Renal Effects of Acute Isosorbide-5-mononitrate Administration in Cirrhosis

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The aim of this study was to assess the effects of an oral dose (20 mg) of isosorbide-5-mononitrate on systemic hemodynamics, kidney function, plasma renin activity and plasma aldosterone and atrial natriuretic peptide concentrations in 16 nonazotemic cirrhotic patients. Isosorbide-5-mononitrate significantly reduced cardiopulmonary pressures, cardiac output, peripheral vascular resistance, mean arterial pressure, renal plasma flow, glomerular filtration rate, free water clearance, sodium excretion and atrial natriuretic peptide concentration and significantly increased renin and aldosterone values. Cardiopulmonary pressures, atrial natriuretic peptide, cardiac output and mean arterial pressure decreased to a similar extent in patients with (n = 9) and without ascites (n = 7). In patients with ascites we noted marked increases in plasma renin activity (3.7 ± 1.1 ng/ml/hr to 6.4 ± 1.8 ng/ml/hr; p = 0.01) and aldosterone level (61.1 ± 17.5 ng/dl to 108.4 ± 36.1 ng/dl; p = 0.01). In contrast, in patients without ascites the elevation of plasma renin activity (0.5 ± 0.16 ng/ml/hr to 0.95 ± 0.27 ng/ml/hr; p = 0.02) and aldosterone level (5.9 ± 1.3 ng/dl to 12.3 ± 3.8 ng/dl; p = 0.02) was mild, and in no case did these parameters increase over the upper normal limit. Isosorbide-5-mononitrate produced a significantly greater reduction of glomerular filtration rate (−21.4% ± 3.3% vs. −8.9% ± 4.2%; p = 0.03) and free water clearance (−82.4% ± 16.1% vs. −34.5% ± 12.3%; p = 0.03) in patients with ascites than in those without. We also saw a trend toward a greater decrease of renal plasma flow in ascitic patients (−29.2% ± 7.1% vs. −9.8% ± 9.8%; p = 0.1). Urinary sodium excretion showed a similar decrease (−43.7% ± 9.8% vs. −56.7% ± 12.5%) in the two groups. These results indicate that the administration of a single oral dose of isosorbide-5-mononitrate stimulates the renin-aldosterone system and impairs kidney function in patients with cirrhosis, especially in those with ascites. (HEPATOLOGY 1993;17:800-806.)

Patients with cirrhosis and portal hypertension usually have hyperdynamic circulation characterized by normal or reduced arterial pressure, hypervolemia and high cardiac output (1). The initial event of this hemodynamic abnormality is thought to be peripheral arteriolar vasodilation, which takes place mainly in the splanchnic circulation (2). It has been proposed that arteriolar vasodilation in cirrhosis is of major importance in the activation of the renin-angiotensin and sympathetic nervous systems and antidiuretic hormone and in the pathogenesis of renal sodium and water retention and ascites formation (3, 4).

In the last decade, great advances have been made in the pharmacological treatment of portal hypertension in cirrhosis, particularly in relation to the mechanism of action and indications of propranolol, the selection of patients for pharmacological therapy and the identification of vasodilatory drugs that effectively reduce portal pressure (5-8). Isosorbide-5-mononitrate (Is-5-Mn), which is being assessed in controlled trials, is a promising agent because it has been shown to reduce hepatic vascular resistance and portal pressure without changing hepatic blood flow and liver function (9, 10). Furthermore, Is-5-Mn enhances the beneficial effect of propranolol on portal hypertension (11, 12). However, the scant attention that has been paid to the possible adverse effects of vasodilators on kidney function in cirrhosis is surprising because they significantly reduce arterial pressure and therefore may further activate endogenous neurohumoral vasoconstrictor systems. The aim of this study was to assess the acute effects of Is-5-Mn on systemic hemodynamics, the renin-aldosterone system, and atrial natriuretic peptide concentration and kidney function in cirrhotic patients with portal hypertension with and without ascites.

PATIENTS AND METHODS

Patients. The study was performed in 16 nonazotemic, nonhyponatremic cirrhotic patients with severe portal hypertension (hepatic venous pressure gradient: 12-26.5 mm Hg). Nine patients had ascites. None of the remaining seven

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TABLE 1. Liver and kidney function and hormonal and hemodynamic measurements before Is-5-Mn administration

Parameters	Patients without ascites (n = 7)[a]	Patients with ascites (n = 9)[a]	p Value
Serum bilirubin (mg/dl)[b]	1.5 ± 0.2	2.8 ± 0.6	NS
Serum albumin (gm/L)[b]	35.5 ± 1.6	30.2 ± 1.3	0.02
Prothrombin time (%)[b]	60 ± 6	49 ± 5	NS
BUN (mg/dl)[b]	16 ± 2	13 ± 1	NS
Serum creatinine (mg/dl)[b]	0.9 ± 0.04	0.8 ± 0.06	NS
Serum sodium (mEq/L)[b]	136 ± 2	133 ± 1	NS
24-hr urine volume (L/day)[b]	1.3 ± 0.5	0.8 ± 0.2	0.05
24-hr UNaV (mEq/day)[b]	48.2 ± 7.5	3.1 ± 1.4	0.001
WHVP (mm Hg)	23 ± 1.7	30.3 ± 1.7	0.01
FHVP (mm Hg)	6.1 ± 1.1	11.1 ± 2.7	NS
HVPG (mm Hg)	16.9 ± 1.2	19.2 ± 2.1	NS
MAP (mm Hg)[c]	85.1 ± 3.8	84.2 ± 4.9	NS
CO (L/min)[c]	7.8 ± 0.8	10 ± 0.3	0.02
RAP (mm Hg)[c]	4.5 ± 0.6	6.6 ± 2.6	NS
PVR (dyn · sec · cm^{-5})[c]	929 ± 127	708 ± 73	NS
PRA (ng/ml/hr)[c]	0.5 ± 0.2	3.7 ± 1.1	0.02
PA (ng/dl)[c]	5.9 ± 1.3	61.1 ± 17.5	0.02
ANP (fmol/ml)[c]	24.2 ± 7.5	26.6 ± 5.4	NS
RPF (ml/min)[c]	637 ± 101	699 ± 64[d]	NS
GFR (ml/min)[c]	101 ± 6	103 ± 11[d]	NS
MUF (ml/min)[c]	18.2 ± 2.3	14.4 ± 2.7[d]	NS
CH_2O (ml/min)[c]	10.1 ± 2	8.8 ± 1.9[d]	NS
UNaV (during water load) (μEq/min)[c]	172 ± 30	63 ± 28[d]	0.02

Normal values: serum bilirubin, 0.6 ± 0.1 mg/dl; serum albumin, 44.5 ± 1 gm/L; prothrombin time, 94% ± 4%; BUN, 17 ± 1 mg/dl; serum creatinine, 0.9 ± 0.08 mg/dl; serum sodium, 140 ± 1 mEq/L; 24-hr urine volume, 1.4 ± 0.3 L/day; 24-hr UNaV, 43.3 ± 8 mEq/day; UNaV, 135 ± 23 μEq/min; WHVP, ≤10 mm Hg; FHVP, ≤5 mm Hg; HVPG, <6 mm Hg; MAP, 87.8 ± 2.7 mm Hg; CO, 5.2 ± 0.1 L/min; RAP, 3.7 ± 0.2 mm Hg; PVR, 1,420 ± 272 dyn · sec · cm^{-5}; PRA, 0.9 ± 0.3 ng/ml/hr; PA, 16 ± 2 ng/dl; ANP, 12 ± 4.7 fmol/ml; RPF, 658 ± 53 ml/min; GFR, 116 ± 6 ml/min; MUF, 16.3 ± 2.4 ml/min; CH_2O, 9.6 ± 0.8 ml/min. Normal values of PRA, PA, ANP, RPF, GFR, MUFR, CH_2O and UNaV were obtained in seven healthy subjects after 5 days of a 50 mEq/day sodium diet and after an intravenous water load (5% glucose) of 20 ml/kg body wt. Urine volume (24-hr) and 24-hr UNaV were also obtained from these subjects. Normal values of MAP, CO, RAP and PVR were obtained in 11 patients admitted to the cardiology unit for study of atypical thoracic pain. All had normal coronary angiography results.

[a]Data expressed as mean ± S.E.M.

[b]Measured on day 5 of the study.

[c]Measured under conditions of intravenous water load (20 ml/kg body wt) with 5% glucose.

[d]Measured in eight patients with ascites.

patients had a previous history of ascites or detectable ascites on ultrasound examination at the time of the study. The diagnosis of cirrhosis was based on liver histological appearance in all cases. The pathogenesis of cirrhosis was alcoholic in nine patients, hepatitis C antibody associated in four, HBsAg positivity associated in two and cryptogenic in one. Patients with arterial hypertension, respiratory or cardiac disease, diabetes mellitus or HCC were not included in the study. No study patient had had bacterial infections, gastrointestinal hemorrhage or hepatic encephalopathy in the 2 mo before the investigation. The study was approved by the Investigation and Ethics Committee of the Hospital Clinic i Provincial of Barcelona. Informed consent was obtained from each patient.

Study Design. Patients were studied after 5 days of a 50 mEq sodium/day diet. None was taking diuretics or any other drug. On day 5 blood samples were taken for standard liver and kidney function tests, and a 24-hr urine collection was performed to determine urinary excretion of electrolytes. Early in the morning of day 6, after patients had fasted overnight and then been administered local anesthesia, a venous catheter introducer (USCI International Inc., Galway, Ireland) was placed in the right femoral vein using the Seldinger technique. A 7F balloon-tipped catheter (Medi Tech; Cooper Scientific Corp., Watertown, MA) was then advanced under fluoroscopic control into the main right hepatic vein. The wedged (occluded) and free hepatic venous pressures (WHVP and FHVP) were then measured. Subsequently the balloon-tipped catheter was removed, and a Swan-Ganz catheter (Edwards Laboratory, Los Angeles, CA) was advanced into the pulmonary artery to measure cardiac output (CO; thermal dilution) and cardiopulmonary pressures. This catheter was kept in place during the entire study.

Immediately afterward, renal plasma flow (RPF; 131I-iodohippurate sodium clearance), glomerular filtration rate (GFR; inulin clearance), maximal urinary flow rate (MUFR), free water clearance (CH_2O) and urinary sodium excretion (UNaV) were sequentially measured in periods of 30 min before (three control periods) and 20 min after (three study periods) an oral dose (20 mg) of Is-5-Mn. These measurements could not be performed in one cirrhotic patient with ascites in whom urine could not be satisfactorily collected. Priming doses of inulin (Inutests; Laevosan-Gesellschaft, Linz, Austria) (50 mg/kg body wt) and [^{131}I]iodohippurate sodium (Hippuran ^{131}I injection DRN 5316; Mallinckrodt, Petten, Holland) (15 μCi) were given intravenously (left or right antecubital vein) followed by a constant infusion of a saline solution containing both substances (inulin, 27 mg/min; [^{131}I]iodohippurate

TABLE 2. Effects of Is-5-Mn on systemic hemodynamics and hormonal and renal parameters in the global series and in compensated and ascitic cirrhotic patients

Parameters	Global series		Compensated cirrhosis		Cirrhosis and ascites	
	Basal	Is-5-Mn	Basal	Is-5-Mn	Basal	Is-5-Mn
MAP (mm Hg)	84.6 ± 3.4[a]	74.8 ± 2.7[b]	85.1 ± 3.8	73.9 ± 3.1[c]	84.2 ± 4.9	75.5 ± 3.7[c]
CO (L/min)	8.9 ± 0.5	8.5 ± 0.5[d]	7.8 ± 0.8	7.4 ± 0.7	10 ± 0.3	9.5 ± 0.3
RAP (mm Hg)	5.6 ± 1.3	2.8 ± 1.1[b]	4.5 ± 0.6	1.6 ± 1.1[d]	6.6 ± 2.6	4.1 ± 2[d]
PVR (dyn · sec · cm^{-5})	805 ± 75	748 ± 55[d]	929 ± 127	822 ± 100[d]	708 ± 73	690 ± 56
PRA (ng/ml/hr)	2.3 ± 0.7	4.0 ± 1.2[c]	0.5 ± 0.2	0.9 ± 0.3[d]	3.7 ± 1.1	6.4 ± 1.8[e]
PA (ng/dl)	36.9 ± 13.6	66.3 ± 23[e]	5.9 ± 1.3	12.3 ± 3.8[d]	61.1 ± 17.5	108.4 ± 36[e]
ANP (fmol/ml)	25.5 ± 4.3	16 ± 3[c]	24.2 ± 7.5	16.1 ± 4.1[d]	26.5 ± 5.4	16 ± 4.6[e]
RPF (ml/min)[f]	672 ± 54	534 ± 66[c]	637 ± 101	570 ± 117	699 ± 64	506 ± 80[c]
GFR (ml/min)[f]	102 ± 6	86 ± 5[b]	101 ± 6	92 ± 5	103 ± 11	81 ± 9[c]
MUFR (ml/min)[f]	16.1 ± 1.8	10.9 ± 1.5[b]	18.2 ± 2.3	14.3 ± 1.6	14.4 ± 2.7	7.9 ± 2.1[c]
CH_2O (ml/min)[f]	9.4 ± 1.4	4.5 ± 1.2[b]	10.1 ± 2	6 ± 1.7[d]	8.8 ± 1.9	3.2 ± 1.5[e]
UNaV (μEq/min)[f]	114 ± 24	58 ± 16[c]	72 ± 30	98 ± 24[d]	63 ± 28	23 ± 9[d]

[a]Data expressed as mean ± S.E.M.
[b]$p = 0.001$.
[c]$p \leq 0.005$.
[d]$p \leq 0.05$.
[e]$p \leq 0.01$.
[f]Measured in seven compensated cirrhotic patients and eight cirrhotic patients with ascites.

sodium, 0.4 μCi/min). After an equilibration period of 60 min, urine was collected—usually by bladder catheterization—in 30-min periods. Urine volume was recorded, and aliquots were separated to measure inulin, [^{131}I]iodohippurate and electrolyte concentration and osmolality. In the middle of each 30-min period, blood samples were taken from the venous catheter introducer placed in the femoral vein to measure inulin and [^{131}I]iodohippurate concentration and osmolality. During the first 45 min of the equilibration period, an intravenous water load (5% glucose) of 20 ml/kg body wt was also given. This water load was kept constant throughout the study by infusing a volume of 5% glucose equal to urine volume. Arterial pressure and heart rate were monitored throughout the study at 5-min intervals with an automatic sphygmomanometer (Omega 1400; In Vivo Research Laboratories Inc., Broken Arrow, OK). During the third control period and the second study period, blood samples were taken from the venous catheter introducer to measure plasma renin activity (PRA) and plasma aldosterone (PA) and atrial natriuretic peptide (ANP) concentrations, and CO and cardiopulmonary pressures were determined. No side effects related to the invasive procedures used in the study were observed in any patient.

Inulin, [^{131}I]iodohippurate and osmolar clearances were calculated by the standard formula U × V/P, where *U* is the urinary concentration or osmolality, *V* the urine volume (ml/min) and *P* the plasma concentration or osmolality. CH_2O was calculated as V − osmolar clearance. Peripheral vascular resistance (PVR; dyn · sec · cm^{-5}) was calculated as (MAP − RAP) × 80/CO, in which *MAP* is the mean arterial pressure (mm Hg), *RAP* is the right atrial pressure (mm Hg) and CO is expressed as liters per minute. Hepatic venous pressure gradient (HVPG) was estimated as WHVP − FHVP. All cardiopulmonary and portal hemodynamic measurements were performed in triplicate and registered on a multichannel recorder (Hewlett Packard 7754B; Hewlett Packard, Andover, MA). Results represent the arithmetic mean of all values obtained. Experiments were performed with patients in the supine position. The approximate duration of the study was 5 hr and 30 min; in no case was it longer than 6 hr.

Analytical Methods. PRA and PA and ANP levels were measured by RIA following methods described in detail elsewhere (13-15). Osmolalities were determined on depression of freezing point (Advanced Instruments, Inc., Needham Heights, MA). Electrolytes were measured on flame photometry (Instrumentation Laboratory, Ascoly Piceno, Italy), and BUN and serum creatinine were assayed with a Technicon autoanalyzer (Technicon Instruments Corp., Tarrytown, NY). Inulin concentration was measured by a colorimetric method (16). [^{131}I]iodohippurate sodium concentration was measured with a gamma-counter (INa [T1] Packard 500C) (Packard Instruments, Groningen, The Netherlands).

Statistical Analysis. Statistical analysis of the results was made with the Statpac-Statistical Analysis Package (Walonick Associates, MN) using paired and unpaired Student's *t* tests, Mann-Whitney's nonparametric test and the Wilcoxon rank-sum test. Results are expressed as mean ± S.E.M. A p value less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics. Table 1 shows the baseline liver and kidney function and hormonal and hemodynamic measurements in the patients studied. Patients with ascites had significantly lower serum albumin concentrations and UNaV and significantly higher WHVP, CO, PRA and PA concentration than did patients with compensated cirrhosis. Cirrhotic patients with ascites also had higher serum bilirubin levels, FHVP and HVPG and lower prothrombin times and PVR than did patients without ascites, although these differences were not statistically significant. MAP and ANP concentrations were almost identical in the two groups. By definition, BUN and serum creatinine levels were within normal limits in all patients studied, with and without ascites. We saw no significant differences between the two groups in RPF and GFR. All patients produced hypotonic urine after the water load.

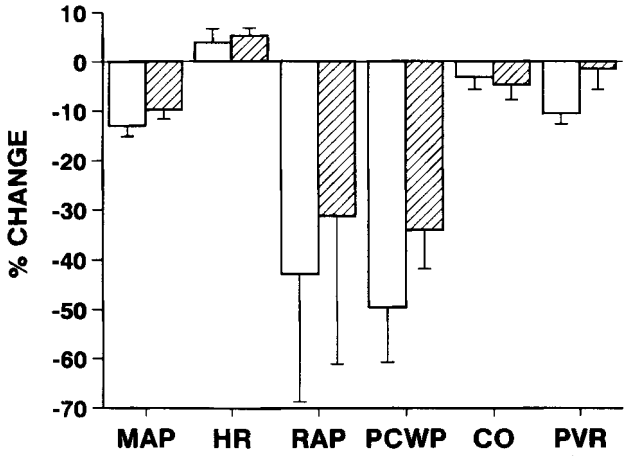

FIG. 1. Effect of Is-5-Mn on systemic hemodynamics. Cirrhotic patients with and without ascites are represented by shaded and white bars, respectively. *HR* = heart rate; *PCWP* = pulmonary capillary wedged pressure; *PVR* = peripheral vascular resistance.

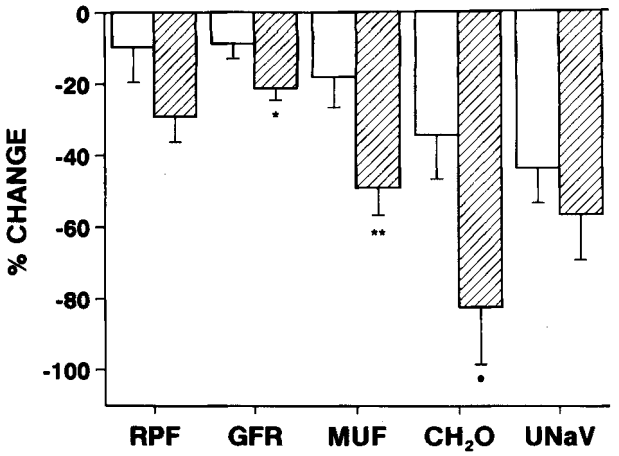

FIG. 2. Effect of Is-5-Mn on kidney function. Cirrhotic patients with and without ascites are represented by shaded and white bars, respectively. *p = 0.03 and **p = 0.02 with respect to values obtained in cirrhotic patients without ascites.

Effects of Is-5-Mn on Systemic Hemodynamics. In all patients the oral administration of Is-5-Mn induced significant reductions in MAP, RAP, pulmonary wedged capillary pressure, CO and PVR and a significant increase in heart rate. The decrease of arterial pressure and the increase in heart rate occurred rapidly, with no significant differences in these parameters between the three study periods after Is-5-Mn administration. The hemodynamic effects of Is-5-Mn in the global series of patients and in patients with and without ascites are shown in Table 2. Figure 1 shows that no significant differences were noted in the percentage changes of these parameters between patients with and without ascites, although we did see a trend toward less pronounced reductions in PVR in the patients with ascites ($-1.5\% \pm 4.2\%$ vs. $-10.5\% \pm 2.2\%$; $p = 0.09$). In fact, PVR decreased significantly in patients without ascites but not in those with ascites (Table 2).

Effects of Is-5-Mn on PRA, PA and ANP. Is-5-Mn induced significant increases in PRA and PA levels in patients with and without ascites (Table 2). However, in patients without ascites the elevation of PRA and PA levels was mild, and in no case did these parameters increase over the upper normal limit (PRA: 0.9 ± 0.3 ng/ml/hr, range = 0.2 to 2.5 ng/ml/hr; PA: 16 ± 2 ng/dl, range = 7 to 22 ng/dl). In contrast, in patients with ascites the administration of Is-5-Mn was associated with marked stimulation of the renin-aldosterone system (Table 2). Is-5-Mn induced significant and comparable decreases of ANP levels in patients with and without ascites (Table 2).

Effects of Is-5-Mn on Kidney Function. In all patients Is-5-Mn induced significant reductions of RPF, GFR, MUFR, CH_2O and UNaV. The renal effects of Is-5-Mn in the global series of patients and in patients with and without ascites are shown in Table 2. Figure 2 shows the percentage changes of these parameters in patients with and without ascites. Is-5-Mn produced significantly greater reductions of GFR, MUFR and CH_2O in patients with ascites than in those without ascites. We also noted a trend toward greater reductions of RPF in patients with ascites. UNaV decreased in a similar proportion in both groups of patients. Figure 3 shows the time course of UNaV after Is-5-Mn administration in patients with and without ascites. Figures 4 and 5 show the individual values of RPF, GFR and CH_2O before and after Is-5-Mn administration in the two groups of patients.

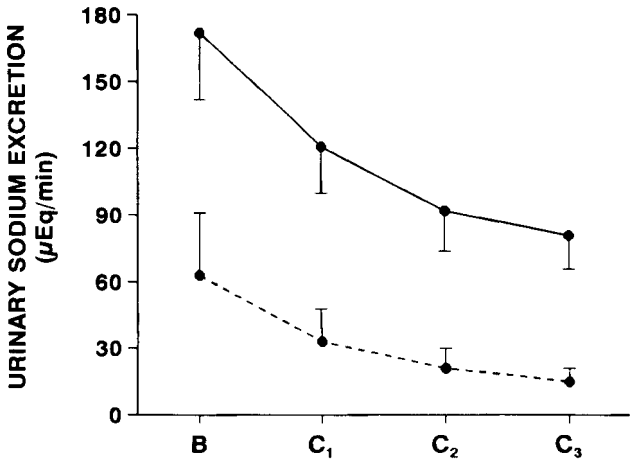

FIG. 3. Time course of UNaV after Is-5-Mn administration in cirrhotic patients without ascites (———) and in those with ascites (– – – –). *B* = baseline; *C1* = first study period; *C2* = second study period; *C3* = third study period. UNaV was measured in eight patients with ascites.

DISCUSSION

Is-5-Mn is a powerful venous and mild arterial dilator (17). After oral administration it has rapid and complete absorption, no first-pass metabolism and a prolonged half-life (5 hr) (18-20). Oral Is-5-Mn administration

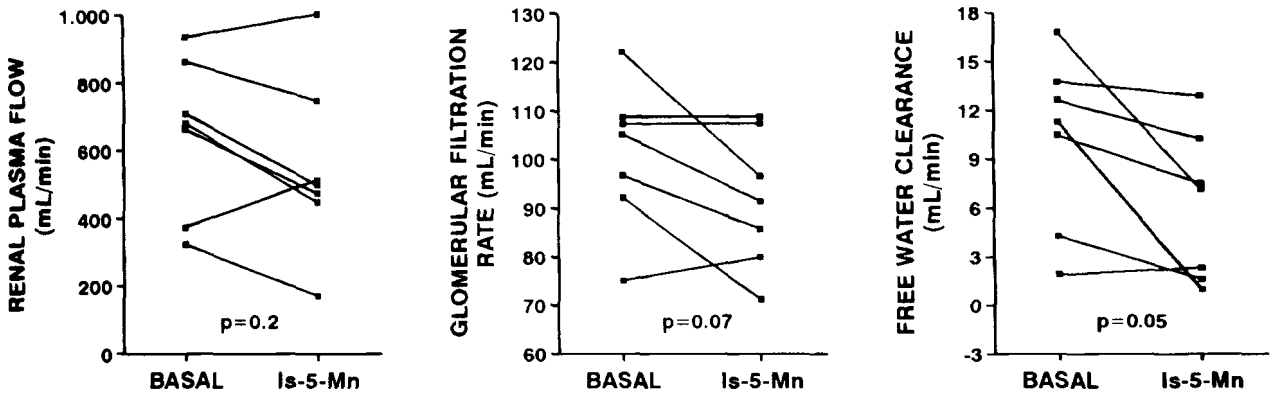

FIG. 4. Individual values of RPF, GFR and CH_2O in patients without ascites under baseline conditions and after Is-5-Mn administration.

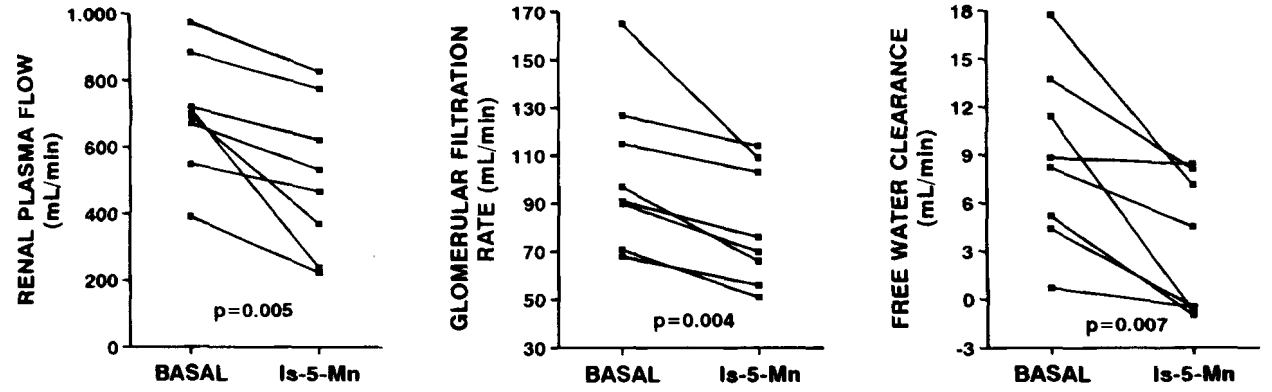

FIG. 5. Individual values of RPF, GFR and CH_2O in patients with ascites under baseline conditions and after Is-5-Mn administration. RPF, GFR and CH_2O were measured in eight patients with ascites.

decreases portal pressure in cirrhotic patients mainly by reducing vascular resistance in the hepatic and portocollateral systems (9). Baroreceptor-mediated splanchnic vasoconstriction may also play a contributory role (9). In addition to its effects on the portal venous system, Is-5-Mn induces significant systemic hemodynamic changes. Short-term studies after administration of Is-5-Mn (20 mg orally) or other organic nitrates in cirrhotic patients with portal hypertension have constantly documented reductions in RAP, pulmonary artery pressure, pulmonary capillary wedged pressure and CO (9, 21-24). The effect on PVR is less constant, with some studies reporting an increase (9, 21) and others a decrease of this parameter (22-24). These findings are consistent with the predominant venodilator action of Is-5-Mn. The net effect of these hemodynamic changes is a decrease in MAP. In this study, the administration of a single dose of Is-5-Mn induced a significant decrease in cardiopulmonary pressures, CO, PVR and MAP. Changes in cardiopulmonary pressures, CO and plasma ANP concentration (which depends on atrial distension) were comparable in cirrhotic patients with and without ascites, suggesting similar venodilator effects of Is-5-Mn in the two groups of patients. MAP also showed a comparable decrease in patients with and without ascites. However, the two groups of patients were different with respect to the effect of Is-5-Mn on PVR. Whereas this parameter decreased significantly in patients without ascites, it did not change in those with ascites.

The short-term administration of Is-5-Mn was associated with significant increases in PRA and PA concentrations in cirrhotic patients with and without ascites. However, the degree of stimulation of the renin-aldosterone system was remarkably different in the two groups. Whereas in patients with ascites we saw marked increases in PRA and PA levels, in patients without ascites these parameters remained within normal limits. Several mechanisms may explain this finding. Because PRA is a sensitive index of effective arterial blood volume, it may be that Is-5-Mn had a greater hemodynamic effect in patients with ascites than in those without ascites, thus producing greater baroreceptor-mediated stimulation of renin release. The lack of differences between both groups in the decreases of MAP and CO induced by Is-5-Mn and the apparent lack of effect of the drug on PVR in the patients with ascites do not rule out this hypothesis because all of these parameters are greatly influenced by endogenous angiotensin II. A direct effect of Is-5-Mn in the juxtaglo-

merular apparatus is unlikely because nitric oxide, which is thought to be the active metabolite of nitrovasodilators, inhibits renin release (25). Finally, it is possible that baroreceptors of the juxtaglomerular apparatus are more sensitive to arterial hypotension in cirrhotic patients with ascites than in those without ascites to protect ascitic cirrhotic patients from further deterioration of their already reduced effective arterial blood volume.

In all the cirrhotic patients studied, Is-5-Mn produced significant decreases in RPF, GFR, maximal urinary flow rate, CH_2O and UNaV. Despite a comparable reduction of MAP, the decrease in kidney function was more intense in patients with ascites than in those without. In patients with ascites the average decreases of RPF and GFR were greater than 20%, whereas it was less than 10% in patients without ascites. The greater activation of the renin-angiotensin system, which is a powerful renal vasoconstrictor, after Is-5-Mn administration in the patients with ascites could have contributed to this different renal hemodynamic response. The average decreases of sodium excretion (57% and 44% in cirrhotic patients with and without ascites, respectively) were higher than those of GFR in the two groups of patients, indicating that the antinatriuretic effect of Is-5-Mn was mainly due to increased tubular sodium reabsorption. The decrease of arterial pressure, the increase of PA level, the suppression of the plasma concentrations of ANP and the probable activation of other endogenous antinatriuretic systems (e.g., the sympathetic nervous system) may account for the increased tubular sodium reabsorption induced by Is-5-Mn. The kidney's ability to excrete free water was the parameter most intensely affected by Is-5-Mn administration. The average decrease of CH_2O was 34% in patients without ascites and 82% in patients with ascites. Four patients with ascites who were able to dilute the urine under baseline conditions had negative CH_2O values after administration of Is-5-Mn.

The relevance of our findings with respect to clinical use of Is-5-Mn in the management of patients with portal hypertension is difficult to ascertain. It is well known that pharmacological tolerance may occur on continuous administration of organic nitrates (26), which reduces the systemic and probably also the renal effects of these compounds. However, long-term (3 mo) oral administration of Is-5-Mn in cirrhotic patients—alone or with propranolol—has been shown to significantly decrease arterial pressure (10, 12), indicating that pharmacological tolerance to this drug is only partial. Therefore long-term therapy with Is-5-Mn may also stimulate the renin-angiotensin-aldosterone system and reduce kidney function in these patients. Although probably less pronounced than those after single Is-5-Mn administration, these side effects may be significant in the long-term therapy of patients with ascites, who are especially sensitive to Is-5-Mn and frequently have impaired RPF, GFR and free water clearance. Because Is-5-Mn enhances the effect of propranolol on portal pressure, the combination of Is-5-Mn and propranolol is being assessed in the prophylaxis of variceal rebleeding (Bosch J, et al., Unpublished data). Because propranolol inhibits renin release (27) and increases GFR in cirrhotic patients with ascites (28), the combined administration of propranolol and Is-5-Mn may be of interest not only because of the two drugs' synergistic effect on portal pressure but also because of their opposite effect on kidney function in these patients.

In conclusion, our results show that the oral administration of a single dose (20 mg) of Is-5-Mn to cirrhotic patients with portal hypertension is associated with significant increases in PRA and PA concentration and reductions of MAP, CO, RPF, GFR, CH_2O and UNaV. The effects of Is-5-Mn on the renin-aldosterone system and kidney function are more intense in the cirrhotic patients with ascites than in cirrhotic patients without ascites. Further studies are needed to assess whether the long-term administration of Is-5-Mn also stimulates the renin-aldosterone system and impairs kidney function in cirrhotic patients with ascites and to determine the clinical implications of these potential hazardous effects. Meanwhile, kidney function should be closely monitored in cirrhotic patients with ascites receiving this drug.

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