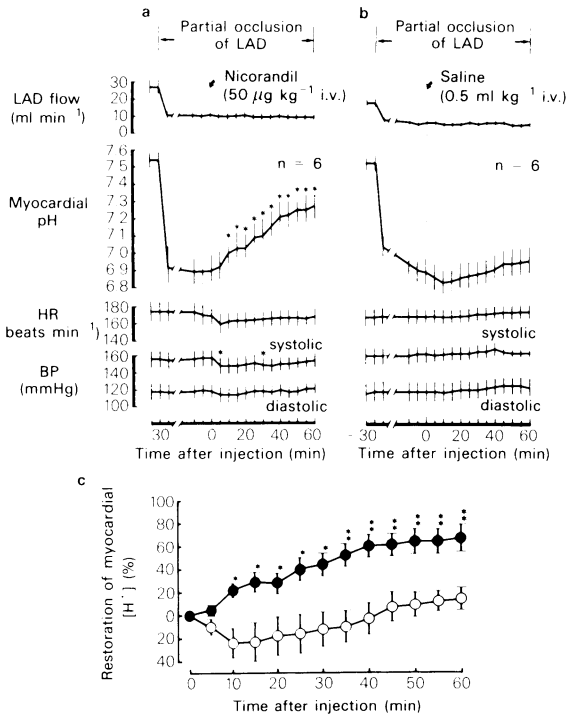

Figure 1 Effect of nicorandil **(a)** or saline **(b)** solution on the left anterior descending coronary artery (LAD) flow, myocardial pH, heart rate (HR), and systolic and diastolic blood pressures (BP) during partial occlusion of LAD in the dog. LAD was partially occluded at −30 min so that the flow was reduced by about 60%; 30 min after partial occlusion (at 0 min) nicorandil or solution was injected. $^{*}P<0.05$, compared with the value at 0 min (paired data analysis). **(c)** Comparison between nicorandil (50 μg kg^{-1}, i.v.) (●) and saline (0.5 ml kg^{-1},i.v.) (○) on the restoration of myocardial hydrogen ion concentration ([H^{+}]) during LAD partial occlusion ($n=6$). The value of myocardial [H^{+}] obtained at −30 min and 0 min was taken as 100 and 0% respectively. Each percent value is calculated from the pH value given in **(a)** and **(b)**. $^{*}P<0.05$, $^{**}P<0.01$ (unpaired data analysis).

Results

Nicorandil experiment (Figure 1a)

The LAD flow, myocardial pH, heart rate, and systolic and diastolic blood pressures immediately before partial occlusion were 27.0 ± 3.5 ml min^{-1}, 7.54 ± 0.05 pH units, 174 ± 13 beats min^{-1}, and 156 ± 11 and 118 ± 10 mmHg, respectively; those 30 min after partial occlusion (0 min in Figure 1), were 10.7 ± 2.0 ml min^{-1}, 6.91 ± 0.08 pH units, 169 ± 11 beats min^{-1}, and 157 ± 10 and 118 ± 9 mmHg, respectively. Thus, myocardial pH decreased by 0.63 units in response to a partial occlusion that resulted in a reduction in LAD flow of about 60%. After an injection of nicorandil (50 μg kg^{-1}), myocardial pH increased rapidly and all the pH values for a period of at least 1 h after the drug injection (except for the values obtained 5 min after the injection) were significantly higher than the pre-injection value. Heart rate and blood pressure did not change after the nicorandil injection, except for systolic blood pressure 5 and 30 min after the injection.

Saline control experiment (Figure 1b)

The LAD flow, myocardial pH, heart rate, and systolic and diastolic blood pressures immediately before partial occlusion were 18.1 ± 1.6 ml min^{-1}, 7.52 ± 0.05 pH units, 162 ± 12 beats min^{-1}, and 161 ± 11 and 118 ± 12 mmHg, respectively; those 30 min after partial occlusion (0 min in Figure 1), were 7.0 ± 1.0 ml min^{-1}, 6.89 ± 0.08 pH units, 163 ± 9 beats min^{-1}, and 162 ± 9 and 118 ± 12 mmHg, respectively. Thus, myocardial pH decreased by 0.63 units in response to a partial occlusion that resulted in a reduction of LAD flow of about 61%. Other parameters did not change significantly after partial occlusion. An injection of saline (0.5 ml kg^{-1}) did not significantly modify any of the parameters.

Discussion

Partial occlusion of LAD reduced myocardial pH by a mean of 0.63 units after a 30 min period of reduced coronary blood flow; this is in agreement with previous studies using this model (Abiko & Sakai, 1980; Ichihara & Abiko, 1982; Izumi *et al.*, 1982; Shibano & Abiko, 1983). The results of the present study indicate that nicorandil attenuates myocardial acidosis during partial occlusion of the LAD, suggesting that the drug improves ischaemic changes in the myocardium. This beneficial action of nicorandil on the ischaemic myocardium is shared by nitroglycerine and propranolol but not by dipyridamole (Ichihara *et al.*, 1979; Abiko & Sakai, 1980; Shibano & Abiko, 1983). The beneficial action of nicorandil is probably because of the coronary vasodilator effect of the drug (Uchida *et al.*, 1978; Taira, *et al.*, 1979; Sakai *et al.* 1981), permitting an increase in perfusion of the ischaemic area by increased blood supply from the non-ischaemic area, in which blood flow has been increased. This assumption is based on the findings of Ogawa *et al.*, 1982. The validity of this assumption, however, requires verification.

References

ABIKO, Y. & SAKAI, K. (1980). Increase of myocardial pH by 1- and d-propranolol during ischemia of the heart in dogs. *Eur. J Pharmac.*, **64,** 239–248.

BENZING, H., GEBERT, G & STROHM, M. (1971/72). Extracellular acid-base changes in the dog myocardium during hypoxia and local ischemia, measured by means of glass micro-electrodes. *Cardiology*, **56,** 85–88.

GEBERT, G., BENZING, H. & STROHM, M. (1971). Changes in the inter-stitial pH of dog myocardium in response to local ischemia, hypoxia, hyper- and hypocapnia, measured continuously by means of glass microelectrodes. *Pflueger's Arch.*, **329,** 72–81.

ICHIHARA, K. & ABIKO, Y. (1982). Effect of diltiazem, a calcium antagonist, on myocardial pH in ischemic canine heart. *J. Pharmac. exp. Ther.*, **222,** 720–725.

ICHIHARA, K., ICHIHARA, M. & ABIKO, Y. (1979). Involvement of *beta* adrenergic receptors in decrease of myocardial pH during ischemia. *J. Pharmac. exp. Ther.*, **209,** 275–281.

IZUMI, T., SAKAI, K. & ABIKO, Y. (1982). Effect of sotalol on ischemic myocardial pH in the dog heart. *Naunyn-Schmiedebergs Arch. Pharmac.* **318,** 340–343.

MURAO, S. & KIMURA, E. (1982). Clinical effects of nicorandil on angina pectoris—a double blind trial in comparison with propranolol. *Rinsho-Yakuri*, **13,** 311–326 (in Japanese).

OGAWA, K., ENOMOTO, I., ITO, T., BAN, M., HASHIMOTO, H. & SAKAI, K. (1982). SG-75 induction of increased coronary outflow and PGE_1 from ischemic areas in dogs with experimental myocardial infarction. *Jap. Heart J.*, **23,** 603–611.

SAKAI, K., NAKANO, H., NAGANO, H. & UCHIDA, Y. (1983). Nicorandil. In *New Drugs Annual: Cardiovascular Drugs.* ed. Scriabine, A. pp. 227–242. New York: Raven Press.

SAKAI, K., SHIRAKI, Y. & NABATA, H. (1981). Cardiovascular effects of a new coronary vasodilator N-(2-hydroxyethyl)nicotinamide nitrate (SG-75): comparison with nitroglycerin and diltiazem. *J. cardiovasc. Pharmac.*, **3,** 139–150.

SHIBANO, T. & ABIKO, Y. (1983). Effects of nitroglycerin, dipyridamole and propranolol on myocardial pH and pO_2 during regional ischemia in the dog heart. *Archs int. Pharmacodyn.*, **264,** 274–289.

TAIRA, N., SATOH, K., YANAGISAWA, T., IMAI, Y. & HIWATARI, M. (1979). Pharmacological profile of a new coronary vasodilator drug, 2-nicotinamidoethyl nitrate (SG-75). *Clin. Exp. Pharmac. Physiol.*, **6,** 301–316.

UCHIDA, Y., YOSHIMOTO, N. & MURAO, S. (1978). Effect of 2-nicotinamido-ethyl nitrate (SG-75) on coronary circulation. *Jap. Heart J.*, **19,** 112–124.

(*Received October 19, 1983.*)