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Portal Hypotensive Effects of Tetrandrine and Verapamil in Portal Hypertensive Rats

TSUN-BIN LIU, HAN-CHIEH LIN*, YI-TSAU HUANG, CHANG-MING SUN† AND CHUANG-YE HONG

*Institute of Traditional Medicine, School of Medicine, National Yang-Ming University, *Division of Gastroenterology, Department of Medicine, Veterans General Hospital, and †National Research Institute of Chinese Medicine, Taipei, Taiwan*

Abstract

The portal hypotensive effects of tetrandrine and verapamil (both calcium-channel blockers) were assessed in portal hypertensive rats.

Portal hypertension was induced by partial portal vein ligation in Sprague–Dawley rats. Both tetrandrine (4, 8, 16 and 24 mg kg^{-1}) and verapamil (0·5, 1·0, 1·5 and 2·0 mg kg^{-1}) induced dose-dependent decreases of portal venous pressure and mean arterial pressure after intravenous infusion. For example, infusion of tetrandrine (16 mg kg^{-1}) induced a maximum reduction of portal venous pressure and mean arterial pressure approximately 1 min after the start of infusion. Portal venous pressure decreased from baseline (12·5 mmHg) to 10·0 mmHg, and mean arterial pressure from baseline (90 mmHg) to 80 mmHg. Heart rate decreased from 250 to 240 beats min^{-1}. At 24 mg kg^{-1}, tetrandrine reduced portal venous pressure and mean arterial pressure to 20·3 ± 2·4% and 28·4 ± 1·4% of baseline, respectively.

Our results show that both tetrandrine and verapamil induce portal pressure reduction in portal hypertensive animals.

Tetrandrine is a bisbenzyltetrahydroisoquinoline alkaloid isolated from the Chinese medicinal herb *Stephania tetrandra* S. Moore which has been used in China as an anti-hypertensive drug (Wang & Lemos 1995). It has been reported as a blocker of the voltage-activated, L-type Ca^{2+} channel in a variety of cells including cardiomyocytes, vascular smooth muscle cells, anterior pituitary cells and neuroblastoma cells, and neurohypophysial nerve terminals (Liu et al 1995; Wang & Lemos 1995). In hypertensive and normotensive rats, intravenous injection of tetrandrine induced a dose-dependent decrease of mean arterial pressure (Qian et al 1983). The potential of tetrandrine as a therapeutic agent in portal hypertension has yet to be explored.

The pharmacological treatment of portal hypertension is directed at the treatment of acute bleeding episodes or the prevention of variceal bleeding (D'Amico et al 1995). Current therapeutic drugs for portal hypertension are quite limited because of their side-effects or low efficacy. Vasopressin and somatostatin are two vasoconstrictors widely used in the treatment of acute variceal bleeding; propranolol is used as a prophylactic drug for prevention of variceal bleeding (Lebrec 1994; D'Amico et al 1995). Severe systemic or coronary vasoconstriction is, nevertheless, the major drawback of vasopressin (D'Amico et al 1995; Imperiale et al 1995), and approximately one third of cirrhotic patients do not respond to propranolol (Lebrec 1994). Verapamil, a calcium-channel blocker, has been shown to reduce portal pressure in experimental animals (Reichen & Le 1986; Reichen et al 1986). In this study, we have investigated the effects of two calcium-channel blockers, tetrandrine and verapamil, on the portal pressure of portal hypertensive rats.

Correspondence: Y.-T. Huang, Institute of Traditional Medicine, School of Medicine, National Yang-Ming University, Taipei 112, Taiwan.

Materials and Methods

Portal hypertensive rats

Partial portal vein ligation was performed by the method of Chojkier & Groszmann (1981) as previously reported (Huang et al 1995). Briefly, male Sprague–Dawley rats, 200–250 g, were anaesthetized with ether. A midline incision was made, and the portal vein proximal to the bifurcation was exposed. A 3–0 silk ligature was made around the portal vein and a piece of PE 50 tubing (Clay Adams, Parsippany, NJ, USA). The PE tubing was then removed and the abdomen closed. Animal studies were approved by the Animal Experiment Committee of the National Yang-Ming University and were conducted humanely.

Pressure measurement

Fourteen days after surgery, the rats were anaesthetized with pentobarbital sodium, 50 mg kg^{-1} after an overnight fast. The ileocolic vein, femoral artery and femoral vein were cannulated with PE 50 tubing for measuring portal venous pressure and arterial blood pressure and for drug administration, respectively. Changes in pressures and heart rate were monitored with a polygraph (RS 3400, Gould, Valley View, OH, USA) by means of strain-gauge transducers (P23XL, Viggo-Spectramed, Oxnard, CA, USA). A steady baseline was recorded for 30 min. A syringe pump (Harvard Apparatus, Millis, MA, USA) was then used to infuse either tetrandrine (4, 8, 16 or 24 mg kg^{-1}) or verapamil (0·5, 1·0, 1·5 or 2·0 mg kg^{-1}) into the rats within a period of 6 min. Each rat received only one drug. After each dose, the rat was left to recover for 30 min. In this way, no tachyphylaxis was observed for either drug. For each dose of either drug it was confirmed that infusion of vehicles did not alter any of the haemodynamic parameters (data not shown). For tetrandrine, results for doses

higher than 24 mg kg^{-1} were not reported as they were confounded by the vehicle effect.

Drugs

Tetrandrine was purchased from Aldrich (Milwaukee, WI, USA) and dissolved in 0·1 N HCl. Verapamil (dissolved in saline) and all other chemicals were purchased from Sigma (St Louis, MO, USA).

Data analysis

Data were expressed as mean ± s.e.m. For each dose, a Student's paired *t*-test was used for comparison of parameters before and after infusion. Dose-response curves were analysed by one-way analysis of variance. $P < 0.05$ was regarded as an indication of significance.

Results

Baseline portal venous pressure (PVP) was significantly increased, whereas mean arterial pressure (MAP) was significantly reduced, compared with those of normal rats, as is typical of this animal model of portal hypertension (Chojkier & Groszmann 1981). As shown in Fig. 1, infusion of tetrandrine (16 mg kg^{-1}) induced a decrease of PVP and MAP in portal hypertensive rats. The maximum reduction of PVP and MAP was at about 1 min after the start of infusion. PVP decreased from baseline (12·5 mmHg) to 10·0 mmHg and MAP from baseline (90 mmHg) to 80 mmHg. Heart rate decreased from 250 to 240 beats min^{-1}. PVP returned to nearly baseline levels in 1 min, whereas it took several minutes for MAP to return to baseline after the end of infusion.

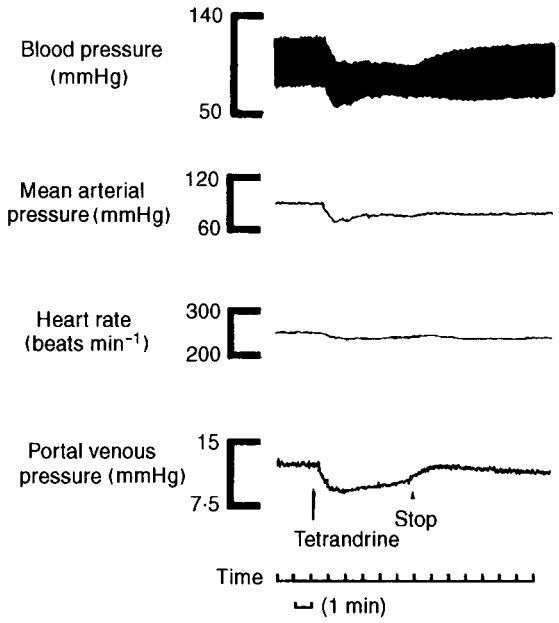

FIG. 1. Blood pressure, mean arterial pressure, heart rate, and portal venous pressure during the infusion of tetrandrine (16 mg kg^{-1}) in an anaesthetized portal hypertensive rat.

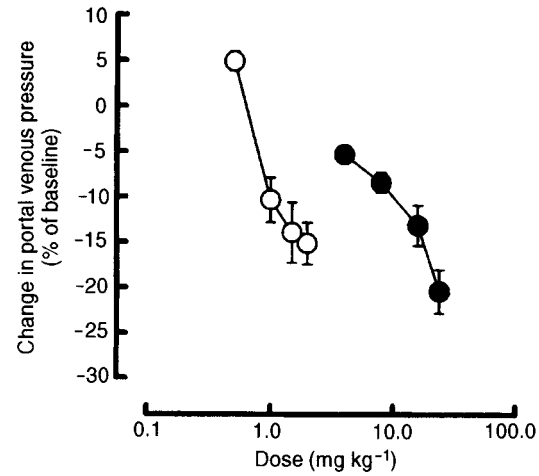

FIG. 2. Curves of response of portal venous pressure to doses of tetrandrine (●) and verapamil (○) in portal hypertensive rats. Changes in portal venous pressure are expressed as percentages of baseline. n = 7 for both tetrandrine and verapamil.

Dose-responses of PVP and MAP to tetrandrine are shown in Table 1 and Figs 2 and 3. Tetrandrine (4, 8, 16 and 24 mg kg^{-1}) induced dose-dependent decreases of PVP and MAP in portal hypertensive rats. At 24 mg kg^{-1}, tetrandrine reduced PVP and MAP to 20·3 ± 2·4% and 28·4 ± 1·4% of baseline, respectively.

Dose-responses of PVP and MAP to verapamil are shown in Table 2 and Figs 2 and 3. Verapamil (0·5, 1·0, 1·5 and 2·0 mg kg^{-1}) induced dose-dependent decreases of PVP and MAP in portal hypertensive rats. At 2 mg kg^{-1}, verapamil reduced PVP and MAP to 15·1 ± 2·3% and 39·4 ± 1·6% of baseline, respectively.

Discussion

Our results showed that both tetrandrine (4–32 mg kg^{-1}) and verapamil (0·5–2·0 mg kg^{-1}) dose-dependently reduced portal

Table 1. Responses of portal venous pressure, mean arterial pressure and heart rate to tetrandrine in anaesthetized portal hypertensive rats.

	Dose (mg kg^{-1})							
	4		8		16		24	
	Before	After	Before	After	Before	After	Before	After
Portal venous pressure (mmHg)	15·1 ± 0·6	14·3 ± 0·6*	14·2 ± 0·6	13·0 ± 0·6*	13·5 ± 0·5	11·8 ± 0·7*	13·4 ± 0·4	10·7 ± 0·5*
Mean arterial pressure (mmHg)	106 ± 5	105 ± 4	105 ± 4	101 ± 3*	105 ± 3	92 ± 3*	98 ± 3	70 ± 3*
Heart rate (beats min^{-1})	288 ± 15	284 ± 14	297 ± 17	291 ± 19	299 ± 17	291 ± 15*	282 ± 21	269 ± 22*

*$P < 0.05$ compared with before (n = 7).

Table 2. Responses of portal venous pressure, mean arterial pressure and heart rate to verapamil in anaesthetized portal hypertensive rats.

	Dose (mg kg^{-1})							
	0·5		1·0		1·5		2·0	
	Before	After	Before	After	Before	After	Before	After
Portal venous pressure (mmHg)	15·8 ± 1·0	16·0 ± 1·2	15·0 ± 1·1	13·6 ± 1·2*	14·5 ± 1·2	12·5 ± 1·4*	14·5 ± 0·6	12·3 ± 0·7*
Mean arterial pressure (mmHg)	108 ± 4	84 ± 6*	109 ± 3	75 ± 2*	95 ± 7	60 ± 7*	98 ± 2	61 ± 2*
Heart rate (beats min^{-1})	293 ± 18	278 ± 20*	295 ± 20	282 ± 21*	288 ± 19	279 ± 22	289 ± 23	267 ± 26*

*$P < 0.05$ compared with before (n = 7).

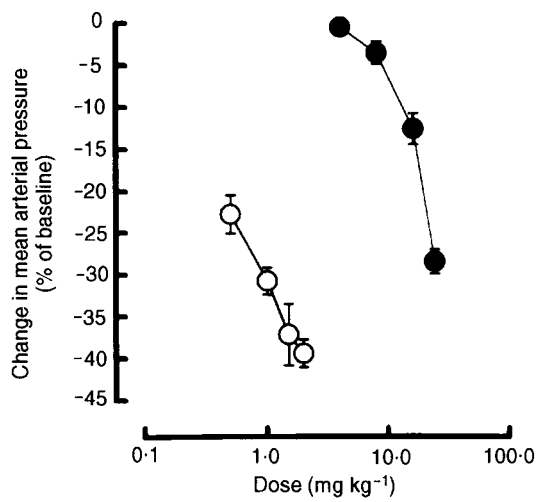

FIG. 3. Curves of response of mean arterial pressure to doses of tetrandrine (●) and verapamil (○) in portal hypertensive rats. Changes in mean arterial pressure are expressed as percentages of baseline. n = 7 for both tetrandrine and verapamil.

venous pressure and mean arterial pressure in portal hypertensive rats.

There are two main types of pharmacological approach to reducing portal hypertension: reduction of portal blood flow or reduction of portal vascular resistance. Reduction of portal blood flow is achieved by use of vasoconstrictors, reduction of portal vascular resistance by the use of vasodilators (Reichen 1990; Lebrec 1994). Some calcium antagonists have been shown to be effective portal hypotensive agents with the benefit of reducing hepatic resistance and thereby improving hepatic micro-exchange function (Reichen & Le 1986; Reichen et al 1986; Reichen 1990). Because, in this regard, the reported effects of verapamil are outstanding among calcium antagonists (Reichen 1990; Lebrec 1994), we chose verapamil as a standard for comparative purposes in this investigation of tetrandrine. Our results showed that both drugs were effective portal hypotensive agents, but verapamil was generally ten times more potent than tetrandrine. In portal-vein-stenosed rats, Lay et al (1990) also showed that within a similar dose range (0·5-2·0 mg kg^{-1}), verapamil induced reduction of portal venous pressure and reduction of portal vascular and splanchnic arterial resistance, providing evidence that verapamil can partially correct splanchnic haemodynamic abnormalities in portal hypertensive animals. Clinical studies by the same group (Kong et al 1986; Lay et al 1988) demonstrated that verapamil is an effective portal hypotensive drug in cirrhotic patients after either short- or long-term treatment.

In this study, bradycardia and blood pressure reduction were observed for both tetrandrine and verapamil (Tables 1 and 2), suggesting direct cardiac effects of these calcium antagonists (Wang & Lemos 1995; Opie 1996).

There has recently been an increasing number of reports demonstrating that combination therapy of portal hypertension with drugs of different mechanisms of action does have the potentially favourable effects both of reducing side effects and enhancing portal hypotensive effects (Reichen 1990; Lebrec 1994). Study is under way in our laboratory to investigate the chronic effects of tetrandrine alone and in combination with other vasoactive drugs in portal hypertensive rats.

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