Propranolol Plus Isosorbide-5-mononitrate for Portal Hypertension in Cirrhosis: Long-term Hemodynamic and Renal Effects

ROSA MARIA MORILLAS,[1] RAMON PLANAS,[1] EDUARD CABRÉ,[1] AMPARO GALÁN,[2] JUAN CARLOS QUER,[1] FAUST FEU,[3] JOAN CARLES GARCÍA PAGÁN,[3] JAUME BOSCH[3] AND MIQUEL ANGEL GASSULL[1]

Departments of [1]Gastroenterology and [2]Biochemistry, Hospital Universitari Germans Trias i Pujol, 08916 Badalona, and [3]Liver Unit, Hospital Clínic i Provincial de Barcelona, 08036 Barcelona, Spain

The effect on kidney function, vasoactive systems and ascites outcome of long-term treatment with propranolol plus isosorbide-5-mononitrate, a combined therapy proven more effective than propranolol alone in decreasing portal pressure in the cirrhotic patient, is unknown. Thirty cirrhotic patients who survived acute variceal bleeding and were treated with propranolol plus isosorbide-5-mononitrate were studied. Portal and systemic hemodynamics (n = 15), inulin clearance, free water clearance, plasma renin activity, aldosterone concentration and prostaglandin E_2 excretion (n = 20) were measured before and after 3 mo of treatment. In addition, data on ascites outcome in the entire series after a mean follow-up of 9.6 mo were compared with those of 30 patients undergoing elective sclerotherapy and with those of 30 patients treated with propranolol alone matched for age, sex, presence of ascites, Child-Pugh class and mean follow-up length included in other randomized controlled trials. Combined therapy significantly decreased the hepatic venous pressure gradient and azygos blood flow. In addition, no changes in inulin clearance, free water clearance, plasma renin activity, aldosterone concentration and prostaglandin E_2 excretion occurred, despite a mild decrease in mean arterial pressure. Moreover, no differences among the three groups of patients studied in ascites outcome were found. These results suggest that long-term treatment with propranolol plus isosorbide-5-mononitrate does not impair kidney function, vasoactive systems or ascites outcome in cirrhotic patients. (HEPATOLOGY 1994;20: 1502-1508.)

Propranolol, a nonselective β-adrenergic blocker, has become widely used in the treatment of portal hypertension. Many studies have shown that continual propranolol administration reduces the risk of bleeding or rebleeding from esophageal varices in patients with cirrhosis (1-5) because it decreases portal pressure and blood flow to the portocollateral circulation (6). Indeed, it has been demonstrated that the clinical benefit obtained with propranolol is correlated with the magnitude of the decrease in portal pressure (7).

Recently it was shown that the association of ISMN, a long-acting venous dilator, with propranolol therapy enhances the reduction in portal pressure caused by propranolol, both in short-term (8) and long-term administration (9), suggesting that this drug combination is better than propranolol alone for the treatment of portal hypertension. However, because this combined therapy results in a moderate but significant decrease in arterial pressure, it may have detrimental effects on kidney function in portal-hypertensive cirrhotic patients, specially in those with sodium retention and ascites (10). Yet the effect of the combined treatment with propranolol and ISMN on kidney function and endogenous neurohumoral systems has not been investigated so far.

This study addressed this question by investigating the long-term effects of propranolol plus ISMN on splanchnic and systemic hemodynamics and kidney function in portal-hypertensive cirrhotic patients treated electively with this drug combination after an episode of variceal hemorrhage. The effects of this therapy on the development of ascites and ascites-related complications was also investigated.

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Other abbreviations used in the text: AzBF, azygos blood flow; CO, cardiac output; FHVP, free hepatic vein pressure; HVPG, hepatic venous portal gradient; ISMN, isosorbide-5-mononitrate; MAP, mean arterial pressure; PA, plasma aldosterone; PGE_2, prostaglandin E_2; PRA, plasma renin activity; SVR, systemic vascular resistance; WHVP, wedged hepatic vein pressure.

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Address reprint requests to: Ramon Planas, M.D., Department of Gastroenterology, Hospital Universitari "Germans Trias i Pujol," Carretera del Canyet s/n, 08916, Badalona, Spain.

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TABLE 1. Baseline data of the three groups of patients included in the study

Parameters	Propranolol + ISMN (n = 30)	Sclerosis (n = 30)	Propranolol (n = 30)
Age (yr)[a]	57.4 ± 1.8	55.8 ± 1.6	55.2 ± 1.7
Sex (M/F)	20/10	20/10	20/10
Child-Pugh score[a]	7.6 ± 0.3	7.4 ± 0.2	7.5 ± 0.3
Ascites (Y/N)	18/12	18/12	18/12
Serum bilirubin (mg/dl)[a]	2.4 ± 0.3	1.9 ± 0.3	3.4 ± 0.7
Serum albumin (gm/L)[a]	31.0 ± 1.0	30.3 ± 0.7	32.6 ± 1.0
Prothrombin ratio (%)[a]	61.9 ± 2.2	66.9 ± 2.9	66.3 ± 3.0
Creatinine (mg/dl)[a]	0.9 ± 0.0	0.9 ± 0.0	0.8 ± 0.0
Plasma sodium (mmol/L)[a]	135.5 ± 0.9	136.3 ± 1.0	138.3 ± 0.9
Urinary sodium (mmol/L)[a]	52.4 ± 9.3	40.6 ± 7.6	46.3 ± 8.1

p = NS for all variables.
[a]Data expressed as mean ± S.E.M.

TABLE 2. Changes in splanchnic and systemic hemodynamics after 3 months of combined propranolol/ISMN administration

Parameters	Basal	Three months	p Value
HVPG (mm Hg)	19.7 ± 0.9[a]	16.1 ± 0.9	< 0.0005
WHVP (mm Hg)	27.7 ± 1.4	22.2 ± 1.1	< 0.0005
FHVP (mm Hg)	7.9 ± 1.2	6.1 ± 0.9	0.151
AzBF (L/min)	0.66 ± 0.05	0.44 ± 0.05	0.001
Heart rate (beats/min)	78.0 ± 2.6	58.9 ± 1.6	< 0.0005
MAP (mm Hg)	81.6 ± 2.4	72.9 ± 2.1	0.001
CO (L/min)	7.6 ± 0.3	5.7 ± 0.2	< 0.0005
SVR (dyne · sec · cm^{-5})	878 ± 53	1068 ± 52	0.005

n = 15 except for HR and MAP (n = 20).
[a]Data expressed as mean ± S.E.M.

PATIENTS AND METHODS

Thirty cirrhotic patients, 20 men and 10 women with a mean age of 57 ± 2 yr, who had survived an episode of acute variceal bleeding were studied after they gave informed consent. The study was approved by the Research Committee of the Hospital Universitari Germans Trias i Pujol. The cause of cirrhosis was alcoholic in 24 patients, but no patient was actively drinking. Eighteen of the 30 patients had ascites at inclusion, 14 of them were on diuretic drugs (100 mg/day spironolactone in 5 patients, 100 mg/day spironolactone plus 40 mg/day furosemide in 4, 200 mg/day spironolactone plus 40 mg/day furosemide in 2 and 200 mg/day spironolactone plus 80 mg/day furosemide in 3). The remaining four patients were on a low-sodium diet alone. Two patients who had had ascites in the past but not at inclusion were receiving maintenance spironolactone therapy (50 mg/day). The severity of liver disease was graded according to the Child-Pugh criteria (11). Baseline data of the patients studied are shown in Table 1.

Study 1: Hemodynamic and Renal Effects. Kidney function studies were carried out in 20 patients (14 men, 6 women; mean age, 56 ± 2 yr) before and after 3 mo of combined therapy. Nine of the 20 patients had ascites at inclusion. Studies were performed in the morning after 5 days of controlled sodium intake (40 to 50 mmol/day). During this period, patients did not receive diuretic drugs. After 2 hr of bed rest an antecubital vein was catheterized. Thirty minutes later, blood samples were drawn to measure PRA and PA concentration. PRA was determined by means of RIA (Clinical Assay; Baxter, Cambridge, MA) of generated angiotensin I after a 3-hr incubation at pH 7.4, 37° C under conditions inhibiting further conversion of angiotensin I (normal values, 1.40 ± 0.92 ng/ml/hr). PA was measured with a commercial kit (Coat-A-Count aldosterone kit; Diagnostic Products Corporation, Los Angeles, CA) (normal values, 4 to 30 ng/dl). Afterward, we determined the glomerular filtration rate by measuring the inulin clearance with a method previously described (12). Free-water clearance after an intravenous water load (20 ml/kg body wt) was also calculated. Urine aliquots were collected in tubes with 0.2 mol/L Tris-HCl buffer (pH 6.5) and stored at −70° C for PGE_2 assay (normal values, 40 to 240 pg/min).

In 15 of these patients, hemodynamic studies before and after 3 mo of combined therapy were also performed, as previously described (13, 14). After the patient fasted overnight, a venous catheter introducer was placed in the right femoral vein according to the Seldinger technique while the patient was under local anaesthesia. We advanced a 7F balloon-tipped catheter into the main right hepatic vein under fluoroscopic control to measure WHVP and FHVP by inflating and releasing the balloon. Portal pressure was estimated from the HVPG (i.e., the difference between WHVP and FHVP). Then, a Swan-Ganz catheter (Edwards Laboratories, Los Angeles, CA) was advanced into the pulmonary artery for measurements of cardiopulmonary pressures and cardiac output. Finally, a continuous thermal dilution catheter was placed in the azygos vein for measurement of AzBF (13, 14). Heart rate was determined from the electrocardiogram. Mean MAP was calculated by means of a noninvasive vital-signs monitor (Dinamap; Critikon, Tampa, FL). SVR was calculated according to the following formula:

$$\text{SVR (dyne} \cdot \text{sec} \cdot \text{cm}^{-5}) = (\text{MAP} - \text{RAP})80/\text{CO}$$

where *RAP* (mm Hg) is right atrial pressure and *CO* (L/min) is the cardiac output. All measurements were performed in

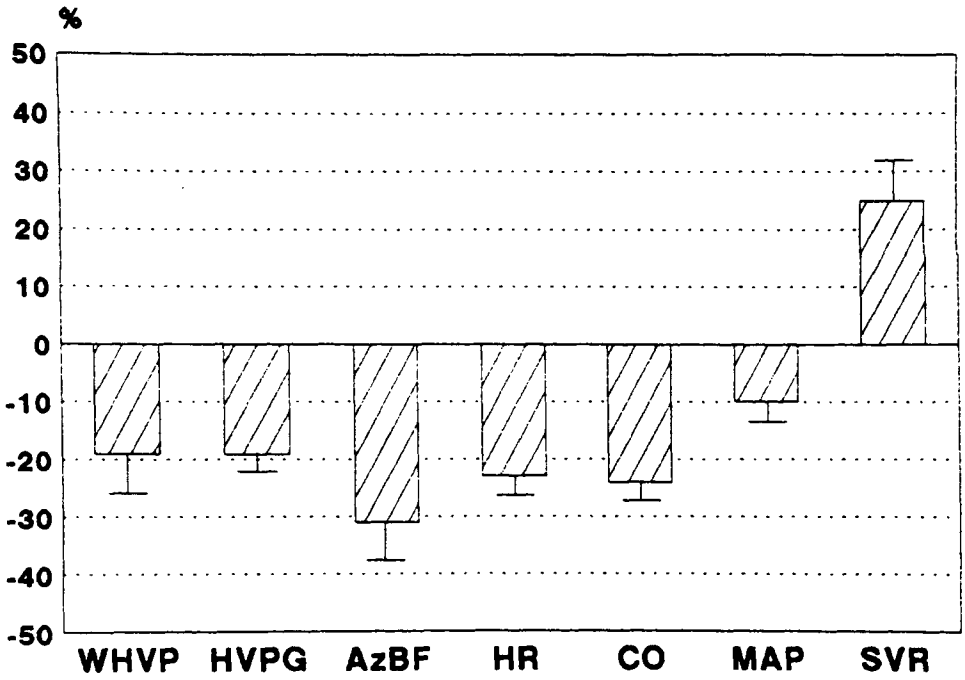

FIG. 1. Effects of 3 mo of combined propranolol/ISMN on splanchnic and systemic hemodynamics. Data are presented as the percent changes in respective baseline values. Vertical lines indicate S.E.M. *HR*, heart rate.

triplicate. Permanent tracing were obtained using a multichannel recorder (Hewlett-Packard 7754B); Medical Products Corp., Andover, MA).

Drug therapy was begun after completion of the baseline evaluation. Patients were started on oral propranolol (20 mg, twice a day). The dosage was increased stepwise at 3-day intervals until the patient's resting heart rate was reduced by 25% or to 55 beats/min. Oral ISMN therapy was started when the patient was stable on maintenance dosage of propranolol. The dosage of ISMN was also progressively increased, from 20 mg at bedtime up to 40 mg twice daily over 2 wk, unless side-effects appeared. The mean maintenance doses of propranolol and ISMN were 114 ± 69 mg/day and 68 ± 20 mg/day, respectively.

Results are reported as mean ± S.E.M. Differences between means before and after 3 mo of therapy were analyzed with Student's *t* test for paired data.

Study 2: Development of Ascites. The clinical effect of propranolol/ISMN therapy on the development of ascites and its complications was assessed in the entire series (n = 30) after a mean follow-up time of 9.6 mo (range, 1 to 25.4 mo). The therapeutic regimen in these patients was the same as that outlined above. The mean daily dosages of propranolol and ISMN for the entire group were 125 ± 70 mg and 66 ± 22 mg, respectively. Patients were followed clinically and biologically every 2 wk during the first month and every month thereafter. At each visit, the compliance to the therapeutic regimen was assessed and the dosage adjusted if necessary.

Another study was performed in which the follow-up data of 30 patients treated with elective sclerotherapy and 30 patients treated with propranolol alone, matched for age (± 5 yr), sex, presence of ascites at inclusion, Child-Pugh class and mean follow-up length, were used for comparison. Controls treated with sclerotherapy were obtained from a series of 89 bleeding cirrhotic patients included in three randomized controlled trials and treated with elective sclerotherapy (15-17), a procedure that should not influence kidney function and ascites formation. Controls treated with propranolol alone were obtained from a series of 58 cirrhotic patients included in a randomized controlled trial after acute variceal bleeding comparing propranolol and sclerotherapy (18). The following endpoints were recorded. The first was development or worsening of ascites, defined by its *de novo* appearance; confirmed by ultrasonography, paracentesis or both in patients without ascites at inclusion; or the need of increased dosages of diuretic drugs in those patients with ascites at inclusion. The second was appearance of functional kidney failure, judged according to the following criteria: increase in serum creatinine concentration more than 50% over baseline values, reaching values over 2 mg/dl; urinary sodium concentration lower than 10 mmol/L; absence of blood, casts and protein in urine; and lack of improvement of kidney function after suppression of diuretic drugs and expansion of plasma volume. The third was development of spontaneous bacterial peritonitis, defined as the presence of suggestive symptoms plus a polymorphonuclear count in ascitic fluid greater than 250 cells/mm^3.

One-way ANOVA with *a posteriori* Duncan test was used to compare baseline variables in the three groups of patients studied. Differences in the frequency of ascites development were assessed with the χ^2 test. Kaplan-Meier curves were used to estimate the probability of ascites and its complications and were compared between case and control groups by means of the log-rank test.

RESULTS

Study 1: Hemodynamic and Renal Effects. The mean HVPG decreased significantly after 3 mo on combined therapy with propranolol plus ISMN, with a mean reduction of 19.03% ± 5.9%. Only 1 of the 15 patients (6.6%) studied did not show a reduction of HVPG after

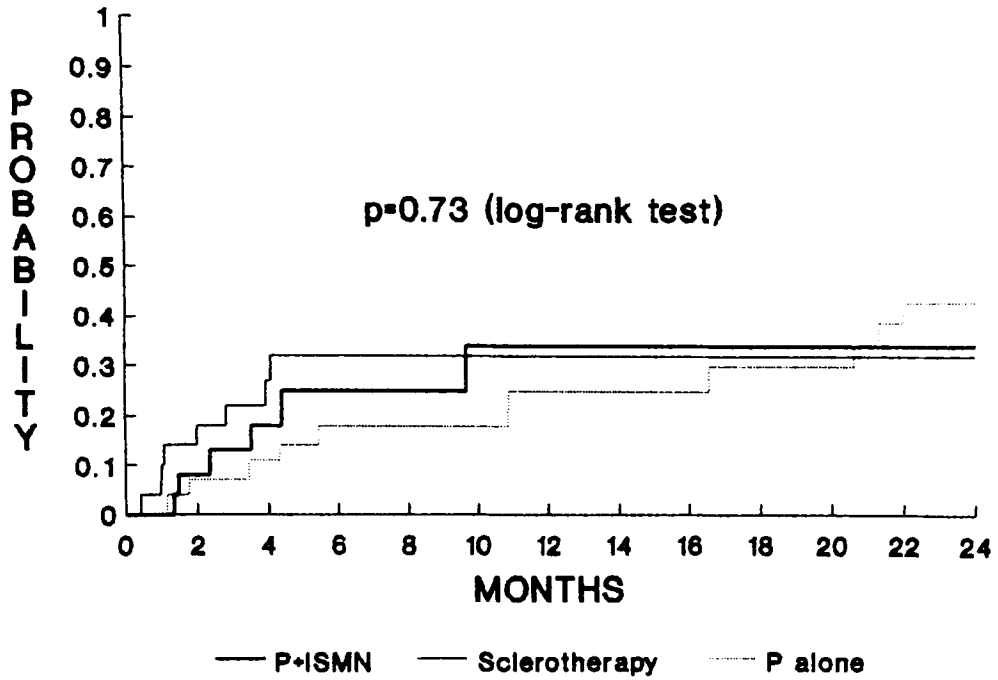

FIG. 2. Probability of ascites development in patients treated with combined therapy vs. those treated with sclerotherapy and propranolol alone. *P*, propranolol.

TABLE 3. Changes in kidney function, free-water clearance, renin-aldosterone system and PGE_2 urinary excretion after 3 mo of combined administration of propranolol plus ISMN in the whole series of patients studied (n = 20)

Parameters	Baseline	3 mo	p Value
Urea (mmol/L)	5.8 ± 0.6[a]	6.3 ± 0.5	0.417
Creatinine (mmol/L)	79.4 ± 3.5	87.3 ± 3.5	0.004
Plasma sodium (mmol/L)	132.3 ± 0.8	133.6 ± 0.6	0.061
Urinary sodium (mmol/L)	42.4 ± 4.5	62.1 ± 5.9	< 0.0005
Urine volume (ml/min)	0.8 ± 0.1	1.0 ± 0.1	0.348
Glomerular filtration rate (ml/min)	101.8 ± 5.7	107.4 ± 6.0	0.250
Free-water clearance (ml/min)	9.0 ± 1.0	10.4 ± 0.8	0.125
PRA (ng/ml/hr)	3.7 ± 1.9	2.1 ± 1.1	0.075
PA (ng/dl)	27.6 ± 8.8	29.5 ± 7.1	0.661
Urinary PGE_2 excretion (pg/min)	185.7 ± 26.8	260.0 ± 39.0	0.096

[a]Data expressed as mean ± S.E.M.

three months of combined therapy. HVPG reduction was mainly due to a decrease in WHVP (mean decrease, 19% ± 3%), whereas FHVP did not change significantly. AzBF also decreased significantly (mean decrease, 31% ± 7%).

Heart rate and CO decreased significantly (mean heart rate decrease, 23% ± 2%; mean CO decrease, 24% ± 3%), and SVR significantly increased (mean increase, 25% ± 7%) after 3 mo of combined therapy. We noted a mild but significant decrease in MAP from 81.6 ± 2.4 to 72.9 ± 2.1 ($p < 0.001$) (mean decrease, 9.9% ± 2.5%) (Fig. 1, Table 2).

Serum urea, electrolytes and urine volume did not change significantly during the 3-mo study period. Serum creatinine showed a mild but significant increase from 79.4 ± 3.5 to 87.3 ± 3.5 μmol/L ($p = 0.004$). Urinary sodium excretion increased significantly from 42.4 ± 4.5 to 62.1 ± 5.9 mmol/L ($p < 0.0005$) (Table 3). Neither the glomerular filtration rate nor the free-water clearance, PRA, PA concentration or urinary excretion of PGE_2 had changed after 3 mo of therapy (Table 3).

Most of the observed changes were similar in patients with and without ascites at inclusion (Tables 4 and 5). However, urinary sodium excretion significantly increased and PRA significantly decreased only in the subgroup of nonascitic patients, whereas serum creatinine and the free-water clearance increased significantly in the subgroup of patients with ascites (Tables 4 and 5).

Study 2: Development or Worsening of Ascites, Kidney Failure and Spontaneous Bacterial Peritonitis. The three groups of patients studied did not differ with regard to age, Child-Pugh score, liver and kidney function tests (Table 1). Development or worsening of

TABLE 4. Changes in kidney function, free-water clearance, renin-aldosterone system and PGE_2 urinary excretion after 3 mo of combined propranolol/ISMN therapy in nonascitic patients (n = 11)

Parameters	Baseline	3 mo	p Value
Urea (mmol/L)	5.2 ± 0.5[a]	5.9 ± 0.8	0.271
Creatinine (mmol/L)	81.1 ± 5.0	85.8 ± 5.4	0.262
Plasma sodium (mmol/L)	132.8 ± 1.2	134.3 ± 0.9	0.177
Urinary sodium (mmol/L)	49.6 ± 15.7	82.6 ± 2.8	< 0.0005
Urine volume (ml/min)	0.9 ± 0.2	1.0 ± 0.2	0.694
Glomerular filtration rate (ml/min)	111.4 ± 7.5	118.9 ± 7.6	0.242
Free-water clearance (ml/min)	10.1 ± 1.7	10.7 ± 1.3	0.703
PRA (ng/ml/hr)	0.6 ± 0.1	0.1 ± 0.0	0.034
PA (ng/dl)	12.4 ± 2.5	10.6 ± 2.1	0.432
Urinary PGE_2 excretion (pg/min)	194.2 ± 43.6	270.7 ± 50.2	0.262

[a]Data expressed as mean ± S.E.M.

TABLE 5. Changes in kidney function, free-water clearance, renin-aldosterone system and PGE_2 urinary excretion after 3 mo of combined propranolol/ISMN therapy in ascitic patients (n = 9)

Parameters	Baseline	3 mo	p Value
Urea (mmol/L)	6.6 ± 1.2[a]	6.7 ± 0.6	0.918
Creatinine (mmol/L)	79.3 ± 5.0	89.2 ± 4.3	< 0.0005
Plasma sodium (mmol/L)	131.6 ± 1.0	132.7 ± 0.8	0.214
Urinary sodium (mmol/L)	33.5 ± 6.4	37.1 ± 5.8	0.133
Urine volume (ml/min)	0.6 ± 0.1	0.9 ± 0.2	0.301
Glomerular filtration rate (ml/min)	90.1 ± 7.3	93.2 ± 7.5	0.693
Free-water clearance (ml/min)	7.6 ± 0.9	10.0 ± 1.0	0.017
PRA (ng/ml/hr)	7.6 ± 3.9	4.6 ± 2.3	0.130
PA (ng/dl)	46.3 ± 17.9	52.5 ± 11.8	0.508
Urinary PGE_2 excretion (pg/min)	175.2 ± 29.5	257.0 ± 64.3	0.241

[a]Data expressed as mean ± S.E.M.

ascites, as previously defined, occurred in 6 patients treated with combined therapy, 8 patients treated with sclerotherapy and 11 patients treated with propranolol alone. Among patients without ascites, it appeared *de novo* in 2 of 12 patients treated with combined therapy, 0 of 12 controls treated with sclerotherapy and 3 of 12 patients treated with propranolol alone ($p = 0.19$, χ^2 test), whereas 4 of 18 patients treated with combined therapy, 8 of 18 controls treated with sclerotherapy and 8 of 18 patients treated with propranolol alone with ascites at inclusion had to increase their daily diuretic intake ($p = 0.28$, χ^2 test). Overall, the 1-yr probability of development of or worsening of ascites was 34% for patients treated with combined therapy vs. 32% in controls treated with sclerotherapy vs. 25% for patients treated with propranolol alone ($p = 0.73$, log-rank test) (Fig. 2).

Functional kidney failure developed in one patient in the combined therapy group, two patients of the sclerotherapy group and two patients of the propranolol group during the follow-up. The 1-yr probability of developing functional kidney failure was not different among the three groups (7% vs. 10% vs. 8%, $p = 0.83$, log-rank test). No case of spontaneous bacterial peritonitis occurred in either patients treated with combined therapy or patients treated with sclerotherapy during follow-up, whereas this occurred in only one patient treated with propranolol alone.

DISCUSSION

The association of long-acting nitrates to propranolol in portal-hypertensive patients enhances the reduction in portal pressure achieved with β-adrenergic blockade, particularly in patients who do not respond to propranolol (8, 9). However, vasodilatory drugs also decrease MAP, which may be associated with undesirable effects on kidney function in cirrhotic patients, specially in those with sodium retention (19). In fact, it has recently highlighted the need to pay attention to the potential adverse effects on kidney function, sodium-water metabolism and ascites formation of drugs to lower portal venous pressure (10). However, no studies about the effect of propranolol plus ISMN therapy on kidney function in cirrhosis with and without ascites have been reported.

Regarding the effects of propranolol on kidney function, different studies have shown that propranolol suppresses renin secretion without changing glomerular filtration rate in cirrhotic patients (20-22). Data on its effect upon kidney sodium handling are controversial, as increased (21, 23, 24), decreased (25), as well as unchanged sodium excretion, (22) have been reported.

On the other hand, a recent study by Salmerón et al. (26) has shown that the oral administration of a single dose of ISMN to cirrhotic patients with portal hypertension increases PRA and PA concentration, mainly in

patients with ascites. These effects could probably be explained by an ISMN-induced reduction of arterial pressure. Moreover a greater reduction in glomerular filtration rate and free-water clearance was observed in patients with than in those without ascites. Recently, Vorobioff et al. (27), reported the long-term hemodynamic and renal effects of the association of propranolol plus isosorbide dinitrate vs. propranolol alone in portal-hypertensive patients. In patients receiving isosorbide dinitrate, mean arterial blood pressure decreased significantly, but not in those receiving propranolol alone. Eight of the 14 patients (57%) with either ascites or history of ascites on combined therapy developed ascites or needed higher diuretic doses, whereas this occurred in no patient treated with propranolol alone. These authors concluded that the decrease in mean arterial blood pressure induced by isosorbide dinitrate is most likely the main determinant of impaired clinical condition in patients with ascites or history of ascites.

This study examined the hemodynamic, humoral and renal effects of combined therapy with propranolol and ISMN in a series of patients with cirrhosis who had survived an episode of variceal hemorrhage, half of whom also had ascites. The study confirms the beneficial effects of this therapy decreasing portal pressure and AzBF, as well as reducing the cardiac index and increasing SVR (8, 9). This combined therapy did not induce changes in glomerular filtration rate and free-water clearance after 3 mo in the whole group of patients. In the subgroup of ascitic cirrhotic patients, serum creatinine showed a mild but significant increase. However, this might be due to reasons other than kidney function impairment, such as changes in the nutritional status; serum creatinine remained in the normal range in all cases, and there were no changes in inulin clearance. Moreover, the renal capacity to excrete water even improved in these patients.

All these changes occurred despite a mild but significant decrease (9.9%) in the MAP, a hemodynamic effect that, at least in theory, could adversely affect kidney function. Our results therefore suggest that the decrease in arterial pressure induced by ISMN is not clinically relevant. In fact, the observed decrease in MAP is lower than that reported with isosorbide dinitrate (27-29). In addition, ISMN has the theoretical advantage when compared to isosorbide dinitrate of its complete bioavailability, a more sustained pharmacological action (30), absence of hepatic metabolism and of a "first-pass" effect (31) and, especially in cirrhosis, its normal pharmacokinetics without evidence of accumulation (32). It is also possible that the opposite effects of propranolol and ISMN on the kidney might account for the lack of renal impairment in this study.

Urinary sodium excretion significantly increased after 3 mo of combined therapy in the whole series of patients studied, the nonascitic patients accounting for this difference. This finding is in agreement with some (21, 23, 24) but not all (22, 25) studies assessing the effect of β-blockade on urinary sodium excretion in cirrhotic patients. The mechanism whereby propranolol plus ISMN increase renal sodium excretion is not known. It could be mediated by the decrease in PRA occurring in these patients, although the possibility of a direct effect of propranolol on tubular sodium handling cannot be ruled out. In fact, although neurogenic tubular sodium reabsorption most often is considered to occur through α-adrenoceptor–mediated stimulation (33), some experimental studies (34) have suggested that neurogenic tubular sodium reabsorption occurs through β-adrenoreceptor stimulation.

Long-term administration of propranolol plus ISMN therapy does not further activate the renin-angiotensin-aldosterone system. The lack of increase in PRA despite a decrease in blood pressure may be due to the direct suppressive effect of renin release caused by propranolol (18-20).

The lack of deleterious effects of a 3-mo course of propranolol plus ISMN on kidney function is further reinforced by our findings during long-term follow-up of our series of 30 patients on continued combination therapy. It should be emphasized that there were no differences in the development or worsening of ascites between patients receiving combined therapy and their matched controls undergoing sclerotherapy or propranolol alone. Although the use of historical controls may have pitfalls, these results suggest that long-term therapy with propranolol plus ISMN does not negatively influence the outcome of ascites in cirrhotic patients. This is in keeping with a recent report suggesting that long-term treatment with either propranolol or ISMN alone do not facilitate the formation or worsening of ascites in these patients (35).

In summary, the findings of this study suggest that long-term oral administration of propranolol plus ISMN in cirrhotic patients with and without ascites is a reasonably safe treatment for portal hypertension, without neither statistically significant nor clinically relevant effects on kidney function, endogenous vasoactive systems or ascites outcome.

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