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Captopril reduces portal pressure effectively in portal hypertensive patients with low portal venous velocity

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Background. The effect of an angiotensin II blockade in lowering the portal pressure in patients with liver cirrhosis and portal hypertension is controversial. This prospective study was undertaken to evaluate the portal hypotensive effect of captopril compared to that of propranolol, and to determine the factors that contribute to a successful reduction in the portal pressure after longterm captopril administration in patients with liver cirrhosis. ***Methods.*** The hepatic venous pressure gradient (HVPG) and portal venous velocity (PVV) were measured both before and 3 months after initiation of the administration of captopril ($n = 29$) or propranolol ($n = 29$) in cirrhotic patients with a variceal bleeding episode. Patients who showed a reduction in the HVPG of more than 20% of the baseline were defined as being responders. ***Results.*** At 3 months, the mean reduction in the HVPG after captopril was less than that after propranolol ($-3.0 \pm 9.3\%$ vs $-28.5\% \pm 4.1\%$; $P < 0.05$). However, of the 29 patients receiving captopril, 9 were classified as being responders. On multivariate analysis with parameters including age, cause, Child-Pugh score, HVPG, and PVV, only low PVV was found to be a significant independent factor for responders (PVV < 12 cm/s; odds ratio [OR], 12.2; 95% confidence interval [CI], 1.47–102.40) in the captopril group. ***Conclusions.*** Longterm captopril administration reduces the portal pressure effectively in cirrhotic patients with a low PVV. This suggests that the reduction in portal pressure after captopril administration is a result of improved portal venous outflow brought about by a decrease in the intrahepatic vascular resistance. When the PVV is below 12 cm/s, a captopril trial might be useful in preventing variceal bleeding in portal hypertensive patients.

Key words: captopril, portal hypertension, liver cirrhosis

Introduction

In cirrhosis, increased intrahepatic vascular resistance has been thought to be a mechanical consequence of the architectural distortion of the liver microcirculation caused by fibrous tissue and regenerative nodules. However, recent studies have suggested that, in addition to this mechanical consequence, there are dynamic components amenable to pharmacological manipulation.[1,2] These reversible components are responsible for approximately 20%–30% of the increased intrahepatic vascular resistance.[1] Hepatic stellate cells are a major dynamic component in the pathogenesis of increased intrahepatic vascular resistance in chronic liver disease.[2,3] The available evidence has shown that angiotensin II induces contraction of the hepatic stellate cells and may participate in the pathogenesis of the increased intrahepatic vascular resistance in chronic liver disease.[4,5] Hence, an angiotensin II blockade has been proposed as a new pharmacological trial in treating portal hypertensive patients with cirrhosis. However, previous reports on the portal hypotensive effect of an angiotensin II blockade provided conflicting results in patients with liver cirrhosis.[6–14] In addition, there are no reports showing the characteristics of patients who responded successfully to the angiotensin II blockade, with a fall in the hepatic venous pressure gradient (HVPG) of more than 20% of the baseline value. Captopril, an angiotensin-converting enzyme inhibitor, blocks the conversion of the inactive angiotensin I to the active form, angiotensin II.

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We performed this prospective study (1) to evaluate the portal hypotensive effect of longterm captopril administration compared with that of propranolol and (2) to determine the factors that contribute to a successful reduction of the portal pressure in portal hypertensive patients with cirrhosis receiving captopril.

Patients and methods

Patients

The study included 62 portal hypertensive patients with cirrhosis of the liver who were treated endoscopically after a variceal bleeding episode. The etiology of cirrhosis was alcohol-induced in 42 patients, hepatitis B surface antigen-associated in 10, and both alcohol-induced and viral in 10. The Ethics Committee of the hospital approved the protocol and patients provided their written informed consent. Patients with severe liver failure (serum bilirubin level >5 mg/dl), hepatic encephalopathy, severe arterial hypotension (mean arterial pressure <60 mmHg), hepatorenal syndrome, and ultrasonographic data suggesting a hepatoma were excluded.

Study protocol

The patients were enrolled in the trial 7 to 10 days after admission, when the gastrointestinal bleeding had ceased and the hemodynamic conditions had returned to normal. Of the 62 patients enrolled in this study, 32 received captopril (Capoten; Squibb, New York, NY, USA) and 30 received propranolol. Captopril was given orally at an initial dose of 25 mg/day. If tolerated, the dose was increased stepwise at 3-day intervals up to 75 mg/day, as long as the systolic blood pressure did not decrease below 90 mmHg. Propranolol was given orally at an initial dose of 20 mg twice daily. The dose was subsequently adjusted over a period of 3 days until the resting heart rate had been reduced by 25% or less than 55 beats per min. The doses ranged from 80 to 240 mg per day. Once the maintenance dose was reached, the treatment was maintained for 3 months. The results of hemodynamic studies were evaluated both prior to and 3 months after the initiation of treatment.

Hemodynamic studies

After the patients had an overnight fast, the right hepatic vein was catheterized percutaneously through the femoral vein, and the pressure was recorded in both the wedge and the free position, using a 7-F balloon-tipped catheter. The portal pressure was estimated from the HVPG, as the difference between wedge hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP). The mean arterial pressure was measured noninvasively with an automatic sphygmomanometer (Hewlett-Packard M1205A; Hewlett-Packard, Palo Alto, CA, USA). The heart rate was derived from continuous electrocardiogram monitoring. The portal venous velocity (PVV) was measured in terms of mean velocity (time-averaged peak velocity) by Doppler ultrasonography (3.5-MHz convex probe; Aloka, Tokyo, Japan). The portal vein was imaged longitudinally with the patient in the supine position, and the Doppler sample point was set at the midpoint between the confluence of the splenic and superior mesenteric veins and the bifurcation of the portal vein at the hepatic hilus. When the sample point was adjusted to the center of the portal vein, the PVV was recorded during a quiet suspended expiration and was averaged over a few seconds (Fig. 1).[15,16] Both the HVPG and PVV were estimated from the average of at least three repeated measurements.

Statistical analysis

The values for results are expressed as means ± SE. A paired *t*-test was used for the statistical analysis of differences between the means at baseline and at the end of the study period within each group, and an unpaired *t*-test was used for comparisons between the groups. Patients who showed a reduction in the HVPG of more than 20% were defined as being responders to the drug. Multivariate analysis by a logistic regression test was used to investigate the factors associated with characteristics of the responders. Significance was established at $P < 0.05$. All statistics were analyzed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA).

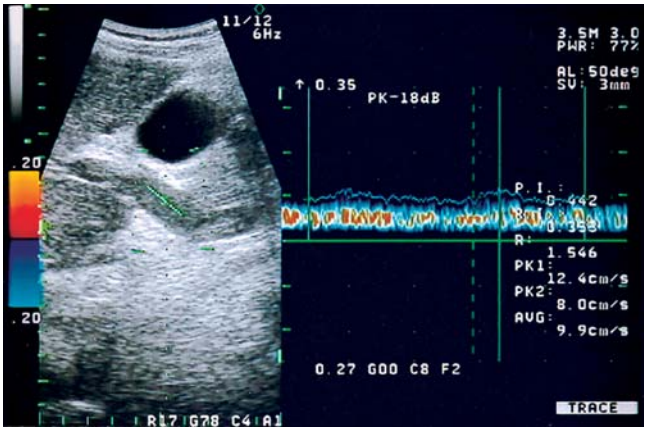

Fig. 1. Measurement of the portal venous velocity. Doppler ultrasonography showed that the portal venous velocity was 9.9 cm/s in the patients with liver cirrhosis

Table 1. Baseline clinical characteristics of the patients

	Captopril ($n = 29$)	Propranolol ($n = 29$)	P
Age (years)	48.6 ± 1.5	49.7 ± 1.8	NS
Sex (male/female)	28/1	27/2	NS
Child-Pugh class (A/B/C)	6/18/5	12/11/6	NS
Etiology (alcohol/viral/combined)	20/5/4	21/2/6	NS
HVPG at inclusion (mmHg)	15.6 ± 0.8	17.3 ± 1.0	NS
PVV at inclusion (cm/s)	15.2 ± 0.7	14.7 ± 0.7	NS

HVPG, hepatic venous pressure gradient; NS, not significant, PVV, portal venous velocity

Table 2. Hemodynamics at the baseline and 3 months after initiation of the administration of captopril or propranolol

	Captopril ($n = 29$)			Propranolol ($n = 29$)		
	Baseline	3 Months	P	Baseline	3 Months	P
WHVP (mmHg)	24.8 ± 1.0	21.1 ± 1.4	0.040	27.5 ± 1.3	26.0 ± 1.3	NS
FHVP (mmHg)	9.3 ± 0.8	7.1 ± 0.7	0.040	10.0 ± 0.9	13.9 ± 1.2	0.019
HVPG (mmHg)	15.6 ± 0.8	13.9 ± 1.1	NS	17.3 ± 1.0	12.1 ± 0.8	<0.001
PVV (cm/s)	15.2 ± 0.7	15.5 ± 0.6	NS	14.7 ± 0.7	11.6 ± 0.5	<0.001
MAP (mmHg)	95.9 ± 1.0	90.4 ± 1.5	<0.001	85.0 ± 2.2	80.3 ± 1.6	NS
HR (beats/min)	80.2 ± 1.1	78.7 ± 1.5	NS	78.2 ± 2.6	56.2 ± 1.5	<0.001

FHVP, free hepatic venous pressure; HR, heart rate; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure; NS, not significant; PVV, portal venous velocity; WHVP, wedge hepatic venous pressure

Results

Thirty-two patients received captopril and 30 received propranolol. Four patients did not complete the study because 3 had suffered variceal bleeding, and 1 died due to hepatic failure during the study period. Consequently, the final analysis included 29 patients receiving captopril and 29 receiving propranolol. There were no differences in any parameters between the captopril and propranolol groups (Table 1). The adverse effects of captopril were orthostatic hypotension, in 5 patients; and dry cough, in 1. Five patients receiving propranolol complained of dizziness. However, these adverse effects were not severe enough to stop medication. Captopril reduced not only the WHVP, from 24.8 ± 1.0 to 21.1 ± 1.4 mmHg ($P = 0.040$) but also reduced the FHVP, from 9.3 ± 0.8 to 7.1 ± 0.7 mmHg ($P = 0.040$). Therefore, captopril did not modify the HVPG, which changed from 15.6 ± 0.8 to 13.9 ± 1.1 mmHg ($P > 0.05$; Table 2). Propranolol did not significantly change the WHVP, which changed from 27.5 ± 1.3 to 26.0 ± 1.3 ($P > 0.05$), but it did cause a marked increase in the FHVP, from 10.0 ± 0.9 to 13.9 ± 1.2 mmHg ($P = 0.019$). As a result, it induced a decrease in the HVPG, from 17.3 ± 1.0 to 12.1 ± 0.8 mmHg ($P < 0.001$; Table 2). The reduction in the HVPG caused by propranolol was greater than that caused by captopril (−28.5 ± 4.1% vs −3.0 ± 9.3%; $P < 0.05$; Fig. 2). The PVV decreased after propranolol administration, but increased after captopril (−19.8 ± 2.8% vs 6.6 ± 5.5%; $P < 0.001$; Fig. 2). In the systemic hemodynamics, captopril caused a greater change in the mean arterial pressure than did propranolol, but the difference was not statistically significant (−5.6 ± 1.4% vs −4.0 ± 3.0%; $P > 0.05$). However, propranolol caused a larger decrease in the heart rate than did

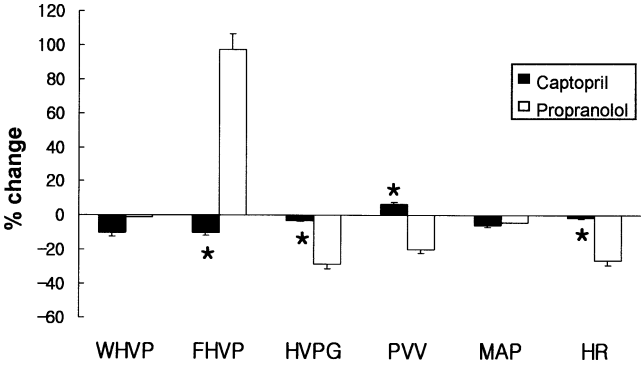

Fig. 2. Comparison of the effects of the longterm administration of captopril and propranolol on hemodynamics. The values for results are expressed as the percentage change from the baseline study. *Asterisks*, significantly different from propranolol. *WHVP*, wedge hepatic venous pressure; *FHVP*, free hepatic venous pressure; *HVPG*, hepatic venous pressure gradient; *PVV*, portal venous velocity; *MAP*, mean arterial pressure; *HR*, heart rate

Table 3. Results of multivariate analysis for the responders in the captopril group

Variables	Odds ratio	95% CI
Age <50 years	0.58	0.08–4.45
Cause (alcohol)	0.49	0.07–3.53
Child-Pugh score <10	1.48	0.05–47.54
Baseline HVPG (mmHg) >16	2.88	0.40–20.57
Baseline PVV (cm/s) <12	12.25	1.47–102.40

CI, confidence interval; HVPG, hepatic venous pressure gradient; PVV, portal venous velocity

captopril ($-26.4 \pm 2.5\%$ vs $-1.5 \pm 2.1\%$; $P < 0.001$; Fig. 2). To identify the characteristics of the patients who responded to captopril, multivariate analysis was performed, with parameters including age (<50 years), cause (alcohol), Child-Pugh score (<10), baseline HVPG (>16 mmHg) and PVV (<12 cm/s). On the multivariate analysis, only a low PVV was a found to be a significant independent factor for responders in the captopril group (PVV < 12 cm/s; odds ratio [OR], 12.2; 95% confidence interval [CI], 1.47–102.40; Table 3).

Discussion

Variceal bleeding is a frequent and severe complication in patients with liver cirrhosis and portal hypertension. The mortality rate associated with each bleeding episode is approximately 25%.[17] Nonselective β-blockers, which induce a reduction in the portal pressure by decreasing the portal inflow, have been widely used to prevent variceal bleeding.[1,2] However, the mean reduction in portal pressure achieved by propranolol was only 15%,[1,18] and one-third of the cirrhotic patients obtained a satisfactory hemodynamic response.[19] Furthermore, approximately 15% of the patients had contraindications to β-blockers or did not tolerate this treatment.[13] Hence, there is a need for alternative drugs to decrease the portal pressure, and thereby reduce the risk of hemorrhage in patients with liver cirrhosis and varices. Angiotensin II is of great importance for regulating the peripheral vascular tone and sodium handling in patients with liver cirrhosis.[20,21] The plasma level of angiotensin II is elevated in cirrhosis, and an intravenous infusion of angiotensin II increases the portal pressure.[22–24] Furthermore, recent studies have shown that angiotensin II type I receptors induce the contraction and proliferation of hepatic stellate cells, cells which play a major role in regulating the intrahepatic vascular resistance in liver cirrhosis.[5] Therefore, angiotensin II is considered to be a potential mediator of intrahepatic portal hypertension in patients with cirrhosis.[23]

Captopril, an angiotensin-converting enzyme inhibitor, blocks the conversion of inactive angiotensin I to its hemodynamically active form, angiotensin II, and, theoretically, may alleviate protal hypertension in patients with liver cirrhosis. There are a few reports evaluating the effects of captopril on portal pressure.[6–9] Significant changes in portal pressure were not detected in any of these studies. However, evaluating the previous studies on portal pressure is difficult because most of them had a small sample number without a control and had a short-term treatment regimen (less than 2 weeks). It has been proved that a reduction in the HVPG of more than 20% of the baseline values is associated with a low risk of an additional variceal hemorrhage.[19,25]

In our study, even though the mean decrease in the HVPG caused by captopril was minimal, one-third of the patients receiving captopril achieved a reduction in the HVPG of more than 20% of the baseline value. Interestingly, in this study, captopril proved to be effective in cirrhotic patients with low portal venous velocity (PVV) on multivariate analysis for the responders. Decreased velocity in the main portal vein results from high intrahepatic vascular resistance. On the other hand, the reduction in portal pressure after captopril administration is the result of improved portal venous outflow, accompanied by a decrease in intrahepatic vascular resistance. In addition, captopril caused a great reduction in the WHVP, whereas propranolol did not. This suggests that captopril plays a role in the decrease of intrahepatic vascular resistance rather than in the decrease of portal inflow. Portal hypertension is the result of increased hepatic vascular resistance and increased portal inflow.[2] Hence, in a patient with low portal venous flow, a drug that decreases the intrahepatic vascular resistance may be helpful in lowering the portal pressure. On the other hand, when there is high portal venous flow, splanchnic vasoconstrictors such as propranolol may favorably influence portal hypertension by reducing the portal inflow.

In summary, captopril may alleviate portal hypertension by decreasing the intrahepatic vascular resistance, while propranolol acts by reducing the portal inflow. According to our findings for PVV measurements, it appears that longterm captopril administration in selected patients with cirrhosis and portal hypertension may assist in lowering the portal pressure and may, thereby, be of value in preventing variceal bleeding. Further investigation along these lines is recommended.

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