

Effects of tetrandrine on gastric mucosa and liver in portal hypertensive rats

Yi Mu, Yao-Zong Shen, Yi-Fang Chu

Yi Mu, Yao-Zong Shen, Yi-Fang Chu, Research Laboratory of Hepatobiliary Surgery, Xuzhou Medical College, and Department of Surgery, Affiliated Hospital of Xuzhou Medical College, Xuzhou 221002, Jiangsu Province, China

Author contributions: All authors contributed equally to the work.

Supported by a grant from the Natural Science Foundation of the Educational Committee of Jiangsu Province, No.920098.

Original title: *China National Journal of New Gastroenterology* (1995-1997) renamed *World Journal of Gastroenterology* (1998-)

Correspondence to: Dr. Yi Mu, Associate Professor, having 15 papers published. Research Laboratory of Hepatobiliary Surgery, Xuzhou Medical College, and Department of Surgery, Affiliated Hospital of Xuzhou Medical College, Xuzhou 221002, Jiangsu Province, China
Telephone: +86-516-5698950-2009

Received: August 8, 1996

Revised: October 2, 1996

Accepted: November 10, 1996

Published online: September 15, 1997

Abstract

AIM: To study the effects of tetrandrine on portal hypertensive gastric mucosal lesions.

METHODS: Portal hypertensive models were induced in Wistar rats by 60% CCl₄ 3 mL/kg body weight through subcutaneous injection, once every 4 d for 56 d. The animals were randomly divided into portal hypertension, tetrandrine and propranolol groups and subsequently, treated by normal saline, tetrandrine and propranolol respectively for 15 d. Some healthy rats were used as control group. Portal venous pressure (PVP), gastric mucosal prostaglandin E₂ (PGE₂) content, gastric mucosal blood flow (GMBF), gastric adherent mucus (GAM), ALT, ALP and serum total bilirubin (STB), were measured and liver tissues were observed histologically.

RESULTS: In tetrandrine group and propranolol group, PVP was significantly lower (1.43 ± 0.13 , 1.45 ± 0.12 vs 1.89 ± 0.18 kPa; $P < 0.01$) and gastric mucosal PGE₂ content (138.59 ± 12.68 , 129.98 ± 14.31 vs 104.65 ± 12.97 pg/mg; $P < 0.01$), GMBF (11.80 ± 3.47 , 10.54 ± 3.63 vs 6.61 ± 2.82 mL·h·kg; $P < 0.05$) and GAM (3.01 ± 0.15 , 2.98 ± 0.21 vs 2.24 ± 0.26 mg; $P < 0.01$) was significantly higher than that in portal hypertension control group. In tetrandrine group intrahepatic proliferative fibrous tissues were reduced and serum ALT (47.67 ± 25.90 vs 189.33 ± 41.21 King U; $P < 0.01$), ALP (0.22 ± 0.04 vs 0.31 ± 0.06 μmol·s⁻¹/L; $P < 0.01$) and STB (4.75 ± 0.76 vs 11.12 ± 2.93 μmol/L; $P < 0.01$) were lowered as compared with those in portal hypertension control group. ALT (209.34 ± 36.91 vs 189.33 ± 41.21 King U; $P > 0.05$) and STB (11.63 ± 3.01 vs 11.12 ± 2.93 μmol/L; $P > 0.05$) in propranolol group were not different

from that in portal hypertension control group, but it showed more marked hepatocellular degeneration and necrosis and elevation of ALP (0.46 ± 0.05 vs 0.31 ± 0.06 μmol·s⁻¹/L; $P < 0.01$).

CONCLUSION: Tetrandrine can improve the functions of gastric mucosa and liver, and facilitate the absorption of intrahepatic proliferative fibrous tissues. Propranolol can aggravate hepatitis though it may improve portal hypertensive gastric mucosal lesions.

Key words: Liver gastric mucosa; Hypertension, portal; Tetrandrine; Propranolol

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Mu Y, Shen YZ, Chu YF. Effects of tetrandrine on gastric mucosa and liver in portal hypertensive rats. *World J Gastroenterol* 1997; 3(3): 192-194 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v3/i3/192.htm> DOI: <http://dx.doi.org/10.3748/wjg.v3.i3.192>

INTRODUCTION

Gastric mucosal lesions (GML) is one of common causes of upper gastrointestinal bleeding in portal hypertensive (PHT) patients with cirrhosis. So far, there have been no ideal therapy for this lesion. Although some reports have suggested that propranolol is effective for GML, attention has been paid to the side effects of this drug^[1]. It has been demonstrated that tetrandrine can lower the portal venous pressure (PVP) with no significant effects on peripheral circulation^[2], and decrease the serum procollagen-III-peptide concentration in cirrhotic patients^[3]. Therefore, in this study we observed the effects of tetrandrine on PVP, the functions of gastric mucosa and liver, and liver histology in PHT rats with cirrhosis, and tetrandrine was compared with propranolol, in an attempt to investigate effects of tetrandrine on PHT GML.

MATERIALS AND METHODS

Animals and portal hypertension induction

A total of 148 male Wistar rats, weighing 200-300 g (254.5 ± 31.4) were used. Of them, 124 were treated by CCl₄, 24 served as normal controls. The 124 rats received 60% CCl₄ (solution in rapeseed oil) 3 mL/kg by subcutaneous injection once every 4 d for 56 d. PHT model was formed in 72 rats, which was confirmed by the histology and the PVP measurement (more than 1.47 kPa).

Experimental groups

The 72 PHT rats were randomly divided into 3 groups, 24 in each: PHT control group, received normal saline 10 mL/kg tid through peritoneal injection, for 15 d; Tetrandrine group, received NS through same administration and forage containing tetrandrine

Table 1 Portal venous pressure (PVP), gastric mucosal prostaglandin E₂ (PGE₂) content, gastric mucosal blood flow (GMBF) and gastric adherent mucus (GAM) ($\bar{x} \pm s$)

Groups	PVP (kPa)	PGE ₂ (pg/mg)	GMBF (mL·h·kg)	GAM (mg)
PHT	1.89 ± 0.18 ^d	104.65 ± 12.97 ^d	6.61 ± 2.82 ^c	2.24 ± 0.26 ^d
Propranolol	1.45 ± 0.12 ^b	129.98 ± 14.31 ^b	10.54 ± 3.63 ^a	2.98 ± 0.21 ^b
Tetrandrine	1.43 ± 0.13 ^b	138.59 ± 12.68 ^b	11.80 ± 3.47 ^a	3.01 ± 0.15 ^b
Normal	1.24 ± 0.10 ^{bc}	162.03 ± 13.84 ^{bd}	18.86 ± 4.37 ^{bd}	3.25 ± 0.16 ^b

^a*P* < 0.05, ^b*P* < 0.01, *vs* portal hypertensive (PHT) controls group; ^c*P* < 0.05, ^d*P* < 0.01, *vs* propranolol group.

Table 2 Alanine aminotransferase (ALT), alkaline phosphatase (ALP) and serum total bilirubin (STB) ($\bar{x} \pm s$)

Groups	ALT (king U)	ALP (μmol·s ⁻¹ /L)	STB (μmol/L)
PHT	189.33 ± 41.21	0.31 ± 0.06 ^d	11.12 ± 2.39
Propranolol	209.34 ± 36.91	0.46 ± 0.05 ^b	11.63 ± 3.01
Tetrandrine	47.67 ± 25.90 ^{bd}	0.22 ± 0.04 ^{ad}	4.75 ± 0.76 ^{bd}
Normal	36.42 ± 21.53 ^{bd}	0.21 ± 0.04 ^{ad}	4.96 ± 0.91 ^{bd}

^a*P* < 0.05, ^b*P* < 0.01 *vs* portal hypertensive (PHT) controls group; ^d*P* < 0.01 *vs* propranolol group.

Table 3 The liver fibrosis degree

Groups	Grade 4 + + +	Grade 3 + +	Grade 2 +	Grade 1 -
PHT	6	2	0	0
Propranolol	4	3	1	0
Tetrandrine ^{ac}	0	4	2	2
Normal ^{bd}	0	0	1	7

^a*P* < 0.05, ^b*P* < 0.01, *vs* portal hypertensive (PHT) controls group; ^c*P* < 0.05, ^d*P* < 0.01, *vs* propranolol group.

(150 mg·kg⁻¹·d) for 15 d; propranolol group, received propranolol 35 mg/kg tid peritoneal injection, for 15 d; normal group, through 24 healthy rats served as controls.

Each group was then randomly divided into 3 subgroups, 8 in each. In the 1st subgroup PVP and gastric mucosal prostaglandin E₂ (PGE₂) content were measured and liver histology and liver function were examined. Gastric mucosal blood flow (GMBF) was measured in the 2nd subgroup and gastric adherent mucus (GAM) measured in the 3rd subgroup.

Methods

PVP measurement. Laparotomy was performed under 60% urethane (5 mL/kg by peritoneal injection) anesthesia in rats fasted for 24 h. The portal vein was punctured with a needle and PVP was measured by a manometer.

Gastric mucosal PGE₂ content measurement. The stomach was excised, then put it on a piece of ice to scrape gastric mucosa. The gastric mucosal PGE₂ content was measured by radioimmunoassay^[4].

Gastric mucosal blood flow measurement. The rats fasted for 24 h, under the same anesthesia, GMBF was measured by neutral red clearance test^[5].

Gastric adherent mucus measurement. The rats fasted for 24 h, under the same anesthesia, the stomach was excised and opened along the lesser curvature, turned over the gastric wall. GAM was measured by alcian blue staining^[6] and result was shown by adherent dye amount.

Liver function test. A blood sample 2.5 mL was taken for determining ALT, ALP and serum total bilirubin (STB). This was performed by the same staff from the laboratory department of our hospital.

Liver histology. The histological specimens were made by the pathology department of our hospital, stained with hematoxylin and eosin (HE) and observed under light microscope.

Statistical analysis

Analyses of variance among groups for data measurement were made with *F* test, and difference between two groups was compared with *q* test. For ranked data, multiple samples were compared with

H test, and difference between two groups was compared with *U* test. Results were considered statistically significant at *P* < 0.05.

RESULTS

There were no significant differences in PVP between tetrandrine and propranolol groups (*P* > 0.05), PVP in both the groups was significantly lower than that in PHT control group (*P* < 0.01), but higher than that in healthy group (*P* < 0.05), (Table 1).

Gastric mucosal PGE₂ content and GMBF showed no significant difference (*P* > 0.05) between tetrandrine and propranolol groups, and were significantly higher in both the groups than that in PHT control group (*P* < 0.01; *P* < 0.05), but lower than that in healthy group (*P* < 0.01), (Table 1).

There was no significant difference in GAM between tetrandrine and propranolol groups (*P* > 0.05). The values in both the groups were significantly higher than that in PHT control group (*P* < 0.01), but without significant difference as compared with the healthy group (*P* > 0.05), (Table 1).

In ALT and STB, difference between PHT and propranolol groups was not significant (*P* > 0.05). ALT and STB were significantly higher than in tetrandrine and healthy groups (*P* < 0.01), with no significant difference (*P* > 0.05) between the latter two groups, (Table 2).

ALP in propranolol group was significantly higher than that in PHT control group (*P* < 0.01), (Table 2). It was significantly higher than that in tetrandrine and healthy groups (*P* < 0.01; *P* < 0.05), with no significant difference (*P* > 0.05) between the latter two groups.

In PHT group, pseudolobules were found in most cases, but hepatocytic degeneration and necrosis were not obvious, few red cells were found in sinusoid of the liver. In propranolol group, pseudolobules or a large quantity of proliferative fibrous tissues were found, hepatocytic degeneration and necrosis were more marked with few red cells found in sinusoid of the liver. In tetrandrine group, intrahepatic proliferative fibrous tissue was less than that in PHT group and pseudolobules disappeared, and many red cells were found in the sinusoid of the liver, no hepatocytic degeneration and necrosis were found.

According to the degree of intrahepatic proliferative fibrous tissue, four grades were established. Grade 4, pseudolobules; Grade 3, a large quantity of fibrous tissue; Grade 2, a little fibrous tissue; Grade 1, no proliferative fibrous tissues were found. Results showed that there was no significant difference between propranolol and PHT groups (*P* > 0.05). In tetrandrine group, fibrous tissue was significantly decreased as compared with that in PHT control group (*P* < 0.05). There was significant difference (*P* < 0.01) between healthy and other groups. These data are shown in Table 3.

DISCUSSION

The pathogenesis of PHT GML was the weakening of gastric mucosal protective mechanism resulting from the structural and functional impairment of mucosal microcirculation consequent upon PHT. Gastric acid and pepsin were not the main causes of this lesion^[7]. Therefore, treating PHT GML by reducing PVP has been a main orientation of study in the world. Gastric mucosal PGE₂ content, GMBF and GAM are important factors of gastric mucosal protective mechanism so that the change of these factors will reflect the therapeutic effects on PHT GML.

It has been reported that propranolol may be effective for PHT GML. Our results showed that propranolol could significantly reduce PVP and increase the gastric mucosal PGE₂ content, GMBF and GAM. Our previous electron microscopic observation showed that propranolol could significantly improve the pathological state of gastric mucosal capillaries and increase the mucigen granules of gastric mucosal epithelial cells^[8]. These demonstrated that propranolol is indeed useful in improving PHT GML. Propranolol is a β adrenoreceptor-blocking agent, and its effect depends on constricting splanchnic blood vessels, decreasing blood flow into the portal venous system, reducing PVP and improving the dilatation state of gastric mucosal microcirculation. Nevertheless, in this study, ALT and STB in propranolol group were not decreased, while ALP

was increased as compared with PHT group. These suggest that propranolol could not decrease hepatocytic damage, but increase the intrahepatic obstruction on the contrary. The liver histologic observation also proved this. Because propranolol reduces PVP through decreasing portal venous blood flow and constricting blood vessel, hepatic blood supply is further reduced, resulting in marked liver damage. Moreover, further reduction of the blood flow passing through the liver causes increased blood ammonia and incidence of cerebrosis.

Effects of tetrandrine on gastric mucosa in PHT rats were almost the same as propranolol, but their mechanisms of decreasing PVP were different. Tetrandrine, a calcium-channel blocking agents, inhibits calcium ion acrossing the calcium channel of vascular smooth muscle by blocking receptors on cell membrane, leading to a decrease in intracellular calcium ion concentration, and relieving excitation-constricting coupling. As a result, smooth muscle loosened, intra and extra-hepatic portal venous resistance decreased and PVP reduced^[2]. Furthermore, it can inhibit the activity of adenylate cyclase on cell membrane, lower the intracellular cyclic adenosine monophosphate (cAMP) levels, thus disturbing the phosphorylation process of thymine, inhibiting the collagen synthesis of hepatocytes and Ito cells^[9]. In this study, we also found that tetrandrine can reduce intrahepatic proliferative fibrous tissues. So PHT GML was improved because of the decreased PVP and portal venous backward blood flow. Besides, results showed that tetrandrine can significantly lower ALT, ALP and STB to the normal. From these results, it is supposed that tetrandrine alleviate hepatocytic necrosis and intrahepatic obstruction. Histologic observation also proved this. These are due to the dilatation of intra and extra-hepatic portal vein and the decrease in intrahepatic fibrous tissue and portal venous

resistance, resulting in increased hepatic blood supply and better hepatic nutritional stat us.

In conclusion, tetrandrine not only can improve the function of gastric mucosa and liver, but also facilitate the absorption of intrahepatic proliferative fibrous tissues. This study suggests that tetrandrine might be a more appropriate drug for PHT GML as compared with propranolol.

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S- Editor: Filipodia L- Editor: Jennifer E- Editor: Hu S



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ISSN 1007-9327

