Enhancement of Portal Pressure Reduction by the Association of Isosorbide-5-Mononitrate to Propranolol Administration in Patients with Cirrhosis

JOAN CARLES GARCIA-PAGÁN, MIQUEL NAVASA, JAIME BOSCH, CONXITA BRU, PILAR PIZCUETA AND JOAN RODÉS

Hepatic Hemodynamics Laboratory, Liver Unit, Hospital Clinic i Provincial, University of Barcelona, Barcelona, Spain

This study investigated whether oral doses of isosorbide-5-mononitrate, a preferential venous dilator that decreases portal pressure, could enhance the effects of propranolol on portal hypertension. Taking part in the study were 28 patients with cirrhosis and portal hypertension. Twenty patients (group 1) had hemodynamic measurements in baseline conditions after beta-blockade by intravenous administration of propranolol and after receiving oral doses of isosorbide-5-mononitrate. The remaining eight patients (group 2) were given oral isosorbide-5-mononitrate while receiving chronic propranolol therapy. In group 1, propranolol significantly reduced portal pressure (estimated as the gradient between wedged and free hepatic venous pressures) from 21.5 ± 3.9 to 18.6 ± 4.2 mm Hg (−13.7%, $p < 0.001$), azygos blood flow (−38%, $p < 0.001$), hepatic blood flow (−12.8%, $p < 0.05$), cardiac output (−24.5%, $p < 0.001$) and heart rate (−18.4%, $p < 0.001$) without significant changes in mean arterial pressure. Addition of oral isosorbide-5-mononitrate caused a further and marked fall in portal pressure (to 15.7 ± 3.1 mm Hg, $p < 0.001$), without additional changes in azygos blood flow but with significant additional reductions in hepatic blood flow (−15.5%, $p < 0.05$), cardiac output (−11.5%, $p < 0.001$) and mean arterial pressure (−22%, $p < 0.001$). The additional effect of isosorbide-5-mononitrate on portal pressure was especially evident in patients who did not respond to propranolol (decrease in portal pressure less than 10%, n = 9), the final reduction in portal pressure after combined therapy being similar in propranolol responders (−26%) and nonresponders (−27%). In group 2, the association of isosorbide-5-mononitrate to chronic propranolol therapy also caused a further significant reduction in portal pressure, from 17.1 ± 3.1 to 15.4 ± 2.1 mm Hg ($p < 0.05$).

Study results indicate that isosorbide-5-mononitrate enhances the beneficial effects of propranolol on portal hypertension in patients with cirrhosis. (HEPATOLOGY 1990;11:230-238.)

Recently several studies have shown that propranolol may significantly reduce the risk of variceal bleeding in patients with cirrhosis and portal hypertension, both in preventing the first hemorrhage (1-5) and also in the prophylaxis of further bleeding episodes in patients who have already bled from their varices (6-8), a beneficial effect thought to be caused by the ability of propranolol to reduce portal pressure and portal-collateral blood flow (9).

In recent years, however, it has become evident that the reduction of portal pressure by propranolol is moderate, averaging 15% (9), and more than 30% of the patients exhibit no decrease in portal pressure despite adequate beta-blockade (9-10). The contradictory findings of some studies on the effectiveness of propranolol in the prevention of variceal bleeding (11-13) may be, at least in part, related to the absence or insufficiency of the fall in portal pressure achieved during therapy. Although the reason for the heterogeneous effect of propranolol on portal pressure is not clear, experimental studies suggest it may be related to an increase in vascular resistance to portal blood flow (PBF) after propranolol is administered (14).

A recent study at our laboratory (15) has shown that the oral administration of isosorbide-5-mononitrate (Is-5-Mn), a preferential venous dilator with prolonged biological activity and no hepatic metabolism (16), caused a significant reduction in portal pressure in patients with cirrhosis. This was due in part to a decrease in hepatic vascular resistance. We proposed, therefore, that in analogy with previous findings on combined nitroglycerin-vasopressin or ketanserin-propranolol administration (17, 18), combining Is-5-Mn with propranolol administration may have a synergis-

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Address reprint requests to: Dr. Jaime Bosch, Hepatic Hemodynamics Laboratory, Liver Unit, Hospital Clinic i Provincial, University of Barcelona, Villaroel 170, 08036 Barcelona, Spain.

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TABLE 1. Clinical data of the 20 patients included in protocol A

Patient No.	Age (yr)	Sex	Etiology	Ascites	Variceal bleeding	Bilirubin (mg/dl)	Albumin (gm/L)	Prothrombin ratio (%)	Child-Pugh class (score)	HVPG[a] (mm Hg)
1	55	F	Cr[b]	No	Yes	2.1	34.9	60	B (7)	24
2	60	M	Etoh[c]	Yes	No	1.5	32	65	B (7)	13
3	62	M	Etoh	No	Yes	2.6	34.9	69	B (7)	20.5
4	72	F	Cr	No	Yes	4.5	28.6	80	B (8)	24
5	45	M	Etoh	Yes	Yes	2.3	36.7	45	B (8)	15
6	57	M	Etoh	No	Yes	1.4	29.6	64	A (6)	22.5
7	51	M	Etoh	Yes	Yes	2.8	36.4	76	B (7)	22
8	58	F	PBC[d]	No	Yes	1.8	31.2	70	A (6)	17
9	57	M	Etoh	Yes	No	2.4	25.2	58	C (11)	24
10	53	M	HBsAg	No	No	2.5	38	70	A (6)	24.5
11	71	M	Etoh	Yes	No	1.4	33.3	65	B (7)	32
12	61	M	Etoh	No	No	2	34.8	55	A (6)	22.5
13	49	F	Cr	No	No	1.1	35.5	75	A (5)	20
14	55	M	Etoh	No	No	2	33	80	A (6)	21.5
15	59	F	Etoh	Yes	Yes	2.3	38.7	69	B (7)	23
16	65	F	Cr	No	No	1.9	33.7	65	A (6)	22
17	63	F	Etoh	No	Yes	1	26.6	100	B (8)	18
18	50	F	Cr	No	No	1.5	37.5	42	A (6)	21
19	63	F	Etoh	Yes	Yes	2.6	34.4	54	B (8)	21
20	65	F	Cr	No	No	1.7	35.2	65	A (5)	23

[a]HVPG = hepatic venous pressure gradient.
[b]Cr = cryptogenetic cirrhosis.
[c]Etoh = alcoholic cirrhosis.
[d]PBC = primary biliary cirrhosis.

tic effect and enhance the reduction in portal pressure. Such an additive effect was first suggested by Kroeger and Groszmann (19) in experiments with rats with portal hypertension caused by partial vein ligation. Studies were made after the administration of propranolol alone and propranolol in combination with nitroglycerin. This study was aimed at verifying this hypothesis using an acute hemodynamic study in a series of patients with cirrhosis and portal hypertension.

PATIENTS AND METHODS

The study involved 28 cirrhotic patients referred for hemodynamic evaluation of portal hypertension. Cirrhosis was alcoholic in 16 patients and nonalcoholic in 12: two posthepatitic, nine cryptogenic, and one primary biliary cirrhosis. All patients had esophageal varices and 17 had experienced variceal bleeding. All patients gave written consent to participate in the study, which was approved by the Clinical Research Committee of the Hospital Clinic i Provincial, University of Barcelona, in September 1987.

Twenty patients (Table 1) were included in protocol A, which investigated the acute effects of propranolol and the effects of the combination of propranolol and Is-5-Mn on systemic and splanchnic hemodynamics. These patients had received no vasoactive drugs for at least 48 hr before the study. After an overnight fast, the patients were transferred to the Hepatic Hemodynamics Laboratory, where two venous catheter introducers (USCI, Billerica, MA) were placed by the Seldinger technique in the right femoral veins of the patients who were under local anesthesia. One was used to advance a 7F balloon-tipped catheter (Medi-Tech, Inc., Watertown, MA), under fluoroscopy, into the main right hepatic vein where it remained for the entire study; the other was used either to advance a Swan-Ganz catheter (American-Edwards Laboratories, Santa Ana, CA) into the pulmonary artery or a continuous thermal dilution catheter (Webster Labs, Inc. Altadena, CA) into the azygos vein. These catheters allowed serial measurements of wedged and free hepatic venous pressures (WHVP and FHVP), cardiopulmonary pressures and cardiac output (CO, thermodilution) and azygos blood flow (AzBF, continuous thermodilution) respectively, according to previously described methods (20-22). A solution of indocyanine green (ICG, Serb, Paris, France), containing 2% human serum albumin, was infused intravenously at a constant rate of 0.2 mg/min. After an equilibration period of 40 min, four samples of peripheral and hepatic venous blood were obtained simultaneously at 2-min intervals for the measurement of hepatic blood flow (HBF) following previously reported methods (15, 23). Steady ICG levels and hepatic extraction above 0.1 were required for the calculation of HBF. PBF velocity was estimated noninvasively by pulsed Doppler flowmetry combined with real-time ultrasonography (Toshiba Medical Systems, Tustin, CA). Details on the use of this method for the measurement of PBF in man have previously been reported (24-26).

All measurements were performed in triplicate in each period of the study, and permanent tracings were obtained on a Hewlett-Packard 7754B multichannel recorder (Hewlett-Packard Co., Waltham, MA). Portal pressure was estimated from the hepatic venous pressure gradient (HVPG), the difference between WHVP and FHVP. Measurements of AzBF by continuous thermodilution were used as an index of blood flow through gastroesophageal collaterals draining into the azygos vein. Mean arterial pressure (MAP) was measured with an automatic sphygmomanometer (Critikon Inc., Tampa, FL) and heart rate (HR) was derived by

TABLE 2. Clinical data of the eight patients included in protocol B

Patient No.	Age (yr)	Sex	Etiology	Ascites	Variceal bleeding	Bilirubin (mg/dl)	Albumin (gm/L)	Prothrombin ratio (%)	Child-Pugh class (score)	HVPGx[a] (mm Hg)	Dose of propranolol (mg/day)
1	47	M	Etoh[b]	No	Yes	1.8	34.4	65	A (6)	20.5	40
2	61	F	Cr[c]	No	No	1.9	35.4	62	A (6)	19	80
3	58	M	Etoh	No	Yes	1.1	32.4	60	A (6)	16	120
4	54	M	Cr	No	Yes	2.4	39.5	100	A (6)	15	80
5	59	M	Cr	No	Yes	1.9	39.2	80	A (5)	17.5	120
6	52	M	Etoh	Yes	Yes	3.4	27.0	40	C (11)	20	40
7	62	M	Cr	No	Yes	2.2	35.2	69	A (6)	17.5	120
8	48	M	HBsAg	Yes	Yes	0.7	36.0	90	A (6)	11	80

[a]HVPGx = hepatic venous pressure while being administered chronic propranolol therapy.
[b]Etoh = alcoholic cirrhosis.
[c]Cr = cryptogenetic cirrhosis.

continuous ECG monitoring. Systemic vascular resistance (SVR) in units of dyn · sec · cm^{-5} was calculated as

$$\frac{80(MAP-RAP)}{CO}$$

where MAP (mm Hg) is the mean arterial pressure, RAP (mm Hg) is the right atrial pressure and CO (L/min) is the cardiac output. The hepatic vascular resistance (HVR) was estimated as

$$\frac{80(WHVP-FHVP)}{HBF}$$

Because HBF represents the sum of hepatic artery and portal vein blood flows, this calculation will underestimate the hepatic resistance to PBF. HBF was calculated as

$$\frac{R_{ICG}}{(A-V)\,1-H_t}$$

where R_{ICG} is the rate of ICG infusion (mg/min), A and V are the plasma ICG concentrations at steady state in arterial and hepatic venous blood respectively, and Ht is the hematocrit.

After obtaining baseline measurements, propranolol was given intravenously (0.1 mg/kg followed by a constant infusion of 2 mg/hr), and the above-mentioned parameters were measured again, beginning 30 min after the propranolol infusion. Patients exhibiting a decrease in HVPG greater than 10% were considered "responders," whereas those failing to achieve such a reduction in HVPG were considered "nonresponders" (9, 10). Once these measurements were completed, while maintaining the continuous propranolol infusion, Is-5-Mn was given orally at a dose of 20 mg (n = 11) or 40 mg (n = 9). Hemodynamic measurements were taken again 30, 60 and 90 min after the administration of Is-5-Mn.

Protocol B included eight cirrhotic patients receiving chronic propranolol therapy: seven to prevent bleeding and one for primary prophylaxis. The study was performed in the course of a hemodynamic investigation after patients were stabilized on propranolol therapy for 3 to 12 mo. Further details on these patients, including the maintenance dose of propranolol, are given in Table 2. On the day of the study, the patients received their usual morning doses of propranolol at 8 AM, and hemodynamic measurements were performed 2 hr later, including WHVP, FHVP, HVPG, MAP, and HR. In addition, measurements of the AzBF, HBF, CO and cardiopulmonary pressures of four patients were taken using the procedures described above. After obtaining these measurements, a 20-mg tablet of Is-5-Mn was given orally, and all hemodynamic parameters were measured again after 60 min.

The results are reported as mean ± S.D. Student's *t* test, analysis of variance, and coefficient of correlation were used in the statistical analysis of the results (27). Statistical significance was established at $p < 0.05$, and the Bonferroni method was used to correct for multiple comparisons (28).

RESULTS

Protocol A

Baseline Values. All patients had severe portal hypertension, manifested by esophageal varices and a marked increase in HVPG, which averaged 21.5 ± 3.9 mm Hg (range = 13 to 32 mm Hg). Individual values are shown in Table 1. There were no differences in the hepatic venous pressures between patients with alcoholic and nonalcoholic cirrhosis, but alcoholic patients had a significantly lower CO than nonalcoholic patients (6.9 ± 1.0 vs. 8.7 ± 1.4 L/min, $p < 0.01$). There were no other significant differences according to the cause of portal hypertension.

In the overall series, portal hypertension was accompanied by marked increases in AzBF (0.58 ± 0.26 L/min) and CO (7.6 ± 1.4 L/min) and by a decreased MAP (85.5 ± 8.6 mm Hg) and SVR (880 ± 183 dyne · sec · cm^{-5}). These baseline findings are similar to those observed in previous studies from our laboratory. There were no significant differences in clinical or hemodynamic baseline values between patients receiving 20 or 40 mg of Is-5-Mn except in MAP, which was significantly lower in patients who were later given 20 mg of Is-5-Mn than in those who were given 40 mg.

Effects of Propranolol and of the Association of Propranolol Plus Is-5-Mn on Portal Pressure and Splanchnic Hemodynamics. Propranolol administration caused a significant reduction in portal pressure, evidenced by a significant decline in HVPG (from 21.5 ± 4 mm Hg to 18.6 ± 4 mm Hg, −13.7% ± 8.0%; $p < 0.001$). This

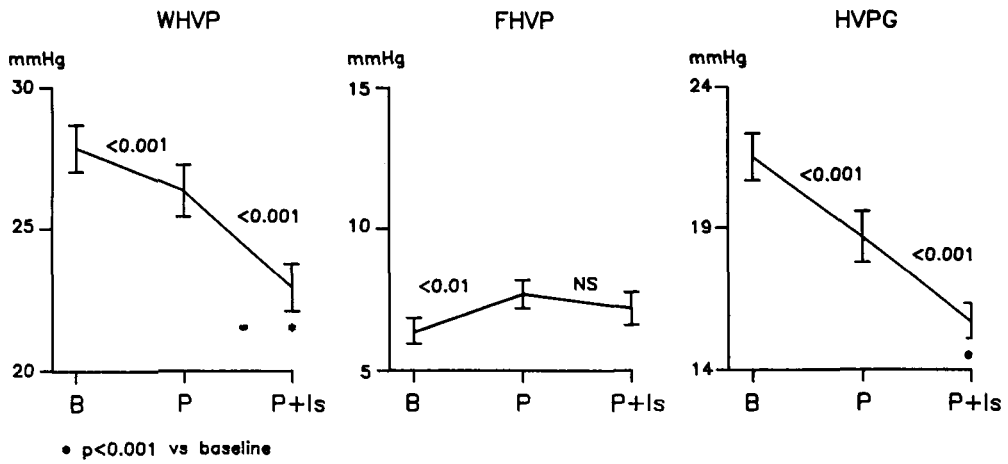

FIG. 1. Effects of propranolol administration *(P)* and administration of propranolol plus Is-5-Mn *(P + Is)* on wedged hepatic venous pressure *(WHVP)*, free hepatic venous pressure *(FHVP)* and hepatic venous pressure gradient *(HVPG)*. (B = baseline values.) (Mean ± S.E.)

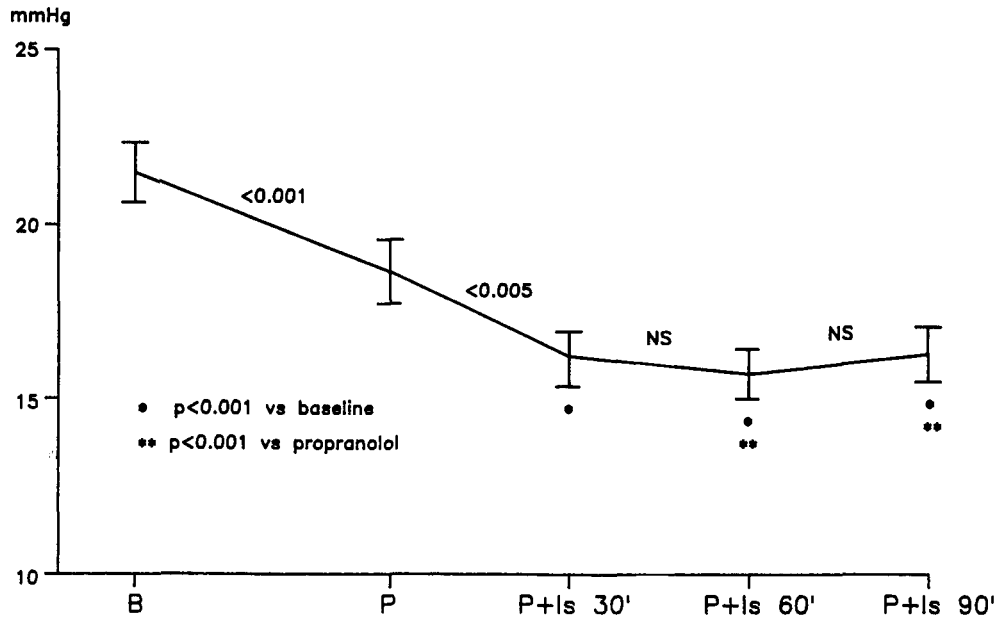

FIG. 2. Time course of effects of propranolol *(P)* and of propranolol plus Is-5-Mn *(P + Is)* on hepatic venous pressure gradient (HVPG). (B = baseline values). HVPG was significantly decreased by propranolol and experienced a further significant reduction during 90 min of observation after administration of Is-5-Mn. (Mean ± S.E.) NS = not significant.

was the result of both a significant reduction in WHVP (mean change −5.5%) and a significant increase in FHVP (Fig. 1).

The administration of oral Is-5-Mn caused a further, significant and sustained reduction in portal pressure. As shown in Figure 2, the additional decrease in HVPG was maintained for the 90 min of observation and was maximal 60 min after the administration of Is-5-Mn. This time point was thereafter chosen to express changes in all hemodynamic parameters. After the combined drug administration, HVPG fell by 26.5% ± 8% below baseline (to 15.7 ± 3 mm Hg, $p < 0.001$), an additional 13.9% reduction in HVPG after the addition of oral Is-5-Mn to propranolol. This additional effect in HVPG was entirely due to a marked fall in WHVP (mean change: −12.5%), without changes in FHVP (Fig. 1).

The effect of propranolol on HVPG varied markedly from patient to patient. HVPG decreased by more than 10% of baseline in 11 patients who were therefore considered "responders" to propranolol. Their mean decrease in HVPG was −19.8% ± 5.2%. But HVPG in

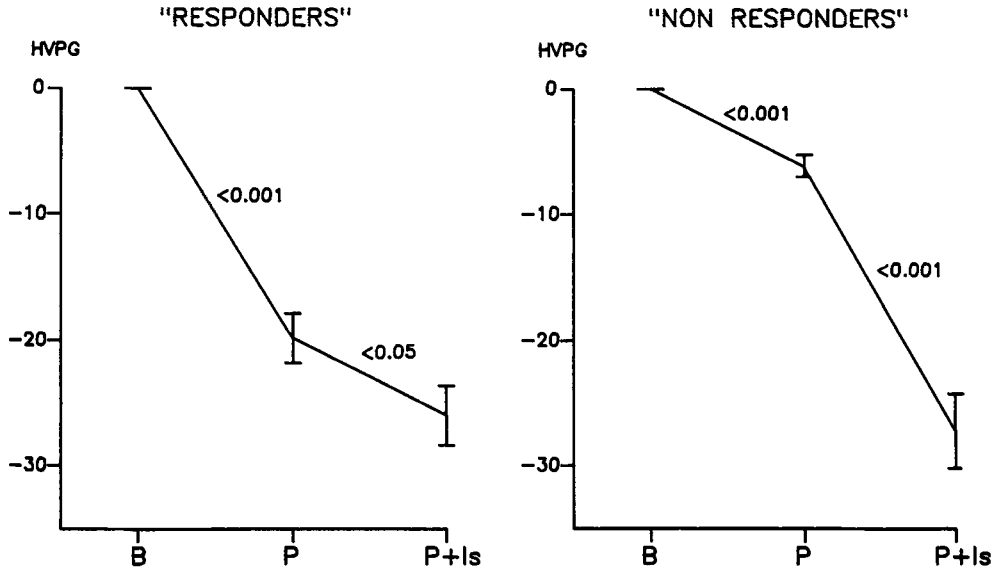

FIG. 3. Effects of propranolol *(P)* and of propranolol plus Is-5-Mn *(P + Is)* on hepatic venous pressure gradient *(HVPG)* in patients responding and nonresponding to propranolol. Data are presented as percent change from baseline *(B)*. (Mean ± S.E.)

TABLE 3. Comparison of changes in hepatic venous pressures in patients responding and nonresponding to propranolol administration

	Responders			Nonresponders		
	Baseline	**Propranolol**	**Prop + Is-5-Mn**	**Baseline**	**Propranolol**	**Prop + Is-5-Mn**
WHVP (mm Hg)	26.7 ± 3.8	24.5 ± 3.3[a]	21.9 ± 2.9[b]	29.3 ± 4.0	28.6 ± 4.4	24.2 ± 5.1[c]
FHVP (mm Hg)	6.3 ± 2.5	8.1 ± 2.7[d]	7.1 ± 2.8	6.3 ± 2.2	7.1 ± 2.1	7.4 ± 2.9
HVPG (mm Hg)	20.4 ± 3.8	16.3 ± 3.2[a]	14.9 ± 2.2[e]	22.9 ± 3.9	21.5 ± 3.6[a]	16.8 ± 3.9[c]

[a]p 0.001 vs. baseline.
[b]p 0.01 vs. propranolol.
[c]p 0.001 vs. propranolol.
[d]p 0.01 vs. baseline.
[e]p 0.05 vs. propranolol.

the remaining nine patients decreased by less than 10% (mean change: −6.3% ± 1.8%), and they were considered "nonresponders." There were no differences in baseline clinical or hemodynamic data between "responders" and "nonresponders."

The enhancing effect of Is-5-Mn on the reduction of HVPG achieved with propranolol was evident in both groups, but especially in nonresponders (Fig. 3). Table 3 shows the changes in WHVP, FHVP and HVPG in propranolol responders and nonresponders. Although an additional 7% fall in HVPG ($p < 0.05$) was seen in the group of responders, this effect was more accentuated in the group of nonresponders; the further reduction in HVPG averaged 22% (from 21.5 ± 3.6 to 16.7 ± 4 mm Hg, $p < 0.001$) (Table 3) (Fig. 3). The final effect of the combination of propranolol and Is-5-Mn on HVPG was similar in both groups (mean reductions: 27% and 26% respectively).

As shown in Figure 4, propranolol decreased HBF and PBF velocity significantly (mean changes: −12.8% ± 19% and −16.4% ± 19.1% respectively), and a further significant reduction was caused by the addition of Is-5-Mn. AzBF decreased markedly after propranolol administration (average decrease: −38% ± 16%, $p < 0.001$), reflecting a decrease in portal-collateral blood flow. This effect was maintained on the subsequent administration of Is-5-Mn (Fig. 4). The calculated HVR was not significantly modified after propranolol was administered (1,788 ± 941 vs. 1,803 ± 951 dyne · sec · cm^{-5}) nor was it affected by the subsequent addition of Is-5-Mn (1,783 ± 684 dyne · sec · cm^{-5}) (NS). There were no differences in the splanchnic hemodynamic effects between patients receiving 20 or 40 mg of Is-5-Mn. Similarly, there were no significant differences in the effects observed in alcoholic patients and nonalcoholic patients. Finally, there were no differences on the effects of propranolol and of the combination of propranolol and Is-5-Mn on

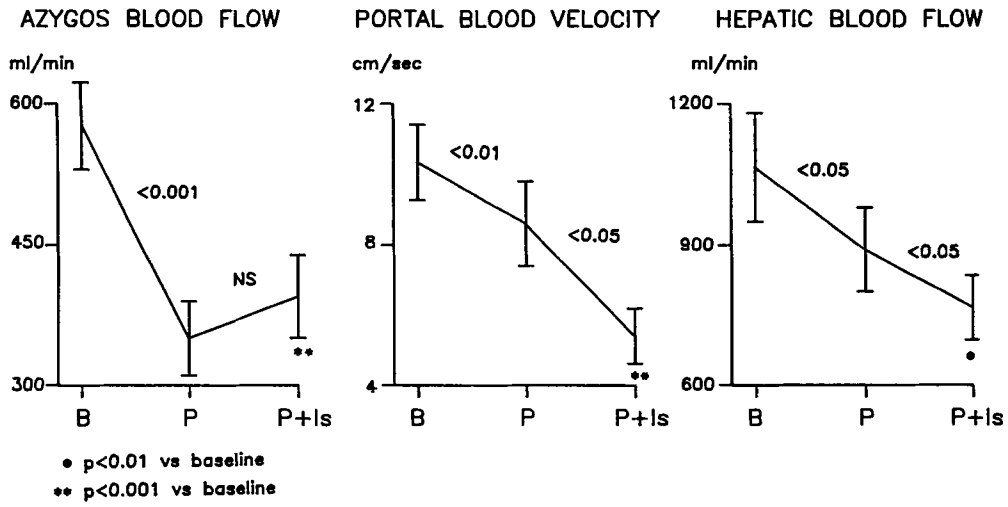

FIG. 4. Effects of propranolol *(P)* and of propranolol plus Is-5-Mn *(P + Is)* on azygos blood flow, portal blood velocity and hepatic blood flow. (Mean ± S.E.) (B = baseline values.)

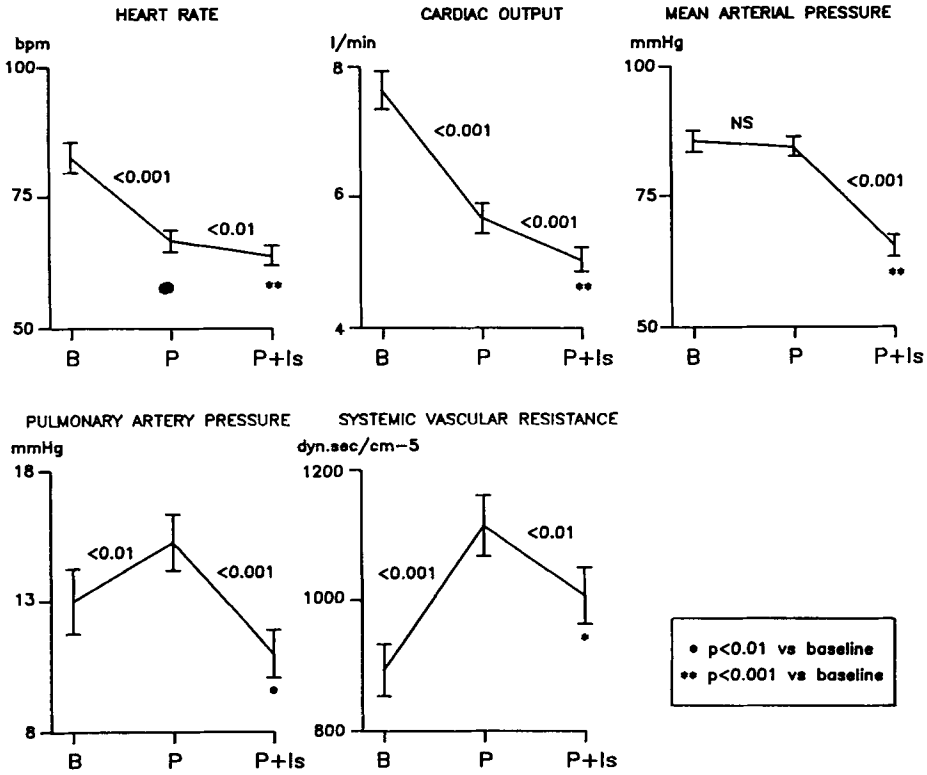

FIG. 5. Effects of propranolol *(P)* and of propranolol plus Is-5-Mn *(P + Is)* on systemic hemodynamics. (Mean ± S.E.) (B = baseline values.)

AzBF, HBF and PBF in propranolol responders and nonresponders.

Effects of Propranolol and of the Combination of Propranolol Plus Is-5-Mn on Systemic Hemodynamics. Beta-adrenergic blockade by propranolol was manifested by significant decreases in HR (−18% ± 6%, $p < 0.001$) and CO (−24.5% ± 11%, $p < 0.001$) (Fig. 5). These changes were associated with an increase in pulmonary artery pressure (PAP) and SVR (Fig. 5). Right atrial pressure (RAP) and pulmonary capillary pressure (PCP) were also increased (3.1 ± 2.6 vs. 6.0 ± 3.0 and 7.1 ± 4.4 vs. 10.2 ± 3.8 mm Hg respectively, $p < 0.01$).

The addition of Is-5-Mn caused marked venous dilatation, evidenced by a significant fall in PAP (Fig. 5), RAP (from 6.0 ± 3.0 to 3.7 ± 2.3 mm Hg, $p < 0.001$)

TABLE 4. Splanchnic and systemic hemodynamics before and after administration of Is-5-Mn in patients receiving chronic propranolol therapy

	Before Is-5-Mn	After Is-5-Mn	p Value
WHVP (mm Hg)	24.3 ± 2.5	21.5 ± 1.6	0.001
FHVP (mm Hg)	7.2 ± 2.0	6.1 ± 1.9	0.01
HVPG (mm Hg)	17.1 ± 3.1	15.4 ± 2.1	0.05
AZBF (L/min)	0.31 ± 0.15	0.28 ± 0.19	NS
HBF (L/min)	1.12 ± 0.33	0.82 ± 0.20	NS
HR (bpm)	57.9 ± 4.2	58.9 ± 6.3	NS
MAP (mm Hg)	84.7 ± 12.0	74.1 ± 11.0	0.01
CO (L/min)	5.9 ± 1.2	4.6 ± 1.4	0.01
PAP (mm Hg)	14.6 ± 5.0	9.6 ± 2.8	0.05

WHVP and FHVP = wedged and free hepatic venous pressure respectively; HVPG = hepatic venous pressure gradient; AzBF = azygos blood flow; HBF = hepatic blood flow; HR = heart rate; MAP = mean arterial pressure; CO = cardiac output; PAP = pulmonary artery pressure.

and PCP (from 10.2 ± 3.8 to 6.8 ± 3.4 mm Hg, $p < 0.001$), which were associated with a further fall in CO (Fig. 5). MAP also decreased significantly (mean change: −22% ± 9.5%, $p < 0.001$).

Changes in hepatic hemodynamics showed no relationship to changes in systemic hemodynamics.

Protocol B

In patients chronically treated with propranolol, the addition of Is-5-Mn also caused a significant further decrease in HVPG (from 17.1 ± 3.1 to 15.4 ± 2.1 mm Hg; $p < 0.05$), the result of a marked decline in WHVP and of a mild reduction in FHVP (Table 4). These changes were accompanied by a slight but significant reduction in MAP (−12.3% ± 8%) without changes in HR (Table 4). AzBF and HBF, measured in four patients, decreased on average by 10.8% and 23% respectively. Cardiopulmonary pressures and CO also decreased after Is-5-Mn was administered (Table 4).

DISCUSSION

Recently, several studies have focused on the possible use of long-acting vasodilators in the treatment of portal hypertension (29-30), a suggestion based on the observation that agents such as saralasin (31), prazosin (32), clonidine (33-34), ketanserin (35-36), isosorbide dinitrate (37-38) and its active metabolite Is-5-Mn (15, 39) may cause prolonged, significant reductions in portal pressure.

These effects have been particularly well characterized in relation to Is-5-Mn. We have previously shown that this drug causes dose-related decreases in portal pressure while maintaining, and even enhancing, the hepatic perfusion, reflecting a reduction in the hepatic resistance (15). It is conceivable therefore, that the combination of Is-5-Mn and propranolol, an agent that decreases portal pressure by reducing the portal-collateral blood flow, may have a synergistic effect enhancing the reduction in portal pressure. The recent demonstration that an increased resistance to PBF hinders the decrease in portal pressure after propranolol administration (14) and that the addition of nitroglycerin enhances the fall in portal pressure caused by propranolol in portal hypertensive rats (19) are additional reasons suggesting that combined propranolol and Is-5-Mn administration might have an additive effect and lower portal pressure in patients with cirrhosis. We also hypothesized that such a drug combination may decrease the incidence of patients "nonresponding" to propranolol, which ranges between 30% and 50%. This would be important because the beneficial effects of propranolol in preventing variceal hemorrhage depend on the reduction of portal pressure (40). This study was designed to answer these questions.

Results of this study clearly demonstrate that Is-5-Mn augments the reduction in HVPG achieved by propranolol. In the overall group of patients, the decrease in HVPG achieved by the combined administration of propranolol and Is-5-Mn was double that achieved by propranolol (26.6% vs. 13.7%). It is also important to remark that although the reduction in HVPG caused by propranolol was due both to a significant decrease in WHVP and to an increase in FHVP, the additional fall in portal pressure achieved after the addition of oral Is-5-Mn to propranolol administration was entirely due to a marked fall in WHVP. As a result, the decrease in WHVP after the combined drug administration was three times greater than that caused by propranolol (17.5% vs. 5.5%). This may be clinically relevant because we have previously shown that changes in the absolute intravariceal pressure are better reflected by changes in WHVP than in changes of HVPG after vasopressin administration (41). It is likely, therefore, that the further and marked reduction in WHVP after the association of Is-5-Mn parallels a marked fall in the pressure of the esophageal varices. Our results suggest, therefore, that the net effect of this drug combination on variceal pressure may be three times greater than that achieved with propranolol alone. Such a reduction in variceal pressure will result in a pronounced decrease of variceal wall tension, which is thought to represent an important determinant of variceal rupture (42-44).

The study also shows that unlike the response to propranolol alone, this drug combination reduces portal pressure in every patient, including those who were "nonresponders" to propranolol, so that the addition of Is-5-Mn totally eliminated "nonresponse" in patients. Actually, the beneficial effect of Is-5-Mn in enhancing the decrease in portal pressure was particularly evident in patients who did not respond to propranolol, to the point that the final decrease in HVPG was identical to that observed in patients initially responding to propranolol (mean decrease in HVPG: −27% and −26%, respectively).

The combined administration of propranolol and Is-5-Mn can produce an additional decrease in HVPG in

two ways. First, the association of Is-5-Mn, a powerful venous dilator, can reduce the portocollateral resistance, an effect previously documented in patients receiving Is-5-Mn (15). Second, Is-5-Mn may contribute to reduce portal pressure by decreasing portal venous inflow, a mechanism in keeping with the observed reduction in PBF velocity and in HBF. As with other nitrates, it is likely that the reduction in portal venous inflow is caused by a reflex splanchnic vasoconstriction produced by a fall in MAP (45-46). This latter effect, the consequence of systemic vasodilatation and reduced cardiac preload and CO, constitutes a worrisome side effect of the combined administration of propranolol and Is-5-Mn. It is, however, possible that the decrease in arterial pressure could be less pronounced in cases of chronic drug administration. This is suggested by our observation that, in patients receiving chronic propranolol therapy, Is-5-Mn caused an additional decrease in portal pressure with a much lower effect on arterial pressure than in the acute study (mean decrease in arterial pressure: −12% and −22% respectively). Another undesirable side effect of the addition of Is-5-Mn to propranolol may be the further reduction in HBF. Although there is no evidence indicating that reduced liver blood flow during propranolol therapy aggravates liver failure in patients with cirrhosis, it is possible that this may be a limitation of combined pharmacological treatment. Clearly, this point should be clarified by long-term studies.

The fact that patients who do not respond to propranolol experienced an exaggerated response to the addition of Is-5-Mn is in accordance with the suggestion from studies in partial portal vein–ligated rats, which indicate that portocollateral resistance is increased by propranolol (14). These studies showed that such an increase in portocollateral resistance hinders the decrease in portal pressure caused by beta-blockade. In that regard the present study confirms that the effects of propranolol on portal pressure and total HBF are less pronounced than the effects on azygos blood flow, an index of blood flow through portocollateral vessels draining into the azygos vein. It is likely that the increased resistance of PBF after propranolol is administered occurs predominantly at the portal vein and in collateral circulation, but to a lesser extent in the intrahepatic circulation. This is suggested by the fact that propranolol does not increase the intrahepatic resistance to PBF in cirrhotic rats (47). On the other hand, the current observation that, in patients who do not respond to propranolol, the addition of Is-5-Mn caused a marked decrease in portal pressure without a further reduction in AzBF, suggests that Is-5-Mn decreases the resistance in the portocollateral vessels. It is likely, therefore, that the extent of portosystemic collaterals may be one of the determinants of the magnitude of the response of portal pressure to propranolol administration.

In summary, this study shows that the addition of Is-5-Mn, the active metabolite of isosorbide dinitrate, to propranolol markedly enhances the reduction of portal pressure achieved by beta-adrenoceptor blockade and decreases the incidence of propranolol "nonresponders." Our data suggest that this drug combination may be of greater therapeutic potential than currently used drugs for the treatment of portal hypertension and points to the need for long-term controlled studies to verify this possibility. This is especially important because it is well known that vasodilating nitrates may induce pharmacological tolerance after prolonged administration (48-49), which may offset the beneficial effects demonstrated by the current investigation. These long-term administration studies should also clarify whether the reductions in arterial pressure and HBF actually represent limiting factors restricting the applicability of combined pharmacological therapy.

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