0270-9139/89/1003-0283$02.00/0
HEPATOLOGY
Vol. 10, No. 3, pp. 283–287, 1989
Printed in U.S.A.

Lack of Effects of Isosorbide-5-mononitrate on Hepatic Hemodynamics in HBsAg-Positive Cirrhosis

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We conducted a randomized controlled hemodynamic study to evaluate the effect of placebo and 20 mg isosorbide-5-mononitrate, a long-acting organic nitrate, in 19 patients with HBsAg-positive cirrhosis by the simultaneous measurement of portal venous pressure and wedged hepatic venous pressure. Baseline values for the two groups were similar. One hour after oral administration of 20 mg isosorbide-5-mononitrate in 10 patients, mean arterial pressure, mean pulmonary arterial pressure and pulmonary capillary wedge pressure significantly decreased from 92 ± 13 (mean ± S.D.) to 82 ± 14 mmHg, from 12.9 ± 4.5 to 9.3 ± 2.4 mmHg and from 6.9 ± 3.4 to 4.3 ± 1.8 mmHg, respectively. However, both portal venous pressure gradient (from 18.1 ± 3.6 to 17.5 ± 3.0 mmHg) and hepatic venous pressure gradient (from 17.8 ± 5.2 to 16.6 ± 5.3 mmHg) remained unchanged during the study. In six patients who received 20 mg isosorbide-5-mononitrate twice daily for 7 days, hepatic venous pressure gradient remained unaltered as compared to basal and 1-hr values. There was no significant change in cardiac index, heart rate or systemic vascular resistance in either immediate (1-hr) or delayed (7-day) studies. Three patients (30%) developed mild headache or dizziness and two patients (20%) demonstrated systolic hypotension (<80 mmHg) during the immediate study. This study shows that isosorbide-5-mononitrate appears to have no effect in treating portal hypertension in patients with HBsAg-positive cirrhosis. In addition, the isosorbide-5-mononitrate may affect the systemic circulation more than the portal circulation.

Isosorbide dinitrate (ISDN), a long-acting organic nitrate, has been shown to decrease portal pressure when given sublingually (1, 2) or orally (3, 4) to cirrhotic patients. The decrease in portal pressure with ISDN was reported to be more predictable than that seen with propranolol (4).

Isosorbide-5-mononitrate (IS-5-MN), the main metabolite of ISDN, offers theoretical advantages over ISDN in patients with liver disease, as it does not require hepatic biotransformation to a vasoactive drug, possesses complete bioavailability and does not accumulate in patients with liver disease (5). The present study was designed to examine the immediate and delayed effects of IS-5-MN on systemic and hepatic hemodynamics in patients with HBsAg-positive cirrhosis and portal hypertension.

MATERIALS AND METHODS

Nineteen patients with HBsAg-positive and histologically proven postnecrotic macronodular cirrhosis (6) were investigated. They were randomly assigned to receive IS-5-MN or placebo. According to Pugh's modification of Child's classification (7), patients were classified as Grade A (16 patients) or B (three patients). The clinical data of the two groups are summarized in Table 1. All patients had esophageal varices, splenomegaly, spider angiomas, increased serum globulin and no evidence of alcohol consumption. None of these patients had bleeding diathesis, hepatocellular carcinoma, hepatic encephalopathy, chronic obstructive lung disease, ascites, heart disease or renal disease.

All patients were informed of the nature, purpose and possible risks of the study before giving their consent to participate. The study protocol was reviewed and approved by the Hospital Ethics Committee.

After an overnight fast, the patients were prepared for portal and hepatic vein catheterization in supine position. All patients received meperidine (25 to 75 mg) 0.5 hr before the procedure. A puncture probe was placed over the right intercostal space between the anterior axillary line and the midaxillary line, and the intrahepatic portal venous branch was punctured using a portal vein needle (Wilson-Cook Medical, Inc.) under ultrasonic guidance (8). The position of the needle was then exchanged for a 5F catheter. The tip of the catheter was placed in the trunk of the portal vein to obtain portal venous pressure (PVP). The location of the tip of the 5F catheter in the portal vein trunk was checked by injection of 2 ml of contrast material. Under fluoroscopic visualization, a Swan-Ganz thermodilution catheter was inserted into the right hepatic vein, via the right femoral vein, using the Seldinger technique. After the recording of free hepatic venous pressure (FHVP), the wedged hepatic venous pressure (WHVP) was measured by occluding the hepatic venous branch by inflating the balloon catheter with 1 to 2 ml of air. Occlusion of the hepatic vein was confirmed by gently injecting a small amount (2 to 3 ml) of contrast medium under fluoroscopy after monitoring the pressure (9). The PVP, WHVP and FHVP were always recorded within a period of 2 min using the same transducer and electronic manometer. The catheters were left in the portal vein and hepatic vein at exactly

Received December 1, 1988; accepted March 6, 1989.
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TABLE 1. Baseline characteristics

	Placebo group (n = 9)	IS-5-MN group (n = 10)
Age		
Mean ± S.D.	60 ± 4	63 ± 6
Range	51–66	51–70
Sex	All male	All male
Pugh's class (A/B)	7/2	9/1
HBsAg	All (+)	All (+)
Biochemistry (mean ± S.D.)		
Serum bilirubin (mg/dl)	1.5 ± 0.6	1.9 ± 1.1
Serum albumin (gm/dl)	3.3 ± 0.6	3.3 ± 0.8
Prothrombin time (%)	79 ± 8	82 ± 7
Serum ALT (units/liter)	75 ± 38	58 ± 25

Normal ranges: bilirubin: <1.6; prothrombin time: >80; albumin: 3.7–5.7; ALT: 5–40. No significant difference between the two groups.

the same site throughout the study. Mean pulmonary artery (MPAP), pulmonary capillary wedged (PCWP), right atrial (RAP) and inferior vena caval (IVCP) pressure were recorded. Arterial pressure was measured using an external sphygmomanometer, and the heart rate (HR) was monitored by electrocardiography. Cardiac index (CI) was determined by Fick's principle (10). The zero reference point was set at the midpoint between the anterior sternal surface and the dorsal surface of the patient. Pressure measurements and CI determinations were made in duplicate in each period of the study. Our pressure measurement of PVP, WHVP and FHVP gave within-measurement coefficients of variation of 1.7% (n = 20), 2.8% (n = 20) and 10% (n = 20) at a pressure of 22, 21 and 5 mmHg, respectively.

After obtaining basal measurements of the systemic and hepatic hemodynamics, placebo or 20 mg IS-5-MN was administered orally according to previously assigned random numbers. The initial hemodynamic measurements were obtained at 15, 30, 45 and 60 min after drug administration. In the IS-5-MN group, a second hemodynamic study was performed after 7 days of continuous oral administration of 20 mg IS-5-MN twice daily. Systemic and hepatic hemodynamics were studied 1 hr after the last dose of IS-5-MN.

The portal venous pressure gradient (PVPG) was calculated as PVP − FHVP, and the hepatic venous pressure gradient (HVPG) as WHVP − FHVP. Mean arterial pressure (MAP) was determined as: [(systolic pressure − diastolic pressure)/3] + diastolic pressure. Systemic vascular resistance (SVR) was calculated by the formula: [(MAP − RAP) × 80]/cardiac output. For analysis of the data, the results were expressed as mean ± S.D. Correlations were assessed using Pearson product-moment correlation. Fisher's exact test, Wilcoxon signed-rank test and Wilcoxon rank-sum test were used for statistical analysis ($\alpha = 0.05$).

RESULTS

Nineteen patients underwent a study to evaluate the systemic and hepatic hemodynamic effects after receiving 20 mg of IS-5-MN orally. The study was divided into two phases: the immediate phase and the delayed phase.

Immediate Hemodynamic Study (1 Hr). Fifteen patients received simultaneous measurements of PVP and WHVP. PVP could not be measured in four other patients because of technical failure in two patients and intolerance to the procedure in the other two patients. In only one patient (8%), PVP exceeded WHVP by more than 4 mmHg. A highly significant correlation between PVP and WHVP was found both before and 1 hr after IS-5-MN (Fig. 1). The IS-5-MN and placebo groups recorded similar baseline systemic and hepatic hemodynamic data (Tables 2 and 3). During the immediate-phase study, placebo did not show any significant effects on the systemic or hepatic hemodynamics. In contrast, the IS-5-MN group did show a significant drop in MAP, MPAP and PCWP (Fig. 2, Table 3), but the PVPG and HVPG remained unchanged (Fig. 3, Table 2). The decrease in systolic pressure was more prominent than that of diastolic pressure after IS-5-MN (11 ± 8% vs. 6 ± 8%, $p < 0.05$).

Delayed Hemodynamic Study (7 Days). A total of six patients received a second hemodynamic study. After 7 days of continuous oral administration of 20 mg IS-5-MN twice daily, HVPG remained unaltered when compared to the basal and 1-hr values (Fig. 3, Table 2). MAP, MPAP and PCWP did not significantly decrease in the delayed study and almost returned to the basal value (Fig. 2, Table 3).

There was a slight decrease in SVR in the immediate study, but it did not reach statistical significance. SVR decreased from 1,131 ± 402 to 1,040 ± 263 dyn per sec per cm^{-5} during the immediate-phase study but increased to 1,177 ± 156 dyn per sec per cm^{-5} in the delayed-phase study. Although RAP appeared to decrease 1 hr after IS-5-MN (from 2.1 ± 1.1 to 1.6 ± 0.9 mmHg), it did not reach statistical significance (p = 0.068). The IS-5-MN did not affect CI, HR or IVCP in either immediate or delayed studies (Table 3).

Side Effects. Mild headache or dizziness was noted by three patients (30%) during the immediate-phase study, but their discomforts gradually disappeared on continuous oral administration of IS-5-MN. Systolic hypotension (<80 mmHg) was recorded in two patients (20%) during the acute-phase study. One of them had a delayed study but failed to demonstrate the hypotensive effect of IS-5-MN. None of the 10 patients had other symptoms which could be ascribed to the treatment.

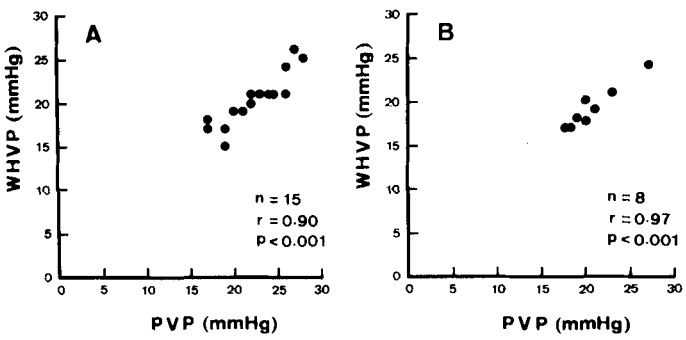

FIG. 1. Relationship between PVP and WHVP (A) before and (B) 1 hr after oral administration of isosorbide-5-mononitrate in patients with HBsAg-positive cirrhosis.

TABLE 2. Hepatic hemodynamic effects (mmHg) of IS-5-MN and placebo groups

	Baseline					1 hr					7 days		
	PVP	WHVP	FHVP	PVPG	HVPG	PVP	WHVP	FHVP	PVPG	HVPG	WHVP	FHVP	HVPG
IS-5-MN group													
1	17	17	3	14	14	20	20	4	16	16			
2	17	18	4	13	14	18	17	3	15	14	14	2	12
3	23	21	3	20	18	21	19	2	19	17	29	7	22
4	19	17	3	16	14	18	17	5	13	12	17	3	14
5	20	19	2	18	17	19	18	2	17	16	14	2	12
6	24	21	4	20	17	23	21	5	18	16	16	2	14
7		28	14		14		25	16		9			
8		33	2		31		31	2		29			
9	28	25	4	24	21	27	24	4	23	20			
10	21	19	1	20	18	20	18	1	19	17	21	4	17
Mean	21.1	21.8	4.0	18.1	17.8	20.8	21.0	4.4	17.5	16.6	18.5	3.3	15.2
± S.D.	3.8	5.3	3.7	3.6	5.2	3.0	4.5	4.3	3.0	5.3	5.8	2.0	3.8
% change[a]						−1	−4	+10	−3	−7	−4	+16	−7
Placebo group													
1	22	21	5	17	16	26	24	6	20	18			
2	19	15	4	15	11	17	14	3	14	11			
3	26	21	7	19	14	22	17	4	18	13			
4	26	24	9	17	15	24	23	8	16	15			
5	27	26	11	16	15	27	24	10	17	14			
6	22	20	8	14	12	24	21	7	17	14			
7	24	21	7	17	14	30	28	11	19	17			
8		18	7		11		16	6		10			
9		20	1		19		19	1		18			
Mean	23.7	20.7	6.6	16.4	14.1	24.3	20.7	6.2	17.3	14.4			
± S.D.	2.9	3.2	4.0	1.6	2.6	4.1	4.5	3.2	2.0	2.9			
% change						+3	0	−6	+5	+2			

[a] Percentage of change in mean compared with baseline data.

TABLE 3. Systemic hemodynamic effects of IS-5-MN and placebo groups

	Placebo		IS-5-MN		
	Baseline	1 hr	Baseline	1 hr	7 days
CI (liters/min·m^2)	4.1 ± 0.7 (9)	3.9 ± 0.5 (9)	4.1 ± 0.7 (9)	3.9 ± 0.9 (9)	3.6 ± 0.4 (5)
MAP (mmHg)	83 ± 9 (9)	83 ± 9 (9)	92 ± 13 (10)[a]	82 ± 14 (10)[a]	91 ± 13 (6)
HR (beats/min)	73 ± 10 (9)	73 ± 9 (9)	71 ± 6 (10)	72 ± 8 (10)	68 ± 10 (6)
MPAP (mmHg)	11.9 ± 3.4 (9)	12.4 ± 3.6 (9)	12.9 ± 4.5 (9)[b]	9.3 ± 2.4 (9)[b]	14.2 ± 4.9 (6)
PCWP (mmHg)	7.2 ± 3.7 (9)	7.3 ± 3.7 (9)	6.9 ± 3.4 (9)[b]	4.3 ± 1.8 (9)[b]	8.2 ± 4.4 (6)
RAP (mmHg)	3.2 ± 2.0 (9)	4.1 ± 2.9 (9)	2.1 ± 1.1 (9)	1.6 ± 0.9 (9)	4.2 ± 2.9 (6)
IVCP (mmHg)	3.0 ± 0.7 (9)	3.0 ± 0.9 (9)	2.6 ± 1.2 (9)	2.8 ± 1.6 (9)	3.7 ± 2.8 (6)
SVR (dyn/sec/cm^{-5})	997 ± 221 (9)	1,012 ± 167 (9)	1,131 ± 402 (9)	1,040 ± 263 (9)	1,177 ± 156 (5)

Numbers in parentheses indicate number of patients.
[a] $p < 0.01$.
[b] $p < 0.05$.

DISCUSSION

A close agreement between PVP and WHVP was shown in this study by simultaneous measurements of PVP and WHVP. These results are different from those of previous studies in nonalcoholic cirrhosis (11, 12). The possibility that measurement of WHVP might underestimate PVP in patients with nonalcoholic cirrhosis has been suggested. The discrepancy is probably due to the differences in the types of patients studied. All of our patients had HBsAg-positive cirrhosis, whereas in the previous series, most patients had nonalcoholic, non-HBsAg-positive cirrhosis. Recently, Valla et al. (13) reported that the measurement of WHVP may not provide a reliable estimation of the magnitude of the changes in PVP during acute administration of a drug acting on the splanchnic circulation, but this was not true with IS-5-MN in our study. The difference may be explained by the use of balloon catheter in our study, which gave more reproducible results than the wedged catheter used by Valla et al. (14).

The present study has failed to document any beneficial effect from IS-5-MN. This was not due to a low dose or a poor absorption of IS-5-MN, as determined by its observed systemic effects including significant falls in MAP, MPAP and PCWP. Similar negative results of nitrates in patients with portal hypertension have been observed by other authors (15–17; Ohnishi K, et al.,

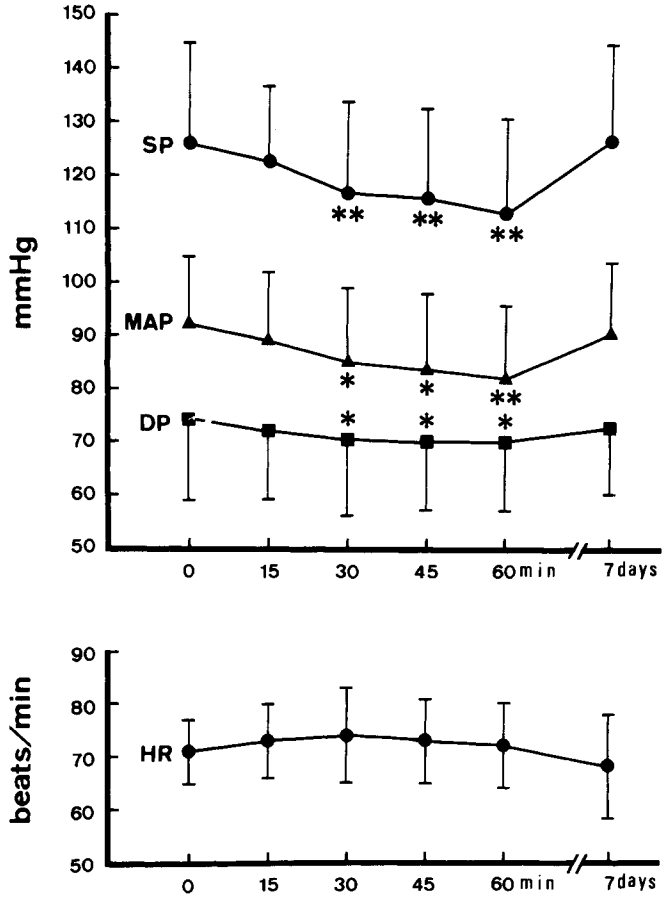

FIG. 2. Changes in systolic pressure (SP), mean arterial pressure (MAP), diastolic pressure (DP) and heart rate (HR) after oral administration of isosorbide-5-mononitrate in patients with HBsAg-positive cirrhosis. Values are mean ± S.D. (*bars*). * = $p < 0.05$; ** = $p < 0.01$.

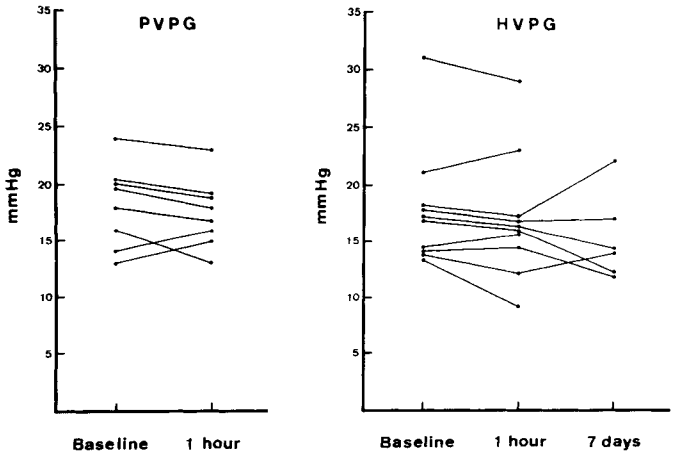

FIG. 3. Individual changes in PVPG and HVPG after oral administration of isosorbide-5-mononitrate in patients with HBsAg-positive cirrhosis.

unpublished observation). In a previous study (18), IS-5-MN significantly reduced HVPG from 23.9 ± 3.4 mmHg to 21.8 ± 3.4 mmHg (a decrease of 9%). These patients, however, did not show a change in arterial pressure, which seems to be important in determining the effect of nitrates on portal hypertension (1, 2, 19). Besides, a reduction of HVPG to ≤12 mmHg should be the aim of pharmacological therapy (20). The clinical significance of a 9% reduction in HVPG, although it was statistically significant, remains to be elucidated. The reason for the discrepancies between our results and previous studies (1–4, 18) is not clear. It could be explained by different etiology of cirrhosis, racial differences and/or the concept of "low dose" and "high dose" (21). At low doses, baroreceptor stimulation due to nitrate-induced arterial hypotension is probably responsible for reflex-mediated splanchnic arterial vasoconstriction and a subsequent reduction in portal venous inflow. At high doses, the reflex sympathetic discharge seen with a low-dose nitrate is presumably overwhelmed, resulting in splanchnic arterial vasodilatation and reduced portal collateral resistance. Besides, factors such as the presence of reflex sympathetic nervous activity (22) and left ventricular function in cirrhotic patients, the induction of nitrate tolerance (23, 24) and the role of hormonal regulation (bile acid, serotonin, glucagon, catecholamine, etc.) (25, 26) that influence hemodynamic response to nitrates should be considered.

It is possible that higher doses of IS-5-MN may be more effective in reducing portal hypertension, by a greater effect on reducing portal vascular resistance and intrahepatic vascular resistance (27). However, the absence of any effect at a dosage of 20 mg makes this unlikely. Besides, a study with higher doses may expose patients to unpredictable hemodynamic change including severe hypotension, as occurred in two of our patients, and increased azygos blood flow (4, 28). Furthermore, vasodilatation accounts for the decrease in MAP, MPAP and PCWP seen in the immediate study, but these effects were absent in the delayed hemodynamic study. Also, in considering the disappearance of headache in all three patients several days after continuous administration of IS-5-MN, the development of tolerance must be considered.

In our study, MAP significantly decreased, but CI and SVR did not change. It could be explained by different reflex sympathetic nervous activity and left ventricular function in individual cirrhotic patients and the administered dose of IS-5-MN. With very low doses, the venous or capacitance system is maximally dilated; arterial dilation and increased arterial conductance occur at relatively low doses of nitrates; and the arterioles or resistance vessels dilate and systemic vascular resistance decreases only with relatively large doses of administered nitrate (29). Therefore, the dose of IS-5-MN used in our study was adequate to dilate the venous system and arteries but not the arterioles. We also found that the decrease in systolic pressure was more prominent than that of diastolic pressure 1 hr after IS-5-MN. This might be explained by the study of Simon et al. (30). In their study, nitroglycerin was found to have a direct effect on peripheral large arteries, causing an increase in arterial diameter and compliance, thus leading to a predominant decrease in systolic pressure. The lack of a reflex tachycardia to the decrease in arterial pressure (Fig. 2) in our study could be attributed to the altered baroreceptor responsiveness in cirrhotic patients (31).

In conclusion, this study shows that IS-5-MN appears to have no effect in reducing portal venous pressure in patients with HBsAg-positive cirrhosis, although it has an effect on the systemic circulation. Sample size calculations based on the direct measurement of portal venous pressure indicated that we would have needed 26 additional patients to demonstrate a statistically significant ($p < 0.05$) reduction of portal venous pressure, and consequently we terminated the study.

Acknowledgments: The authors thank K. Y. Suen for case collection and data arrangement, and S. H. Wu for secretarial assistance.

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