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Systemic and Portal Hemodynamic Response to Propranolol in Patients with Portal Hypertension Due to Hepatitis C Virus

Key Words

Anti-hepatitis C virus
Cirrhosis
 β -Blocker
Middle East

Abstract

Objective: Propranolol, a β -adrenergic blocker, has been reported to reduce portal pressure in patients with alcoholic cirrhosis and thereby might be useful in the prophylaxis of variceal bleeding. Since it is not known if the response of patients with portal hypertension due to hepatitis C virus is similar, systemic and portal hemodynamic response to propranolol was evaluated in 10 patients with portal hypertension and hepatitis C virus infection. **Methods:** Patients were studied before the intravenous infusion of 0.15 mg/kg propranolol, and 30 min after the infusion. **Results:** Propranolol induced highly significant systemic hemodynamic effects, reducing heart rate from 65 ± 6 to 57 ± 5 ($p < 0.0001$) and cardiac output from 6.7 ± 1.6 to 5.0 ± 1.1 (liters/min, $p < 0.0005$). The effect on the pulmonary circulation was a mild increase in diastolic pulmonary artery pressure. Propranolol induced a mild and insignificant decrease in wedged hepatic vein pressure (WHVP), from 32 ± 6 to 29 ± 5 mm Hg, and hepatic venous pressure gradient from 18 ± 3 to 16 ± 5 mm Hg ($p > 0.05$). Decrease of WHVP of more than 5 mm Hg occurred only in 3 out of 10 patients. **Conclusion:** It is suggested that propranolol may be useful only in some patients with portal hypertension associated with hepatitis C virus infection.

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Introduction

Propranolol, a β -adrenergic blocker, has been reported to reduce portal pressure in patients with alcoholic cirrhosis and thereby might be useful in the prophylaxis of variceal bleeding [1, 2]. However, it is not known if the response of patients with portal hypertension due to hepatitis C virus (HCV) infection is similar. Therefore, the hemodynamic effects of propranolol were studied in patients with portal hypertension associated with HCV infection to assess its usefulness in the treatment of portal hypertension.

Patients and Methods

Ten male patients (mean age 43 ± 5 years, range 37–50) referred to our Gastroenterology Unit for transvenous biopsy were studied. All were Egyptians except one Pakistani. All patients were anti-HCV positive in serum by second-generation ELISA (Abbott, Chicago, Ill., USA) and had a hepatic venous pressure

gradient (HVPG) above 12 mm Hg on hepatic catheterization. Presence of anti-HCV was confirmed by supplemental testing using nitrocellulose solid phase immunodot assay (Matrix, Abbott). Only repeatedly reactive samples were defined as positive. All patients were confirmed to have hepatic histology consistent with HCV infection. Cirrhosis was confirmed on liver biopsy in 5 of the 10 patients. In the other 5 cirrhosis was suspected but could not be confirmed because of the small and fragmented liver tissue. However, they had indirect evidence of cirrhosis in the form of edema, palmar erythema, spider nevi, gynecomastia or abnormal prothrombin time and ultrasonographic features of cirrhosis, along with HVPG of over 12 mm Hg. None of the patients had ascites or encephalopathy. The spleen was palpable in 6 patients. Another 6 patients had evidence of hypersplenism in the form of low platelet counts. The serum bilirubin, albumin, alanine aminotransferase, alkaline phosphatase, prothrombin time, blood hemoglobin, white blood cell and platelets counts are shown in table 1. None were HBsAg positive, and none indicated a history of alcoholic intake nor intravenous drug abuse. None of the patients were taking any vasoactive medication. A control group of patients with liver cirrhosis without HCV infection was not available for study as 80% of the patients referred to us for transvenous liver biopsy

Table 1. Investigative and histopathologic data

Tjno	Bil	Alb	ALT	AP	PT	Hb	WBC	Plat	Pathology
68	26	33	1.2	0.9	6	16.0	2.2	39	CH with fibrosis
71	49	34	2.7	1.4	8	13.7	4.0	91	CH with fibrosis
74	22	33	1.2	0.4	4	14.1	5.5	23	cirrhosis, CH
76	13	44	7.0	1.0	3	15.5	4.9	142	CH with fibrosis
79	15	34	3.1	0.7	2	15.3	5.1	63	CH with fibrosis
95	28	34	0.1	1.0	3	13.8	5.4	63	cirrhosis, CH
99	27	22	1.8	1.0	4	14.4	6.4	138	cirrhosis, CH
100	21	38	4.7	0.7	2	14.3	3.8	72	cirrhosis, CH
101	15	41	2.8	0.6	7	13.4	6.5	137	CH with fibrosis
103	13	30	1.6	1.3	5	14.9	6.4	101	cirrhosis, VH

Tjno = Serial number; Bil = serum bilirubin, $\mu\text{mol/l}$; Alb = serum albumin, g/l; ALT = alanine aminotransferase $\times$ upper limit of normal; AP = serum alkaline phosphatase $\times$ upper limit of normal; PT = prothrombin time $>$ control, s; Hb = hemoglobin, g/dl; WBC = white blood cell count, $\times$ 1,000/ml; Plat = platelet count, $\times$ 1,000/ml; CH = chronic hepatitis.

were anti-HCV positive. Systemic and regional hemodynamics were studied the morning after an overnight fast as described previously [3]. Pulmonary artery and capillary pressures and cardiac output were measured with a Swan-Ganz catheter. The cardiac output was measured in triplicate by the thermodilution method using an American Edwards COM-2 cardiac output computer, and the mean value was used. Hepatic blood flow was measured by the indocyanine green continuous infusion method. Multiple peripheral and hepatic blood samples were drawn simultaneously at 2-min intervals. Indocyanine green absorbance was read at 780 nm. HVPG was calculated as the difference between the wedged and free hepatic venous pressures. Heart rate was determined by continuous ECG monitoring. Arterial pressure was measured by an external monitoring sphygmomanometer. Mean arterial pressure was determined as $[\text{systolic} - \text{diastolic pressure}/3] + \text{diastolic pressure}$. Systemic vascular resistance was calculated by the formula: $(\text{mean arterial pressure} - \text{right atrial pressure}) \times 80/\text{cardiac output}$. All measurements were taken before and 30 min after completing the intravenous infusion over 10 min of 0.15 mg/kg body weight propranolol. Research guidelines of the Ethical Committee, Faculty of Medicine, Kuwait University for the Protection of Human Subjects were followed. Consent was obtained from each

patient after explaining the purpose, nature and risks involved in all procedures used. Values are reported as mean $\pm$ standard deviation. Basal and postpropranolol values are compared by the paired Student's *t* test. Significance is set at a two-tailed *p* value of <0.05 .

Results

The effects of propranolol on systemic and splanchnic hemodynamic measurements are given in tables 2 and 3. Propranolol induced highly significant systemic hemodynamic effects, reducing the heart rate from 65 ± 6 to 57 ± 5 ($p < 0.0001$), cardiac output from 6.7 ± 1.6 to 5.0 ± 1.1 (liters/min, $p < 0.0005$) and cardiac index from 3.6 ± 0.9 to 2.7 ± 0.6 liters/min/m². The effect on the pulmonary circulation was a mild increase in diastolic pulmonary artery pressure from 6 ± 2 to 9 ± 2 mm Hg ($p = 0.04$). The systolic pulmonary artery pressure before and after the administration of propranolol was 32 ± 6 and 35 ± 6 mm, respectively. These effects are as ex-

Table 2. Systemic effects of 0.15 mg/kg body weight propranolol in patients with anti-HCV-positive cirrhosis

Patient No.	Cardiac index liters/min/m ²		Mean arterial pressure mm Hg		Systemic vascular resistance, dyn/s/cm ⁻⁵	
	basal	30 min after	basal	30 min after	basal	30 min after
1	3.13	2.09	100	93	1,130	1,562
2	3.54	2.81	94	97	1,079	1,408
3	2.92	2.76	89	99	1,244	1,459
4	2.75	2.13	111	105	1,780	2,000
5	3.22	2.69	116	121	1,254	1,557
6	3.39	2.69	109	113	1,346	1,728
7	5.00	3.88	102	102	694	968
8	3.40	2.60	100	105	953	1,400
9	2.82	1.77	92	86	1,192	1,850
10	5.72	3.31	102	108	792	1,469
Mean	3.59	2.67	102	103	1,146	1,540
SD	0.93	0.58	8	9	289	268

pected. Propranolol induced a mild and insignificant decrease in wedged hepatic vein pressure (WHVP) and HVPG. Decrease of HVPG of 5 mm Hg or more occurred in 3 patients. In 3 patients the postpropranolol HVPG was ≤ 12 mm Hg (table 3). No correlation was found between changes in cardiac index, pulse rate, WHVP and HVPG.

Discussion

Propranolol produced significant systemic effects and no significant decrease in WHVP or HVPG. Increased HVPG in these patients with portal hypertension reflects increased sinusoidal resistance. It may therefore be assumed that propranolol does not significantly reduce sinusoidal resistance in patients with cirrhosis due to HCV, unlike in patients with alcoholic cirrhosis. However, decrease in HVPG was 5 mm Hg or more in 3 of the 10 patients. The objective of portal pressure re-

duction is to reduce the likelihood of bleeding. Variceal hemorrhage generally does not occur if HVPG is below 12 mm Hg [4, 5]. In 3 of our patients, the postpropranolol HVPG was ≤ 12 mm Hg. In one study, in patients with HBsAg-positive cirrhosis, propranolol consistently reduced WHVP from 25 ± 10 to 21 ± 9 ($p < 0.01$) and HVPG from 16 ± 4 to 12 ± 4 ($p < 0.01$) [6]. It therefore appears that patients with cirrhosis due to HCV may respond to propranolol differently from patients with cirrhosis due to hepatitis B virus infection.

Three other aspects of treatment of portal hypertension with propranolol have recently been brought to attention. First, daily variations in portal blood flow occur and propranolol may affect these variations [7]. Second, the portal pressure response to β -blockade may be greater in cirrhotic patients without varices than in those with varices [5]. Third, the addition of nitrates to β -blocker may be effective in decreasing portal pressure in poor respond-

Table 3. Splanchnic effects of 0.15 mg/kg body weight propranolol in patients with anti-HCV-positive cirrhosis

Patient No.	WHVP mm Hg		Free hepatic venous pressure, mm Hg		HVPG mm Hg		Hepatic blood flow, liters/min	
	basal	30 min after	basal	30 min after	basal	30 min after	basal	30 min after
1	35	28	17	11	18	17	0.99	0.94
2	32	34	17	11	15	23	–	–
3	30	28	7	8	23	20	0.33	0.58
4	18	21	6	13	12	8	0.89	0.56
5	32	32	15	15	17	17	1.78	1.13
6	34	32	13	13	21	19	–	–
7	40	34	21	15	19	19	1.61	1.68
8	39	36	19	21	20	15	2.73	1.90
9	33	20	19	14	14	6	1.45	1.46
10	27	28	10	16	17	12	–	–
Mean	32	29	14	14	18	16	1.4	1.2
SD	6	5	5	3	3	5	0.7	0.5

ers to β -blocker alone [8]. It would be interesting to assess these aspects in future studies in patients with portal hypertension due to HCV. The minority of patients with portal hypertension due to HCV who are likely to benefit from propranolol therapy may be selected by studying its effect on the portal pressure.

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