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Acute and chronic haemodynamic effects of naftazone in portal hypertensive rats [1]

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Abstract

It has been demonstrated that hyperproduction of nitric oxide (NO) plays a major role in the vasodilatation of cirrhosis; thus, the vasodilatation might be reversed by an inhibition of NO production. Experimental studies in isolated aortic rings showed that naftazone inhibits the effects of NO production. The aim of this study was to evaluate the haemodynamic effects of acute and chronic administration of naftazone in rats with portal hypertension. Haemodynamic values were measured either before and 10 min after intravenous administration of 432 μg/kg of naftazone or after 4 days of oral administration of 10 mg/kg per day. Acute administration of naftazone significantly reduced portal pressure in portal vein-stenosed and cirrhotic rats. This reduction was related to a decrease in the resistance of the liver and collateral circulation and it was associated with an increased cardiac output. Oral administration of naftazone significantly decreased portal pressure in rats with portal vein stenosis; this decrease depended on a significant reduction of portal blood flow. In both groups, arterial pressure did not change significantly. These haemodynamic effects differed from those observed following prazosin or propranolol administration. However, these effects were similar but less marked than those observed following *N*-nitro-L-arginine administration in systemic and splanchnic arterial territories. In conclusion, acute and oral administration of naftazone significantly reduces portal pressure by two different mechanisms in portal hypertensive rats. The exact mechanism has, however, to be elucidated.
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1. Introduction

Naftazone (1,2-naphthoquinone-2-semicarbazone) is an orally administered drug which protects the vascular system (Berson, 1977; Winand, 1977). An inhibitory effect on nitric oxide (NO) synthesis has been recently demonstrated in vitro, which could explain its clinical activity. Naftazone has been shown to inhibit the constitutive form of nitric oxide synthase (NO synthase III) in rat endothelial cells and some metabolites of naftazone could also inhibit the induction and activity of the inducible form of NO synthase II in murine peritoneal macrophages (Ouazzani et al., 1995). Portal hypertension in humans and animals is associated with a hyperdynamic circulation, characterized by vasodilatation and increased cardiac output and organ blood flow (Mahl and Groszmann, 1991). Clinical and experimental findings have shown evidence of a vascular overproduction of NO in the splanchnic territory (Bomzon and Blendis, 1994; Sogni et al., 1995). Thus, in this syndrome, the therapeutic consequences of NO inhibitory drugs could be of interest. The aim of this study was to measure the effect of naftazone on systemic and splanchnic hemodynamics in vivo in rats with portal hypertension after both acute intravenous and chronic oral administration. To explain the haemodynamic effects of this drug, the results obtained after oral administration of naftazone were compared with those for certain drugs which are known to decrease portal hypertension, such as the non-selective β-adrenoceptor antagonist, propranolol (Lebrec, 1994), the

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α-adrenoceptor antagonist, prazosin (Cummings et al., 1988) and the specific NO synthase inhibitor, N^{ω}-nitro-L-arginine methyl ester (L-NAME) (Moncada et al., 1991).

2. Materials and methods

2.1. Animals

Ninety-four male Sprague–Dawley rats (Charles River Laboratories, Saint-Aubin-lès-Elbeuf, France) were divided into three groups. The first group included 18 normal rats. The second group included 58 rats with portal hypertension induced by partial ligation of the portal vein, as previously described (Blanchet and Lebrec, 1982; Lee et al., 1985). Briefly, under ether anaesthesia, the abdomen was opened and the portal vein was exposed. A polyethylene catheter with an external diameter of 0.96 mm (Biotrol Pharma, Paris, France) was passed alongside the vein and a 3.0 silk thread was used to ligate both the catheter and the vessel. The catheter was then removed and the abdominal incision was closed. The haemodynamic study was performed 2 weeks later, when portal hypertension had fully developed. The third group contained 18 rats with secondary biliary cirrhosis due to bile duct ligation. The surgical procedure was performed under ether anaesthesia as previously described (Lee et al., 1986). The haemodynamic study was performed 4 weeks after surgery. All rats were allowed free access to food and water until 14–16 h before the study, when food was withdrawn. Both normal and portal hypertensive rats weighed between 300 and 380 g. Protocols performed in this laboratory were approved by the French Agriculture Office in conformity with European legislation for research involving animals and with the ethics advisory board committee for animal experiments of Cassenne Laboratory.

2.2. Haemodynamic measurements

The day before haemodynamic measurements, catheters were inserted while rats were under pentobarbital anaesthesia. All catheters were passed through subcutaneous tunnels at the back of the neck. All rats were free in cages and were fully conscious during measurements. A 0.7 mm diameter polyethylene catheter was placed in the left femoral vein for intravenous drug administration. Mean arterial pressure was measured with a catheter (PE-10, Clay Adams, NJ) inserted in the left femoral artery; heart rate was calculated. Mean arterial pressure and heart rate were monitored using a multichannel recorder (Philips CM 130, Eindhoven, The Netherlands). For portal pressure measurements, the abdomen was opened and a polyethylene catheter (0.7 mm diameter) was inserted into a small ileal vein and gently advanced up to the bifurcation of the superior mesenteric and splenic veins. For cardiac output and organ blood flow measurements, a 0.7 mm diameter polyethylene catheter with a silastic medical-grade tube tip (Dow Corning Corporation Medical Products, Midland, MI) was advanced into the left ventricle via the right carotid artery. This catheter was used for microsphere injections. Cardiac output and organ blood flows were determined in each rat by using the radioactive microsphere method (16 ± 3 μm in diameter, specific activity 10 mCi/g; New England Nuclear, Boston, MA), as previously described (Malik et al., 1976). Briefly, 0.1 ml of a suspension of ^{141}Ce-labelled microspheres (approximately 60 000) was suspended in Ficoll 70 (10%, Pharmacia Fine Chemicals AB, Uppsala, Sweden) and Tween 80 (0.01%). After ultrasonic agitation, the microspheres were injected into the left ventricle over 20 s and the catheter was flushed with 0.9 ml of saline to obtain baseline measurements before drug administration. The reference sample was drawn into a motor-driven syringe at a rate of 0.8 ml/min for 75 s during microsphere injection. For a second determination of cardiac output and organ blood flows, an injection of ^{113}Sn-labelled microspheres was performed according to the same protocol. Rats were then killed with an overdose of pentobarbitone sodium. Individual organs were dissected and placed in separate tubes for counting with a gamma-counter (MINAXI g, Autogamma 5000 series; Packard, Instruments Co., Downers Grove, IL) at energy settings of 115–165 and 310–345 keV for ^{141}Ce and ^{113}Sn, respectively. The error in the measurement of the radioactivity induced by the spillover of ^{113}Sn into the ^{141}Ce channel was corrected by using ^{113}Sn and ^{141}Ce standards. Adequate microsphere mixing was assumed with a difference of $< 10\%$ between the right and left kidneys. Cardiac output (ml/min) was calculated with the following formula (radioactivity injected (cpm)/reference blood sample radioactivity (cpm) $\times$ 0.8). The cardiac index was expressed per 100 g body wt. Regional blood flows were calculated with the following formula: organ blood flow (ml/min per 100 g) = (organ radioactivity (cpm)/radioactivity injected (cpm)) $\times$ cardiac index (ml/min per 100 g). Portal tributary blood flow was calculated as the sum of spleen, stomach, small intestine, colon and mesenteric with pancreas blood flows. Systemic vascular resistance ($(\text{dyn} \cdot \text{cm}^{-5} \cdot 100\ \text{g}) \times 10^3$) was calculated with the following formula: ((mean arterial pressure (mmHg) $\times$ 80/cardiac index (ml/min per 100 g)). Portal territory vascular resistance ($(\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5} \cdot 100\ \text{g}) \times 10^3$) was calculated with the following formula: (mean arterial pressure (mmHg) − portal pressure (mmHg)) $\times$ 80/portal tributary blood flow (ml/min 100 g). Hepatocollateral vascular resistance ($(\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5} \cdot 100\ \text{g}) \times 10^3$) was calculated with the following formula: portal pressure (mmHg) $\times$ 80/portal tributary blood flow (ml/min per 100 g).

2.3. Experiments

2.3.1. Experiment 1

This set of experiments was performed in 6 normal rats, 6 portal-vein stenosed rats and 6 cirrhotic rats. Heart rate

and mean arterial pressure were measured following intravenous boluses of increasing doses of naftazone (0, 9, 18, 36, 108, 216, 432, 864 and 1728 μg/kg). Because rats were not allowed to recover after each dose, results obtained represent the response to cumulative doses. The effect of the volume (approximately 2 ml) of solvent (dimethyl-sulfoxide 1%, DMSO) corresponding to the volume of the highest dose of naftazone (1728 μg/kg) on mean arterial pressure and heart rate was also tested.

2.3.2. Experiment 2

Systemic and splanchnic hemodynamics were measured before and 10 min after intravenous bolus administration of naftazone (432 μg/kg per min, which represented a volume of approximately 0.5 ml). This dose was chosen because it produced a significant increase in mean arterial pressure in all groups of rats (experiment 1). This protocol was performed with 8 rats from each group (normal, portal vein stenosis, cirrhosis). The same protocol was also performed with 4 rats from each group before and 10 min after intravenous bolus administration of the volume of vehicle corresponding to that of the 432 μg/kg dose of naftazone.

2.3.3. Experiment 3

Systemic and splanchnic hemodynamics were measured in portal vein-stenosed rats 4 days after the start of administration of naftazone gavage (10 mg/kg per day; $n = 8$) and were compared to the results for rats which had received the same amount of DMSO (5 ml/kg per day; $n = 8$). Similar hemodynamic studies were performed following per os administration for 3 days of prazosin (prazosin hydrochloride, 0.6 mg/kg per day; $n = 8$) (Koshy et al., 1992) or propranolol (DL-propranolol hydrochloride, 75 mg/kg per day; $n = 8$) (Lin et al., 1991). Systemic and splanchnic hemodynamics were also compared to those measured after 14 days of L-NAME administration (approximately 25 mg/kg per day; $n = 8$) (Pilette et al., 1996).

2.4. Drugs

Naftazone was provided by Cassenne Laboratory (France). For a stock solution, naftazone was diluted in DMSO (21.5 mg/ml). For intravenous use, the stock solution was diluted 1:100 in saline. For intragastric use, the stock solution was associated with 1% methylcellulose (2 mg/ml). Other drugs were from Sigma chemicals. Prazosin was used as an α-adrenoceptor antagonist. Propranolol was used as a non-selective β-adrenoceptor antagonist. N^{ω} nitro-L-arginine methyl ester (L-NAME) was used as a nitric oxide synthase inhibitor and was diluted in drinking water that was changed daily (1 mg/ml per day, corresponding to approximately 25 mg/kg per day).

2.5. Statistical analysis

Values are means ± S.E.M. Results were analysed by Student's *t*-test for values obtained before and after naftazone administration and by one-way analysis of variance (ANOVA) for multiple comparisons. P-value < 0.05 was considered significant.

3. Results

No deaths occurred after drug administration in any experiment.

3.1. Experiment 1

Compared to basal values, a dose-dependent increase in mean arterial pressure was observed during naftazone administration in all 3 groups of rats but no difference between the 3 groups of rats was observed. A significant increase for each group was observed for the dose of 432 μg/kg compared to basal values (Fig. 1). During naftazone administration, the heart rate only significantly increased in normal rats after the dose of 432 μg/kg while no effect was observed in portal vein-stenosed and cirrhotic rats. Administration of vehicle had no effect on mean arterial pressure or heart rate.

3.2. Experiment 2

Naftazone i.v. significantly increased cardiac index in normal (+19%), portal vein-stenosed (+22%) and cirrhotic (+19%) rats and decreased systemic vascular resistance in portal vein-stenosed (−21%) rats (Table 1). Naftazone decreased portal pressure and hepato-collateral vascular resistance in portal vein-stenosed (−18 and −24%,

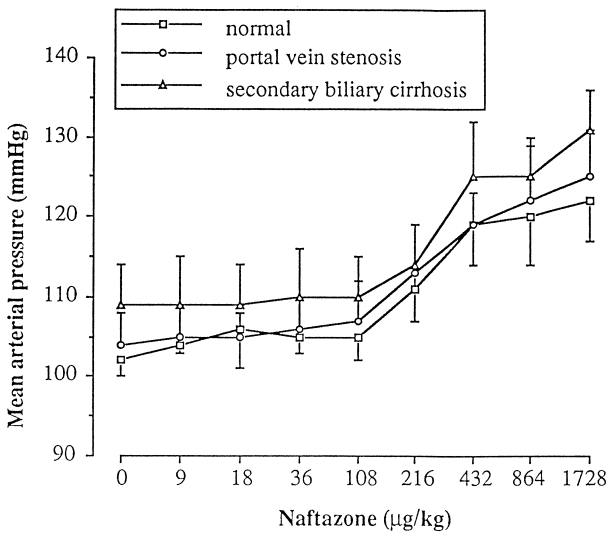

Fig. 1. Dose–response curve of cumulative doses of naftazone on mean arterial pressure in 3 groups of rats. No difference was observed between each group. A significant increase for each group was observed from the dose of 432 μg/kg compared to basal values.

Table 1
Haemodynamic values before and after naftazone i.v. (432 μg/kg) or the same volume of solvent (DMSO 1%) in rats

	Substances	Normal		Portal vein stenosis		Cirrhosis	
		before	after	before	after	before	after
Mean arterial pressure (mmHg)	naftazone ($n=8$)	96 ± 4[a]	112 ± 6	100 ± 6	101 ± 5	95 ± 5	102 ± 4
	solvent ($n=4$)	113 ± 6	119 ± 5	107 ± 4	111 ± 5	108 ± 2	108 ± 1
Heart rate (beats/min)	naftazone ($n=8$)	389 ± 14	389 ± 11	408 ± 8	380 ± 10[b]	373 ± 10	362 ± 11[b]
	solvent ($n=4$)	381 ± 26	370 ± 26	379 ± 8	392 ± 10	390 ± 24	391 ± 10
Cardiac index (ml/min per 100 g)	naftazone ($n=8$)	26.5 ± 1.2	31.5 ± 1.2[b]	31.9 ± 1.0	39.0 ± 1.9[b]	38.7 ± 3.9	45.9 ± 4.4[b]
	solvent ($n=4$)	24.3 ± 0.8	25.6 ± 1.1	32.0 ± 1.3	31.4 ± 1.2	34.0 ± 1.4	33.8 ± 1.2
Systemic vascular resistance ($dyn \cdot s \cdot cm^{-5} \cdot 100\ g^{-1} \cdot 10^3$)	naftazone ($n=8$)	295 ± 19	290 ± 29	266 ± 22	210 ± 13[b]	209 ± 18	186 ± 15
	solvent ($n=4$)	375 ± 28	366 ± 15	272 ± 12	286 ± 11	259 ± 10	64 ± 9
Portal pressure (mmHg)	naftazone ($n=8$)	7.1 ± 0.4	7.0 ± 0.4	13.0 ± 0.4	10.7 ± 0.6[b]	12.4 ± 0.7	10.4 ± 0.7[b]
	solvent ($n=4$)	6.0 ± 0.1	6.3 ± 0.3	13.0 ± 0.4	12.9 ± 0.4	12.0 ± 0.3	11.8 ± 0.3
Portal tributary blood flow (ml/min per 100 g)	naftazone ($n=8$)	4.4 ± 0.3	4.7 ± 0.3	5.4 ± 0.2	5.9 ± 0.4	4.8 ± 0.5	5.4 ± 0.7
	solvent ($n=4$)	3.5 ± 0.3	3.5 ± 0.4	6.6 ± 0.3	5.2 ± 0.7	5.6 ± 0.2	5.7 ± 0.5
Portal territory vascular resistance ($dyn \cdot s \cdot cm^{-5} \cdot 100\ g^{-1} \cdot 10^3$)	naftazone ($n=8$)	1167 ± 120	1845 ± 178	1315 ± 110	1257 ± 103	1514 ± 221	1456 ± 149
	solvent ($n=4$)	2496 ± 215	2749 ± 356	1163 ± 88	1569 ± 167	1389 ± 58	1388 ± 114
Hepato-collateral vascular resistance ($dyn \cdot s \cdot cm^{-5} \cdot 100\ g^{-1} \cdot 10^3$)	naftazone ($n=8$)	134 ± 13	122 ± 10	196 ± 9	148 ± 10[b]	220 ± 23	167 ± 15[b]
	solvent ($n=4$)	140 ± 11	155 ± 29	159 ± 11	206 ± 20	173 ± 7	167 ± 14
Hepatic artery blood flow (ml/min per 100 g)	naftazone ($n=8$)	0.30 ± 0.08	40 ± 0.13	0.43 ± 0.05	0.55 ± 0.13	0.36 ± 0.06	0.36 ± 0.08
	solvent ($n=4$)	0.18 ± 0.03	0.16 ± 0.02	0.39 ± 0.08	0.30 ± 0.11	0.29 ± 0.06	0.32 ± 0.08

[a] Means ± S.E.M.
[b] $P < 0.05$ compared to values before naftazone.

Table 2
Haemodynamic effects of chronic per os administration of solvent (DMSO 1%), naftazone (10 mg/kg per day), prazosine (0.6 mg/kg per day), propranolol (75 mg/kg per day) and L-NAME (25 mg/kg per day) in rats with portal vein stenosis

	Solvent ($n=8$)	Naftazone ($n=8$)	Prazosin ($n=8$)	Propranolol ($n=8$)	L-NAME ($n=8$)
Mean arterial pressure (mmHg)	103 ± 3[a]	108 ± 3	92 ± 6[b]	108 ± 3	153 ± 4[b]
Heart rate (beats/min)	387 ± 14	359 ± 14	379 ± 25	330 ± 13[b]	392 ± 7
Cardiac index (ml/min per 100 g)	29.3 ± 2.3	24.7 ± 0.6[b]	27.6 ± 1.2	23.9 ± 0.9[b]	21.8 ± 1.9[b]
Systemic vascular resistance ($dyn \cdot s \cdot cm^{-5} \cdot 100\ g^{-1} \cdot 10^3$)	281 ± 22	351 ± 13[b]	268 ± 18	365 ± 20[b]	598 ± 60[b]
Portal pressure (mmHg)	15.1 ± 0.4	11.1 ± 0.9[b]	12.5 ± 0.5[b]	12.7 ± 0.7[b]	13.1 ± 0.5[b]
Portal tributary blood flow (ml/min per 100 g)	7.1 ± 0.4	5.6 ± 0.5[b]	7.7 ± 1.1	3.6 ± 0.9[b]	3.7 ± 0.3[b]
Portal territory vascular resistance ($dyn \cdot s \cdot cm^{-5} \cdot 100\ g^{-1} \cdot 10^3$)	1021 ± 71	1441 ± 111	910 ± 104	2163 ± 386[b]	3233 ± 330[b]
Hepato-collateral vascular resistance ($dyn \cdot s \cdot cm^{-5} \cdot 100\ g^{-1} \cdot 10^3$)	175 ± 9	168 ± 20	152 ± 25	349 ± 88[b]	304 ± 32[b]
Hepatic artery blood flow (ml/min per 100 g)	1.02 ± 0.08	0.83 ± 0.12	0.66 ± 0.13	0.54 ± 0.22[b]	0.50 ± 0.17[b]

[a] Means ± S.E.M.
[b] $P < 0.05$ compared to solvent.

respectively) and cirrhotic (−16 and −24%, respectively) rats. In contrast, no change in portal tributary blood flow and portal territory vascular resistance was observed after naftazone administration. Acute vehicle administration had no effect on systemic or splanchnic hemodynamics.

3.3. Experiment 3

There was no change in systemic and splanchnic hemodynamics after oral administration of vehicle to portal vein-stenosed rats (Table 2). Naftazone decreased portal pressure (−26%) and portal tributary blood flow (−21%) while no change was found in portal territory and hepato-collateral vascular resistances.

The α-adrenoceptor antagonist prazosin decreased mean arterial pressure (−11%) and portal pressure (−17%) (Table 2). At this dose, oral administration of prazosin had no significant effect on splanchnic vascular resistance but there was a tendency towards a decrease in portal territory and hepato-collateral vascular resistance. The non-selective β-adrenoceptor antagonist, propranolol, had a vasoconstrictive effect, resulting in an increase in systemic (+30%), portal (+112%) and hepato-collateral (+99%) vascular resistances and inhibited cardiac function, resulting in decreased cardiac index (−18%) and heart rate (−15%) (Table 2). Finally, propranolol decreased portal tributary blood flow (−49%) and portal pressure (−18%).

The oral administration of the NO synthase inhibitor L-NAME also increased mean arterial pressure (+49%) as well as systemic (+113%), portal territory (+217%) and hepato-collateral (+74%) vascular resistances (Table 2). L-NAME decreased cardiac index (−26%), portal tributary blood flow (−48%) and portal pressure (−13%).

4. Discussion

Intravenous and chronic oral administration of naftazone resulted in a decrease in portal pressure in portal hypertensive rats with liver disease (secondary biliary cirrhosis) or with a normal liver (portal vein stenosis). In both models of portal hypertension, intravenous naftazone decreased the collateral vascular resistance in the splanchnic system but did not affect portal territory vascular resistance. Moreover, despite an increase in cardiac index, portal tributary blood flow was unchanged. The mechanisms underlying the portal hypotensive effect of naftazone differed according to the route of administration. Oral administration of naftazone caused a decrease in portal pressure in portal hypertensive rats. This mode of administration had no effect on hepato-collateral vascular resistance but caused a systemic and splanchnic arterial vasoconstrictive effect which decreased portal tributary blood flow. These haemodynamic effects were similar to those observed with a specific NO synthase inhibitor. It is not clear, however, if the differences between the intravenous and oral administration of naftazone were due to the route of administration or to the duration of treatment (bolus versus 4 days).

Several hemodynamic studies performed in human and animal models have explained the mechanism responsible for the decrease in portal pressure with non-selective β-adrenoceptor antagonists such as propranolol, which is extensively used in the prevention of gastrointestinal bleeding in patients with portal hypertension (Lebrec, 1994). In patients with cirrhosis, propranolol produces a significant decrease in heart rate and cardiac output, associated with a decrease in portal tributary blood flow and collateral blood flow as shown by a reduction in azygos blood flow, which is a reflection of superior portosystemic shunts (Calès et al., 1984). In the present study, performed in portal hypertensive rats, the hemodynamic effects of orally administered propranolol are consistent with previous results (Calès et al., 1985; Lin et al., 1991). Thus, oral naftazone administration has systemic and splanchnic hemodynamic effects different from those of propranolol.

Certain studies have demonstrated a decrease in portal pressure after administration of α-adrenoceptor antagonists such as prazosin (Mills et al., 1984; Albillos et al., 1995). The systemic arterial and venodilating effect of this substance probably contributes to its effect on the splanchnic circulation (Lebrec, 1994). However, in rats with portal vein stenosis, prazosin only caused a slight decrease in portal pressure (Cummings et al., 1988). In our study, only a decrease in mean arterial pressure and portal pressure was observed after chronic oral administration of prazosin. The systemic effects of naftazone differed from those of prazosin, since naftazone had no significant effect on mean arterial pressure but decreased portal tributary blood flow.

In portal hypertensive rats, the inhibition of NO synthase produced a vasoconstrictive effect both in the systemic and splanchnic territories (Piczueta et al., 1992; Sogni et al., 1992). Little is known about the effect of NO synthase inhibition on portal pressure in humans; however, in portal hypertensive animals, acute NO synthase inhibition has no effect or produces only a slight decrease in portal pressure (Piczueta et al., 1992; Sogni et al., 1992). In this study, chronic administration of L-NAME produced a slight but significant decrease in portal pressure. After oral administration, both naftazone and L-NAME increased systemic vascular resistance but naftazone did not modify the mean arterial pressure. Both substances decreased portal pressure by decreasing portal tributary blood flow; however, in the splanchnic territory, L-NAME increased hepato-collateral vascular resistance while naftazone did not. In other words, L-NAME produced a marked vasoconstrictive effect in both the systemic and splanchnic territories, whereas naftazone produced a mild arterial vasoconstrictive effect that was significant only in the systemic circulation. There is no clear explanation for these different results. In rats with portal vein stenosis, there is marked development of porto-collateral shunts and 80 to

100% of portal blood flow does not reach the hepatic sinusoidal bed (Lebrec, 1991). Under physiological conditions, naftazone is extensively metabolized by the liver into sulpho- and glucuronoconjugates (Herber et al., 1995). In rats with portal vein stenosis, the effect of the hepatic first pass could be altered, which may result in an increase in the systemic delivery of unmetabolized naftazone. Since naftazone per se is probably responsible for the inhibition of constitutive NO synthase (Herber et al., 1995), the effect of naftazone on the systemic circulation might be due to the NO-inhibiting action of this drug observed in vitro.

In conclusion, naftazone decreased portal pressure in portal hypertensive rats after both acute intravenous and oral chronic administration. The mechanism of this effect was different depending on the mode of administration. Moreover, the mechanism of the portal hypotensive effect of naftazone after chronic oral administration was different from that of an α-adrenoceptor antagonist or a non-selective β-adrenoceptor antagonist. As opposed to acute effects, continuous oral administration of naftazone had systemic and splanchnic arterial haemodynamic effects similar to those produced by specific NO synthase inhibitors. In regard to its original beneficial haemodynamic effect in portal hypertensive rats, naftazone should be tested in patients with portal hypertension.

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