J. Pharm. Pharmacol. 1984, 36: 175–181
Received August 1, 1983

Hypotensive effects and biotransformation of nicorandil, a new antianginal agent, administered to rats by different routes: comparison with nitroglycerin and isosorbide dinitrate

KAZUSHIGE SAKAI†, MICHITAKA AKIMA, YOSHIKAZU HINOHARA* AND NORIKO OBATAKE*

*Department of †Pharmacology and *Biochemistry, Research Laboratories, Chugai Pharmaceutical Co., Ltd., Takada, Toshima-ku, Tokyo 171, Japan*

The effects of nicorandil, *N*-(2-hydroxyethyl)nicotinamide nitrate (ester), in reducing systemic blood pressure (SBP) in rats were studied in comparison with isosorbide dinitrate and nitroglycerin. The drugs were administered to pentobarbitone-anaesthetized rats by jugular vein (i.v.), portal vein (p.v.), intrajejunal (i.j.), intraperitoneal (i.p.) and subcutaneous (s.c.) routes. Nicorandil was absorbed rapidly through all routes, and caused marked hypotension dose-dependently. With isosorbide dinitrate and nitroglycerin, unlike nicorandil, the p.v. dose required to induce a vasodepressor response was significantly greater than that required to cause a comparable response after i.v. administration. In non-recirculating rat liver perfusion experiments, nicorandil was reduced only 5–10% during a single passage through the liver, while nitroglycerin was reduced over 95%. In recirculating liver perfusion experiments, the progressive decrease of nicorandil in the blood recirculated was accompanied by a corresponding increase of SG-86, a denitrate compound of nicorandil (its main metabolite). Sixty min after dosing, nicorandil was decreased by approximately 73% of the initial nicorandil blood concentration and SG-86 was increased by approximately 70%. The extent of degradation of nicorandil in liver homogenates, examined by thin-layer chromatography, was in the following order: rat = guinea-pig > dog = monkey > pig. In these species a close inverse relationship is apparent between the rate of liver nicorandil degradation and hypotensive effects of nicorandil.

Nicorandil, *N*-(2-hydroxyethyl)nicotinamide nitrate (ester), is a newly developed, orally active antianginal drug (Sakai et al 1983b; see review) that is rapidly absorbed from the oral cavity and gastrointestinal tract in dogs, and effects marked coronary vasodilation (Uchida et al 1978a; Taira et al 1979). Further, studies in anaesthetized dogs demonstrated that nicorandil administered i.v. significantly increases coronary blood flow, has little influence on myocardial oxygen consumption, contractility, and atrioventricular conduction (Nakagawa et al 1979; Taira et al 1979; Sakai et al 1981), and ameliorates both the cyclic reduction of coronary blood flow and the ST elevation of ecg caused by subtotal occlusion of the left anterior descending coronary artery (Uchida et al 1978b). Thus, nicorandil possesses many desirable pharmacological characteristics as an effective antianginal agent. The pharmacological profile of nicorandil is in part similar to that of nitroglycerin (Sakai et al 1981), but also shows some differences, e.g. unlike nitroglycerin, nicorandil develops neither tolerance nor cross-tolerance to nitroglycerin (Nabata et al 1981). The chemical structure of nicorandil includes a nitrate moiety, which plays an essential role in its pharmacological activity (Taira et al 1979; Sakai et al 1980b). There have been conflicts in the literature concerning the metabolism of the organic nitrates and the efficacy of those orally administered, particularly as long-acting prophylactic agents (Needleman et al 1972; Commarato et al 1973; Reed et al 1977). Previously, after experiments using rat vascularly perfused isolated small intestine, we suggested that gut metabolism of nicorandil is negligible and that pre-systemic elimination of nicorandil after oral administration is primarily hepatic (Sakai et al 1980b). However, a systematic evaluation of the pharmacological effects of nicorandil by routes of administration which necessitate passage through the liver was lacking.

We have examined the hypotensive effects of nicorandil, compared with nitroglycerin and isosorbide dinitrate, administered to rats by different routes, and ascertained the rate and capacity of hepatic biotransformation of nicorandil, using rat isolated perfused liver and liver homogenates from various animals.

† Correspondence.

METHODS

Male albino Sprague-Dawley rats, 400–500 g, were allowed free access to food and water.

Systemic blood pressure (SBP) measurements

The animals were anaesthetized with pentobarbitone-Na 60 mg kg^{-1} i.p. supplemented with 40 mg kg^{-1} s.c. after 30 min, and placed on heated tables to maintain rectal temperature between 36 and 38 °C. Heparin-Na (1000 u kg^{-1}) was injected into the femoral vein, and the SBP was measured from the right femoral artery with a Nihon Kohden pressure transducer (MPU-0·5, Tokyo, Japan). To inject drugs, a 30 mm, 25 gauge needle with a polyethylene tube (PE 10) was inserted either into a branch of the portal vein (p.v.), or the jejunum (i.j.), or subcutaneously (s.c.) or peritoneally (i.p.) by a direct puncture, and fixed there with biotissue adhesive (Aron Alpha A, Sankyo, Tokyo). The i.v. drug application was made into the right jugular vein. Drugs were dissolved in or diluted with 0·9% NaCl (saline). Each solution was injected, over 10 s in a volume of 0·05 ml/100 g. A dose was given after the effect of the preceding dose had disappeared, depending on the duration of the effect. Different animal groups were used for evaluation of different routes of administration. All recordings were made on a chart by using a Nihon Kohden WI-680G recorder. Peak responses to drugs were expressed as the percentage changes in SBP from preadministration levels.

Isolated liver perfusion

Surgical procedures

Under pentobarbitone anaesthesia (60 mg kg^{-1} i.p.), the rat was tracheotomized, and a polyethylene tube was inserted in the trachea. The operative procedure for removal of the liver was described by Hems et al (1966). Briefly, the anterior abdomen was opened through mid-lines and midtransverse incisions. The intestines were then displaced to the left, exposing the liver, portal vein, right kidney, inferior vena cava and the bile duct. The bile duct was cannulated by a polyethylene tube (PE 50) and secured with a ligature. At this stage, positive-pressure respiration with room air was initiated with a respirator (Takashima Co., Tokyo, Japan) at a rate of 50 min^{-1} and a tidal volume of 2 ml/100 g. The thorax was opened by a transverse incision just above and along the line of the insertion of the diaphragm. After the injection of heparin-Na (500 u kg^{-1}) into the femoral vein, the hepatic artery and the inferior vena cava were tied and cut off. Polyethylene cannulae (ID 3 mm) were inserted into the portal vein and the thoracic vena cava, respectively. The liver was then transferred to an acrylic plastic box (B in Fig. 1). The portal and the thoracic vena cava cannulae were connected to the perfusion circuit and perfusion was through the portal vein at a constant rate of ca 30 ml min^{-1} by means of a peristaltic pump (Watson-Marlow Ltd., Type 100). The output of the pump was precalibrated and rechecked at the end of the experiment. Mean perfusion pressure (approx. 20 cm H_2O) was measured with a pressure transducer (Nihon Kohden, MPU-0·5) near the portal cannula. The perfusion procedures and apparatus were the same as described by Sakai et al (1980a), except for a devised acrylic plastic box.

Experiments were done in non-recirculating and recirculating series. In the non-recirculating experiments, the isolated liver was perfused through the portal vein with Krebs-Henseleit (K-H) bicarbonate solution. The perfusion medium included (in mM): NaCl, 119; KCl, 4·8; $CaCl_2.2H_2O$, 2·5; KH_2PO_4, 1·2; $MgSO_4.7H_2O$, 1·2; $NaHCO_3$, 24·8 and glucose, 10; and was aerated thoroughly with a gas phase mixture containing 95% O_2 : 5% CO_2. The oxygen tension of the perfusate (pH 7·4) was always in excess of 550 mmHg. The temperature of the perfusate was maintained between 37 and 38 °C, as it entered the liver which was perfused for 10 min with the K-H bicarbonate solution and then switched to the drug-containing K-H bicarbonate solution (nicorandil 6 μg ml^{-1} or nitroglycerin 2 μg ml^{-1}). The effluent fluid (2 ml) from the vena cava cannula was collected in a syringe 10 min after the onset of the perfusion with the drug-containing solution.

In the recirculating experiments, the isolated liver was perfused with 100 ml of the heparinized rat blood (2 volumes of whole blood and 3 volumes of K-H bicarbonate solution) recycled from a devised oxygenator-reservoir (Sakai et al 1980a; see A in Fig. 1) at a fixed flow rate through the portal vein. Venous blood from the vena cava was returned by gravity to the reservoir portion of a glass oxygenator-reservoir. The perfusate flowed down through the oxygenator portion to the reservoir portion; during the passage the perfusate was equilibrated with 95% O_2 : 5% CO_2. The oxygen tension of the perfusate was always in excess of 250 mmHg at 38 °C. The pH of the perfusate was maintained at 7·4. The experimental set-up is illustrated schematically in Fig. 1. The preparation became stable within 10 min of the onset of perfusion, as determined by changes in perfusion pressure. Then, nicorandil (0·6 mg) was

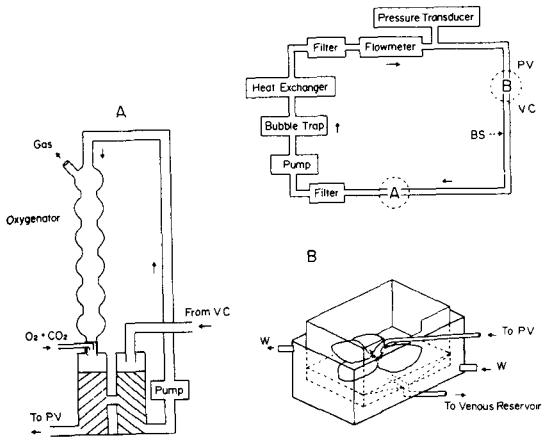
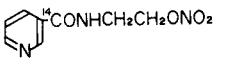


FIG. 1. Diagram of the recirculating perfusion system. Blood from the thoracic vena cava (v.c.) was returned by gravity to the reservoir portion of an oxygenator-reservoir primed with about 50 ml blood and then led to the oxygenator portion (50 cm high) at a fixed flow rate of 30 ml min^{-1}. The oxygenated blood (about 30 ml min^{-1}) was delivered via a different pump into the portal vein (p.v.). W, circulating warm water. B.S., blood sampling.

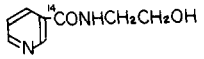
introduced into the perfusion system, and the liver was perfused thereafter for 60 min. The venous blood (1 ml) from the vena cava cannula was collected in syringes at 3, 5, 10, 20, 30, 45 and 60 min, and the plasma was separated immediately.

Analytical methods

The concentrations of nicorandil and SG-86 (Fig. 2) in the specimens were determined according to the procedure described previously (Sakai et al 1980b). Nitroglycerin analysis was according to the procedure reported by Johnson et al (1972).



N-(2-Hydroxyethyl)nicotinamide nitrate ester (Nicorandil)



N-(2-Hydroxyethyl)nicotinamide (SG-86)

FIG. 2. Chemical structure of nicorandil and SG-86 (its main metabolite).

Metabolism of nicorandil in liver homogenates of various species

The mixture containing 0·466 ml of 0·1 M phosphate buffer (pH 7·4), 3·95 mg of NADP-Na, 14·1 mg of G-6-P-Na_2, 0·034 ml of G-6-P dehydrogenase (140 u ml^{-1}), 0·1 ml of 0·5 M $MgCl_2$ and [^{14}C]nicorandil (1·22 μCi/200 μg) was shaken vigorously for 10 min. At time zero, 0·1 ml portions of the substrate and co-factor mixture were transferred to glass stoppered centrifuge tubes, to which was added 0·1 ml of the 10 000*g* supernatant fraction of 25% liver homogenates from one of the various species (rhesus monkey, pig, beagle dog, guinea-pig and rat). After incubation at 37 °C for 60 min, 50 μl of 99·5% ethanol was added, the mixture was shaken for 10 min and centrifuged at 4 °C for 10 min at 3000 rev min^{-1}. The supernatant (10 μl) was chromatographed on Silica gel plate (F-254, 0·25 mm thick, E. Merck) in solvent (benzene–EtOH (4 : 1)), and detected by radiochromatoscanner (Berthold TLC-scanner LB 276, Berlin, West Germany) and uv lamp (λ = 2537 Å).

Miscellaneous

Nicorandil (*N*-(2-hydroxyethyl)nicotinamide nitrate (ester)), and SG-86 (*N*-(2-hydroxyethyl)-nicotinamide) (main metabolite of nicorandil) were synthesized in the Chugai Research Laboratories. ^{14}C-Labelled nicorandil and [^{14}C]SG-86 (Fig. 2) also were synthesized by Dr Tohira in the Chugai Research Laboratories. The specific activities of [^{14}C]nicorandil and [^{14}C]SG-86 were 6·2 and 7·5 μCi mg^{-1}, respectively, with radiochemical purity above 97·4%.

The other drugs used were nitroglycerin (ampoule, water soluble type, Nippon Kayaku Co., Tokyo, Japan) and isosorbide dinitrate (Eizai, Tokyo, Japan).

Statistical analysis

The data in the text are expressed as mean ± s.e. Student's *t*-test for unpaired observations was used for statistical evaluation of the data; *P* values smaller than 0·05 were considered to be statistically significant.

RESULTS

Hypotensive effects of nicorandil, isosorbide dinitrate and nitroglycerin following administration to rats by different routes

After completion of the surgical procedure, a minimum of 30 min was allowed for stabilization of the preparation. Experiments were carried out on 60 preparations: Basal values of SBP (mean), 112·8 ± 0·6 mmHg; body weights, 455·7 ± 7·9 g.

The original tracings for the hypotensive effect of

nicorandil after i.v., p.v., i.j., i.p and s.c. administrations are presented in Fig. 3 and the dose-response curves are demonstrated in Fig. 4. In each series of experiments, no blood pressure response was elicited when equivalent volumes of saline were injected by the different routes. Single doses (30 μg kg^{-1}–3 mg kg^{-1}) of nicorandil administered i.v. and p.v. decreased SBP in dose-dependent fashion. Onset of the effect was rapid, and the maximum was reached within 90 s. As shown in Fig. 4, the dose-response curves after i.v. and p.v. nicorandil were almost coincident. There were no significant differences in the duration (Table 1) and magnitude of the hypotensive effects (Figs 3 and 4) between i.v. and p.v. applications of nicorandil. On the other hand, nicorandil administered i.j., i.p. and s.c. slowly decreased the SBP, with maximal response after 3 min. The time of recovery depended on the dose and the application route used, although the effect after i.j., i.p. and s.c. administration lasted longer than that after i.v. and p.v. injection.

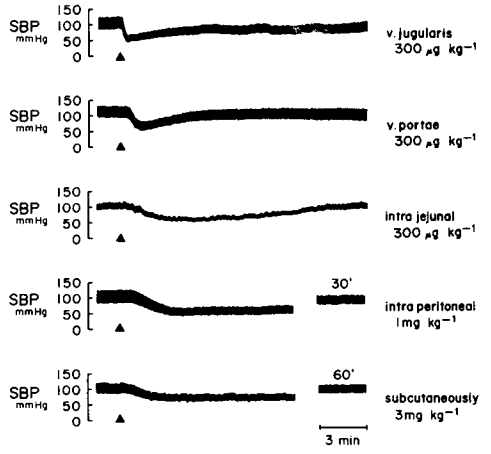


FIG. 3. Effects of nicorandil on systemic blood pressure (SBP) in anaesthetized rats following administration by different routes.

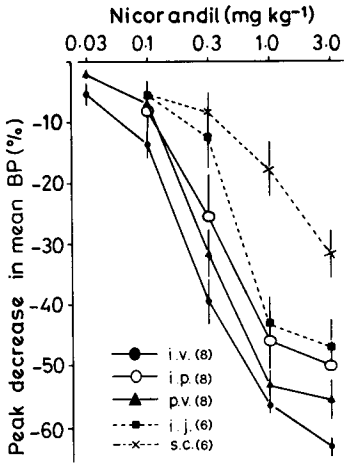


FIG. 4. Dose-response curves of the nicorandil effect on mean systemic blood pressure (SBP) in anaesthetized rats following different routes of administration. Values are the means of peak % decreases from the preadministration level. The vertical bars represent ± s.e.m. and the number of experiments is given in parentheses.

Table 1. Time reaching peak response and duration of the hypotensive effect in rats following i.v. and p.v. injections of nicorandil.

	Administration route			
	i.v. (8)	p.v. (8)	i.v. (8)	p.v. (8)
Dose (mg kg^{-1})	Peak (min)		Duration (min)	
0·1	0·70 ± 0·06	1·46 ± 0·29	5·88 ± 0·76	4·81 ± 0·69
	$P < 0·05$		NS	
0·3	0·59 ± 0·05	1·41 ± 0·11	11·26 ± 1·31	9·74 ± 1·89
	$P < 0·001$		NS	
1·0	0·71 ± 0·10	1·26 ± 0·06	20·19 ± 2·75	20·75 ± 4·91
	$P < 0·001$		NS	

Values represent mean ± s.e.m. and number of experiments is shown in parentheses. N.S., no significant differences between i.v. and p.v. groups.

A bolus i.v. injection of nitroglycerin caused a rapid but brief decrease in SBP. The peak depressor response obtained by i.v. injection of nitroglycerin (10 μg kg^{-1}) was 60% of the control SBP. The magnitude and duration of the effect was dose-dependent. As shown in Figs 5 and 6, in an i.v. dose (10 μg kg^{-1}) of nitroglycerin large enough to induce prominent hypotension, nitroglycerin caused no effect on SBP when the drug was injected into the portal vein. Such a difference in vasodepressor potency between i.v. and p.v. was also observed with administrations of isosorbide dinitrate (Figs 5 and 6).

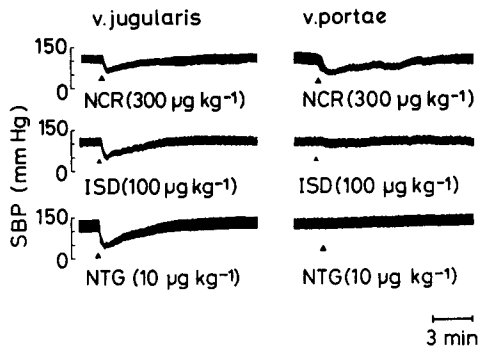


FIG. 5. Comparison of systemic blood pressure (SBP) response to i.v. or p.v. administration of nicorandil (NCR), isosorbide dinitrate (ISD) and nitroglycerin (NTG) to anaesthetized rats.

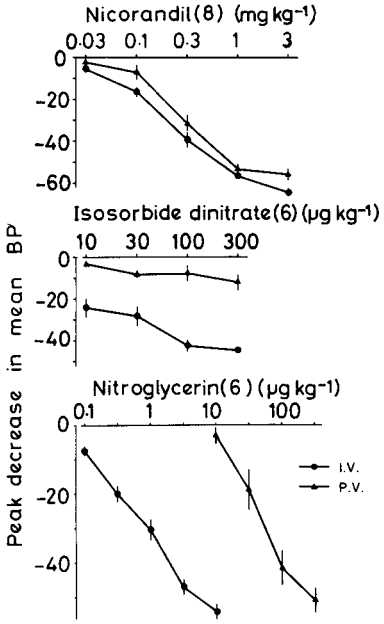


FIG. 6. Dose-response curves for mean systemic blood pressure (SBP) changes in anaesthetized rats following i.v. or p.v. administration of nicorandil, isosorbide dinitrate and nitroglycerin. Vertical bars represent ± s.e.m. and the number of experiments is given in parentheses.

A single i.v. injection of isosorbide dinitrate (100 μg kg^{-1}) caused a blood pressure decrease of 40% of the control but only a 10% decrease after p.v. administration (middle part in Fig. 5). Thus, with isosorbide dinitrate and nitroglycerin, unlike nicorandil, the p.v. dose required to produce a depressor response was significantly greater than that required to cause a comparable response after i.v. administration. The relative potencies of nicorandil and nitroglycerin by these different administration routes are compared in Table 2.

Nicorandil and nitroglycerin clearance of the isolated perfused rat liver

A comparison of the rate of degradation of nicorandil and nitroglycerin was performed in non-recirculating perfusion experiments. After perfusion for 10 min with K-H bicarbonate solution, the liver was switched to the K-H bicarbonate solution, containing either nicorandil (6 μg ml^{-1}) or nitroglycerin (2 μg ml^{-1}). Since the flow rate of the liver perfusion was about 30 ml min^{-1}, the nicorandil and nitroglycerin passed the liver at a rate of 180 and 60 μg min^{-1}, respectively. Compared with the doses inducing the hypotensive effect in-vivo, these rates are extremely high. At 10 min after the onset of the perfusion with the drug-containing K-H bicarbonate solution, the effluent fluid was sampled and analysed. Unlike nicorandil, nitroglycerin, even at the high concentration used in this test, was degraded as fast as it was presented to the liver: the residues of nicorandil and nitroglycerin in the effluent fluid were 92·3 ± 1·2% (n = 5) and 3·9 ± 2·1% (n = 5), respectively.

In recirculating liver perfusion experiments the progressive fall of nicorandil concentration in the circulating blood was accompanied by a corresponding rise in the drug's metabolites. Thus, SG-86 (a main metabolite of nicorandil) increased in the blood as the parent drug concentration decreased (Fig. 7).

Table 2. Comparison of hypotensive activities of nicorandil and nitroglycerin administered to rats by different routes.

Nitrates	Route	ED30[a] (95% Confidence limits) μg kg^{-1}	Relative potencies
Nicorandil	i.v.	186·3 (139·5–248·5)	100
	p.v.	232·7 (157·8–343·0)	80·0
	i.j.	260·7 (143·9–354·8)	71·4
	i.p.	454·4 (255·7–845·3)	40·9
Nitroglycerin	i.v.	2·8 (2·2–3·5)	100
	p.v.	64·3 (25·0–259·0)	4·3

[a] The dose required to decrease mean systemic blood pressure (SBP) by 30% from the preadministration level (see the Results) was selected for determining relative potencies, since a 30% decrease in mean SBP was generally located on the midpoint of the dose-response curve (Fig. 4).

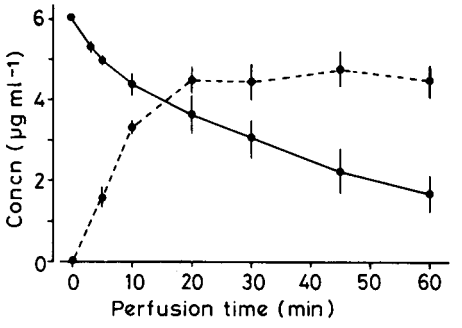


FIG. 7. Plasma concentration-time curves for nicorandil (——) and its main metabolite SG-86 (- - - -) in the isolated rat liver recirculated with blood. Vertical bars represent ± s.e.m. of 4 experiments.

Maximal SG-86 concentration occurred 20 min after dosing with nicorandil and then reached a plateau level. Sixty min after dosing, nicorandil had decreased by 73% of the initial nicorandil concentration and SG-86 was increased by approximately 70%.

Metabolism of nicorandil in liver homogenates of various species

The degree of degradation of nicorandil was examined in liver homogenates of rats, guinea-pigs, dogs, monkeys and pigs. After the mixture of substrate ([^{14}C]nicorandil), co-factors and liver homogenate was incubated at 37 °C for 60 min, samples were collected and analysed by thin-layer chromatography. Under these conditions, nicorandil was metabolized in the liver homogenates of various species in the descending order: rat = guinea-pig > dog = monkey > pig. Approximately 20% of the parent drug was metabolized in the rat and guinea-pig liver homogenates and 10% in the dog and monkey liver homogenates, but, hardly any degradation occurred in the pig liver homogenates. In these homogenates, nicorandil was metabolized to SG-86, nicotinuric acid (nicotinyl glycine) and several unknown substances. In the liver homogenates of all the species tested, the common main metabolite formed during the incubation was SG-86, a denitrate compound of nicorandil. The data are summarized in Table 3.

Table 3. Comparison of degradation rate of nicorandil in liver homogenates of various species.

Species	Nicorandil	SG-86	Nicotinuric acid	Unknown substances
Rat	81·25 ± 1·55	14·28 ± 1·54	1·17 ± 0·10	2·00 ± 0·09
Guinea-pig	82·03 ± 0·06	10·04 ± 0·22	0·22 ± 0·07	6·10 ± 0·50
Dog	90·61 ± 0·88	4·23 ± 0·45	0·21 ± 0·02	3·65 ± 0·51
Pig	98·43 ± 0·08	0·72 ± 0·12	0·26 ± 0·08	not detected
Monkey	89·28 ± 1·42	5·97 ± 0·65	1·15 ± 0·24	0·29 ± 0·60

Values: mean ± s.e.m. of 4 experiments. The residues of nicorandil and the metabolites are expressed as percentage of the initial nicorandil concentration. All enzyme measurements are corrected for nicorandil nonenzymatic reaction rate. R_F values; nicorandil, 0·62; SG-86, 0·24; nicotinuric acid, 0·0.

DISCUSSION

In the present experiments nicorandil administered to rats by different routes was rapidly absorbed and was active by all routes. The current investigations have indicated that after oral dosing, the conventional nitrates are absorbed from the gastrointestinal tract into the portal circulation and completely degraded by the liver before reaching the systemic circulation. Therefore they can have little chance of producing physiological effects (Shlevin 1982). This has been termed the 'first-pass effect'. However, as larger doses of the drug are ingested, the hepatic extraction becomes saturated, allowing more of the parent drug to reach the systemic circulation.

Thus, conventional vasoactive organic nitrates are not orally inactive but require much larger doses to elicit a desired physiological response compared to the doses required when administered sublingually or intravenously. According to the present study, with nitroglycerin given into the portal vein, a 23-fold higher dosage was necessary to reach a comparable fall in SBP than after i.v. dosing. Our results accord well with those reported by Heinzow & Ziegler (1981) who found that nitroglycerin was adequately effective when given to rats by p.v. administration at 25-fold higher doses. The metabolism of nitroglycerin depends on the endogenous glutathione reserve and the reaction is catalysed by the liver enzyme, glutathione-organic nitrate reductase (Needleman & Hunter 1965). By this system nitroglycerin administered orally appears to be denitrated rapidly in the liver. Needleman & Krantz (1965) and Needleman et al (1969) reported that in dogs, glyceryl dinitrates have only about 5% of the vasodepressor activity of nitroglycerin, and glyceryl mononitrate is inactive. Bogaert et al (1968) reported similar results. In view of this, it should be noted that there were no significant differences in the duration and magnitude of the hypotensive effect between i.v. and p.v. application of the same dose range of nicorandil.

In the present non-recirculating rat liver perfusion experiment, more than 95% of the initial nitroglycerin concentration was metabolized by a single passage of the liver, whereas nicorandil was degraded less than 10%. This, taken together with the results of SBP after p.v. administration in rats, indicates that nicorandil is not readily metabolized by a single passage of the liver.

Previously, using vascularly perfused isolated rat small intestine (Sakai et al 1980a), we observed that no extensive denitration of nicorandil administered intraduodenally occurred during absorption from the intestinal tract. Its conversion to SG-86 (a denitrated main metabolite of nicorandil) was assumed to take place during the passage of the drug through the liver (Sakai et al 1980b). Actually, in the recirculating liver perfusion experiment, as nicorandil concentration in circulating blood decreased, SG-86 concentration increased.

Like many organic nitrate esters, nicorandil appears to be partly denitrated by liver glutathione-

organic nitrate reductase (Hinohara, unpublished data). It is speculated, however, that the mononitrate form of the nitrates may be more resistant to metabolic breakdown in the liver, and that the metabolic degradative pathways of nicorandil seem to be significantly different from that of nitroglycerin or isosorbide dinitrate.

In liver homogenates of various species, the extent of degradation of nicorandil varied from species to species. Nicorandil was metabolized to SG-86, nicotinuric acid and unknown substances in descending order: rat = guinea-pig > dog = monkey > pig. Since SG-86 (Taira et al 1979; Sakai et al 1980b) and nicotinuric acid (Sakai, unpublished data) had virtually no hypotensive action in dose comparable with those of nicorandil, the duration of pharmacological effects of nicorandil seems to depend largely on the degree of biotransformation of nicorandil to the de-nitrated compounds in the liver. Indeed, nicorandil administered i.v. in a dose of 300 $\mu g\,kg^{-1}$ decreased SBP, over about 10 min in rats, 40 min in dogs (Shiraki et al 1981) and 80 min in pigs (Sakai et al 1983a): the effect of nicorandil appears to be much longer in the pig and the dog, species which are phylogenetically closer to humans than the rat and the guinea-pig.

In the present study, it was concluded that nicorandil, unlike conventional nitrates, is probably slowly metabolized to SG-86 and the other substances by the liver during passage through the portal system, and therefore easily enters the general circulation, resulting in greater bioavailability after oral dosing.

REFERENCES

Bogaert, M. G., Rosseel, M. T., De Schaepdryver, A. F. (1968) Arch. Int. Pharmacodyn. Ther. 176: 458–460

Commarato, M., Winbury, M. M., Kaplan, H. R. (1973) J. Pharmacol. Exp Ther. 187: 300–307

Heinzow, B., Ziegler, A. (1981) J. Cardiovasc. Pharmacol. 3: 573–580

Hems, R., Ross, B. D., Berry, M. N., Krebs, H. A. (1966) Biochem. J. 101: 284–292

Johnson, E. M., Jr., Harkey, A. B., Blehm, D. J., Needleman, P. (1972) J. Pharmacol. Exp. Ther. 182: 56–62

Nabata, H., Shiraki, Y., Sakai, K. (1981) Jpn. J. Pharmacol. 31: 511–519

Nakagawa, Y., Takeda, K., Katano, Y., Tsukada, Y., Kitagawa, T., Otorii, T., Imai, S. (1979) Jpn. Heart J. 20: 881–895

Needleman, P., Blehm, D. J., Rotskoff, K. S. (1969) J. Pharmacol. Exp. Ther. 165: 286–288

Needleman, P., Hunter, F. E., Jr. (1965) Mol. Pharmacol. 1: 77–86

Needleman, P., Krantz, C., Jr. (1965) Biochem. Pharmacol. 14: 1225–1230

Needleman, P., Lang, S., Johnson, E. M., Jr. (1972) J. Pharmacol. Exp. Ther. 181: 489–497

Reed, D. E., Akester, J. M., Prather, J. F., Tuckosh, J. R., McCurdy, D. H., Yeh, C. (1977) Ibid. 202: 32–37

Sakai, K., Akima, M., Hinohara, Y., Sasaki, M., Niki, R. (1980a) Jpn. J. Pharmacol. 30: 231–241

Sakai, K., Akima, M., Shiraki, Y., Hoshino, E. (1983a) J. Pharmacol. Exp. Ther. 227: 220–228

Sakai, K., Nakano, H., Nagano, H., Uchida, Y. (1983b) in: Scriabine, A. (ed.) New Drugs Annual: Cardiovascular Drugs, Nicorandil, Raven Press, New York, pp 227–242

Sakai, K., Ohba, Y., Akima, M., Kamiyama, H., Hinohara, Y., Nakano, H. (1980b) Jpn. J. Pharmacol. 30: 881–890

Sakai, K., Shiraki, Y., Nabata, H. (1981) J. Cardiovasc. Pharmacol. 3: 139–150

Shiraki, Y., Akima, M., Nabata, H., Ohba, Y., Hoshino, E., Sakai, K. (1981) Jpn. J. Pharmacol. 31: 921–929

Shlevin, H. H. (1982) Life Sci. 30: 1233–1246

Taira, N., Satoh, K., Yanagisawa, T., Imai, Y., Hiwatari, M. (1979) Clin. Exp. Pharmacol. Physiol. 6: 301–316

Uchida, Y., Yoshimoto, N., Murao, S. (1978a) Jpn. Heart J. 19: 112–124

Uchida, Y., Yoshimoto, M., Murao, S. (1978b) Ibid. 19: 904–912