Long-term Administration of Isosorbide-5-mononitrate Does Not Impair Renal Function in Cirrhotic Patients

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Isosorbide-5-mononitrate (Is-5-Mn), alone or combined with β-blockers, has been proposed for prophylaxis of variceal bleeding in cirrhosis. However, renal insufficiency, might be an important undesirable effect of this therapy, especially in patients with ascites. We assessed the changes in renal function induced in 26 cirrhotic patients by acute or chronic administration of Is-5-Mn. The acute administration of 20 mg of Is-5-Mn to 21 patients reduced mean blood pressure (83.4 ± 2.4 vs. 92.8 ± 3.4 mm Hg, $P < .001$), urine volume (5.5 ± 0.8 vs. 8.7 ± 1.1 mL/min, $P < .05$), urine sodium excretion (114 ± 19 vs. 244 ± 41 μEq/min, $P < .001$), urine potassium excretion (41 ± 3.4 vs. 67 ± 8.5 μEq/min, $P < .001$), and atrial natriuretic factor (74 ± 10 vs. 98 ± 12 pg/mL, $P < .005$). The glomerular filtration rate was decreased in the 11 patients with ascites (57 ± 9 vs. 68 ± 12 mL/min, $P < .05$), and plasma renin activity was increased in 4 ascitics. Twenty-one patients (16 from the acute study + 5 other patients) were given Is-5-Mn for 3 months at the dose of 80 mg/d. This did not affect blood pressure and renal function in patients without ascites, but reduced mean blood pressure (91.9 ± 3.4 vs. 89.6 ± 3 mm Hg, $P < .05$), urine volume (5.8 ± 1.1 vs. 3.4 ± 0.9 mL/min, $P < .05$), and urine sodium excretion (205 ± 38 vs. 99 ± 16 μEq/min, $P < .01$) in those with ascites. There were no changes in glomerular filtration rate and renal plasma flow, while plasma renin activity increased in only 3 patients with ascites and 1 without.

Systemic hemodynamics and renal function of cirrhotic patients, especially those with ascites, are affected adversely by acute administration of Is-5-Mn. Long-term administration of the drug is well tolerated by compensated patients and does not affect renal plasma flow nor glomerular filtration rate, but can induce hypotension and sodium retention in patients with ascites. (Hepatology 1996;23:1135-1140.)

Isosorbide-5-mononitrate (Is-5-Mn) reduces hepatic vascular resistance and portal pressure in cirrhotic livers, without affecting hepatic blood flow or liver function[1-3] and, when administered for a long period, is able to reduce azygos blood flow.[4] Is-5-Mn also enhances the beneficial effect of propranolol on portal hypertension.[5,6] Recent studies have shown that Is-5-Mn is able to reduce the incidence of first episodes of bleeding from esophageal varices when given alone[7] or to reduce the rate of rebleeding when given during a course of sclerotherapy.[8] It is to be expected that Is-5-Mn will be used, alone or combined with β-blockers, in future trials on patients with portal hypertension. Salmeron et al.,[9] however, reported that a single oral dose of Is-5-Mn stimulates the renin-aldosterone system and impairs the renal function of cirrhotic patients. Vorobioff et al.[10] showed that long-term administration of isosorbide dinitrate in combination with propranolol impaired the sodium metabolism of a few patients with ascites who needed higher doses of diuretics. On the contrary, neither Morillas et al.[11] nor Merkel et al.[12] observed any detrimental effects on renal function after 3 or 6 months of therapy with a combination of Is-5-Mn and β-blockers. These studies make it uncertain whether or not long-term administration of a nitrate compound alone is beneficial or detrimental for cirrhotic patients. This question prompted us to investigate the effects of both acute and chronic administration of Is-5-Mn on blood pressure, renal function, and hormones of cirrhotic patients with and without ascites.

PATIENTS AND METHODS

The study was performed in 26 nonazotemic cirrhotic patients (18 men and 8 women). The criteria for inclusion were: diagnosis of cirrhosis based on clinical and laboratory data and on previous liver histology; presence of esophageal varices with a risk of bleeding of >11% at 1 year according to the North Italian Endoscopic Club, Padua, Italy, predictive scoring system[13]; no previous episodes of bleeding; no cardiac or kidney diseases nor cancer; and stable hemodynamic conditions. Patients taking vasoactive drugs or potentially nephrotoxic drugs were excluded, as well as patients considered to be unreliable or who continued to drink alcohol. The protocol was approved by the local ethical committee, and an informed consent to participate was obtained from each patient.

Abbreviations: Is-5-Mn, isosorbide-5-mononitrate; HR, heart rate; PAH, *p*-aminohippuric acid; PRA, plasma renin activity; PA, plasma aldosterone; ANF, atrial natriuretic factor; MAP, mean arterial pressure; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; CH_2O, free water clearance; UV, urine volume; UNaV, urine sodium excretion rate; FENa, fractional sodium excretion; UKV, urine potassium excretion rate.

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Received August 8, 1995; accepted December 23, 1995.

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0270-9139/96/2305-0030$3.00/0

The origin of cirrhosis was viral for 19 cases (17 hepatitis C virus and 2 hepatitis B virus associated), alcoholic for 4, mixed for 2, and cryptogenic for one. The diet was free for patients without ascites and restricted to 80 mmoles/d of sodium for patients with ascites. The patients with ascites were taking the diuretics at daily doses ranging from 50 to 300 mg of K-kanrenoate and from 12.5 to 75 mg of furosemide. As we wished to perform a pragmatic study, diuretics were not stopped but the last doses were given 24 hours before the assessment of renal function.

Sixteen patients participated in both studies. Only 5 in the first study and only 5 in the second study.

Study 1. The acute effects of Is-5-Mn were studied in 21 patients (11 with and 10 without ascites). After an overnight fast, patients were invited to rest in the supine position and a polyethylene catheter was inserted into an antecubital vein for fluid infusion. A second catheter was inserted in the other arm for blood sampling. After 1 hour of bed rest, arterial pressure and heart rate (HR) were measured, priming doses of inulin (Polyfructosan 25%, Inutest, Laevosan Gesellschaft, Linz, Austria, 0.2 mL/kg) and of *p*-aminohippuric acid (PAH, Acido Paraminoippurico 20%, Jacopo Monico Laboratori, Mestre, Italy, 0.05 mL/kg) in 5% glucose were given intravenously in a total water load of 10 mL/kg body weight, followed by constant infusion of both substances titrated to maintain the plasma concentrations of inulin at 15 to 20 mg/dL and of hippurate at 1.5 to 2.5 mg/dL. After a 1-hour equilibration period, we collected three consecutive 30-minute urine samples (baseline evaluation). Then, an oral dose of Is-5-Mn (20 mg) was administered and the following 20-minute urine sample was discarded. Three further 30-minute urine samples were collected for postdrug evaluation. Urine was collected by spontaneous voiding and blood samples were also collected after initial water loading and at the midpoints of each urine collection. Blood pressure and HR were also monitored every 10 minutes. Urine volumes were always compensated by infusion of additional amounts of 5% glucose solution.

Study 2. The chronic effects of Is-5-Mn were studied in 21 patients (12 with and 9 without ascites). After study of the baseline kidney function, as reported for the first 3 urine collections of Study 1, patients were treated orally with 80 mg Is-5-Mn for 90 days. The drug was administered first at the daily dose of 20 mg, which was then doubled every 4 to 5 days up to 40 mg twice per day. Every patient was examined weekly until his or her final dose was reached and then every patient was examined monthly. Compliance in taking the drug was assessed by counting the unused tablets. Twelve hours after the administration of the last dose of Is-5-Mn, kidney function and hormonal pattern were reevaluated in the same way as in the baseline study.

In five patients (three with and two without ascites), the effects of a rechallenge were also studied by giving an oral dose of Is-5-Mn (20 mg) after the end of study 2 and repeating the same urine and blood collections after an interval of 20 minutes.

Inulin, PAH, sodium, potassium, and osmolality were measured in all urine samples. Inulin, PAH, creatinine, sodium, potassium, osmolality, plasma renin activity (PRA), plasma aldosterone (PA), and atrial natriuretic factor (ANF) were measured in plasma samples. The concentrations of inulin and PAH were determined by photocolorimetric methods.[14,15] Creatinine was measured by autoanalyzer. Electrolytes were measured with an IL 243 flame photometer (Instrumentation Laboratory, Lexington, MA) and osmolality with a Fiske osmometer (Fiske Associates, Inc., Uxbridge, MA). PRA and PA were measured with specific radioimmunoassays with commercial kits (Biodata, Milano, Italy; and Sclavo, Siena, Italy). Blood samples for ANF determination were collected in chilled tubes containing ethylenediaminetetraacetic acid and aprotinin (1,000 U/mL). These were rapidly centrifuged at 4°C and the supernatants were extracted on C-18 Sep-Pack cartridges (Waters Millipore Corp., Milford, MA) according to a method previously reported.[16] Radioimmunoassays for ANF was performed with reagents obtained from the Nichols Institute Diagnostic (San Juan Capistrano, CA). Mean arterial pressure (MAP) was calculated as diastolic pressure + 1/3 pulse pressure. Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were calculated by standard equations for clearances using plasma and urine concentrations of PAH and inulin. Free water clearance (CH_2O) was calculated as V − osmolar clearance, in which V is the urine volume in mL/min. The arithmetic means of the three clearance periods obtained before and after Is-5-Mn administration were used to report the data for baseline and postdrug periods in both study 1 and study 2.

TABLE 1. Baseline Clinical and Laboratory Data for Cirrhotic Patients With and Without Ascites

Data	Patients With Ascites (n = 16)	Patients Without Ascites (n = 10)	*P*
Age (yr)	60 ± 1.9	57 ± 2.8	NS
MAP (mm Hg)	90 ± 2.7	95.6 ± 3.4	NS
HR (beats/min)	69.6 ± 2.4	65 ± 2.7	NS
Child Pugh (score)	8.5 ± 0.5	6.3 ± 0.2	.001
Serum bilirubin (mg/dL)	2 ± 0.3	1.3 ± 0.15	NS
PT (ratio)	1.3 ± 0.05	1.24 ± 0.02	NS
Serum albumin (mg/dL)	3.5 ± 0.11	4 ± 0.15	.015
ALT (U/L)	62 ± 11	87 ± 22	NS
Hemoglobin (g/dL)	11.8 ± 0.4	13 ± 0.5	NS
Serum sodium (mEq)	131 ± 1.1	136 ± 1.9	.02
Serum potassium (mEq)	4.3 ± 0.15	3.9 ± 0.11	NS
Serum creatinine (mg/dL)	1 ± 0.06	0.9 ± 0.07	NS
UNaV (μEq/min)	243 ± 49	208 ± 40	NS
PRA (ng/mL/h)	6.7 ± 1.6	0.8 ± 0.22	.008
PA (pg/mL)	275 ± 42	77 ± 15	.001
ANF (pg/mL)	99 ± 15	109 ± 16	NS

NOTE. Data are reported as means ± SEM.

Abbreviations: ALT, alanine transaminase; PT, prothrombin time; NS, not significant.

All data are reported as means ± SEM. Baseline data of patients with and without ascites were compared using the Student's *t* test or the χ^2 test with Yates' correction. The *t* test for paired data was employed to compare data obtained before and after acute administration of 20 mg of Is-5-Mn, and data obtained before and after 90 days of therapy in study 2. A *P* value less than .05 was considered statistically significant.

RESULTS

Table 1 shows the baseline clinical and laboratory data for the 26 patients. Patients with ascites had higher Child-Pugh scores, higher values of PRA and PA, and lower values of albumin and of plasma sodium than patients without ascites. The urinary sodium excretion rates were similar in patients with and without

TABLE 2. Acute Effects of 20 mg of Is-5-Mn on Blood Pressure, Renal Function, and Hormone Pattern in Cirrhotic Patients With and Without Ascites

		Global Series		Cirrhosis With Ascites		Cirrhosis Without Ascites	
		Basal	Is-5-Mn	Basal	Is-5-Mn	Basal	Is-5-Mn
MAP	(mm Hg)	92.8 ± 3.4	83.4 ± 2.4*	90.2 ± 3.8	80.4 ± 3.3*	95.6 ± 3.6	86.7 ± 3.4*
HR	(beats/min)	65 ± 2	65 ± 2	66 ± 2	66 ± 2	65 ± 3	64 ± 2
GFR	(mL/min 1.73 m^2)	76 ± 12	72 ± 9	68 ± 12	57 ± 9§	84 ± 10	89 ± 14
ERPF	(mL/min 1.73 m^2)	326 ± 51	301 ± 40	367 ± 83	302 ± 65	268 ± 42	299 ± 43
UV	(mL/min)	8.7 ± 1.1	5.5 ± 0.8§	6.5 ± 1.2	4.3 ± 1§	11.1 ± 1.7	6.8 ± 1.1
UNaV	(μEq/min)	244 ± 41	113 ± 19*	276 ± 30	124 ± 32†	208 ± 43	103 ± 15§
FENa	(%)	1.9 ± 0.3	1 ± 0.2*	2.3 ± 0.6	1.2 ± 0.4‡	1.4 ± 0.2	0.7 ± 0.1§
UKV	(μEq/min)	67 ± 8	41 ± 3.4	68 ± 9	42 ± 4†	66 ± 15	39 ± 5
CH_20	(mL/min)	4.7 ± 1	2.8 ± 0.7	2.4 ± 0.9	1.7 ± 0.8	7.2 ± 1.7	4 ± 1.3
PRA	(ng/mL/h)	4.1 ± 1.3	6.6 ± 2	7.1 ± 2	11.7 ± 3.2	0.8 ± 0.2	0.9 ± 0.2
PA	(pg/mL)	187 ± 38	224 ± 57	287 ± 56	363 ± 92	77 ± 15	71 ± 12
ANF	(pg/mL)	98 ± 12	74 ± 10†	98 ± 17	71 ± 16‡	98 ± 11	77 ± 12

* $P < .001$ vs. Basal.
† $P < .005$ vs. Basal.
‡ $P < .01$ vs. Basal.
§ $P < .05$ vs. Basal.

ascites, and this was because we studied ascitic patients on diuretic therapy.

Study 1. In patients given a single oral dose, Is-5-Mn caused rapid falls in blood pressure, urine volume (UV), urine sodium excretion rate (UNaV), fractional sodium excretion (FENa), urine potassium excretion rate (UKV), and ANF (Table 2). The decreases in MAP, UNaV, and FENa were statistically significant in both groups of patients, with and without ascites, whereas the decreases in UV, UKV, GFR, and ANF were statistically significant only in patients with ascites (Table 2). Fig. 1 shows the individual changes in PRA and PA. A 50% increase above the value of 3 ng/mL/h for PRA was observed in four cases after administering Is-5-Mn. A 50% increase above the value of 500 pg/mL for PA was observed in 2 cases. All these patients had ascites.

Study 2. All patients complied with the study protocol, as assessed by pill counts and attendance to scheduled visits. There were no serious complications related to the administration of Is-5-Mn. Ten patients reported transient headaches and 1 of them also had ankle edema in the first days of treatment. None had symptomatic hypotension. In patients without ascites the administration of Is-5-Mn for 90 days did not affect blood pressure nor any other parameter. On the contrary, MAP was significantly decreased and HR was significantly increased in the group of patients with ascites, in whom UV, UNaV, and FENa were also decreased at the end of the study (Table 3). However, we did not observe any important clinical consequences and did not find it necessary to increase the doses of diuretics for any patient. CH_2O values decreased after Is-5-Mn therapy, but the difference from baseline values was statistically significant only for the global series of patients. Fig. 2 shows the individual changes in PRA and PA in patients with and without ascites. There was a 50% increase of PRA above the value of 3 ng/mL/h for 4 patients (3 with and 1 without ascites), and a 50% increase of PA above the value of 500 pg/mL for 2 patients with ascites. In 5 patients (3 with and 2 without ascites), a rechallenge with 20 mg of Is-5-Mn caused effects similar to those found in study 1 (Table 4).

DISCUSSION

The beneficial effect of preventing some risk by the chronic administration of drugs is sometimes counter-

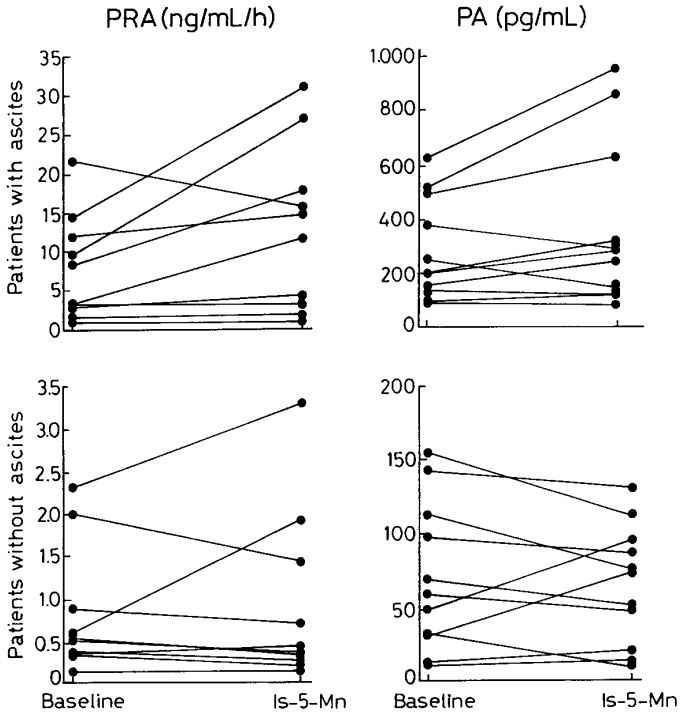

FIG. 1. Individual values of plasma renin activity and plasma aldosterone in cirrhotic patients with and without ascites under baseline conditions and after administration of 20 mg of Is-5-Mn.

TABLE 3. Effects of Chronic Administration of Is-5-Mn (40 mg, Twice Per Day, for 90 Days) on Blood Pressure, Renal Function, and Hormone Pattern of Cirrhotic Patients With and Without Ascites

		Global Series		Cirrhosis With Ascites		Cirrhosis Without Ascites	
		Basal	Is-5-Mn	Basal	Is-5-Mn	Basal	Is-5-Mn
MAP	(mm Hg)	93.8 ± 2.6	91.5 ± 2.2	91.9 ± 3.4	89.6 ± 3§	96.4 ± 3.9	94 ± 3.4
HR	(beats/min)	68 ± 2	70 ± 2	71 ± 3	75 ± 3§	64 ± 3	63 ± 3
GFR	(mL/min 1.73 m^2)	72 ± 8	76 ± 12	63 ± 12	68 ± 16	84 ± 12	97 ± 17
ERPF	(mL/min 1.73 m^2)	317 ± 79	440 ± 108	426 ± 145	461 ± 205	208 ± 33	419 ± 102
UV	(mL/min)	8.1 ± 1.2	5.9 ± 1.1	5.8 ± 1.1	3.4 ± 0.9†	11.1 ± 1.9	9.2 ± 1.8
UNaV	(μEq/min)	203 ± 29	152 ± 24	205 ± 38	99 ± 16*	199 ± 47	222 ± 44
FENa	(%)	1.8 ± 0.4	1.3 ± 0.3†	2.2 ± 0.6	1.3 ± 0.5*	1.3 ± 0.2	1.3 ± 0.3
UKV	(μEq/min)	58 ± 8	70 ± 15	54 ± 8	45 ± 8	63 ± 16	103 ± 32
CH_20	(mL/min)	4.4 ± 1.1	2.3 ± 0.8†	2.2 ± 0.9	0.7 ± 0.8	7.3 ± 1.9	4.3 ± 1.4
PRA	(ng/mL/h)	3 ± 0.9	4.7 ± 1.5	4.7 ± 1.5	7.5 ± 2.3	0.8 ± 0.3	0.9 ± 0.3
PA	(pg/mL)	180 ± 37	223 ± 44	262 ± 53	334 ± 60	73 ± 17	75 ± 12
ANF	(pg/mL)	107 ± 13	92 ± 13	105 ± 18	90 ± 20	110 ± 19	94 ± 15

* $P < .01$ vs. Basal.
† $P < .05$ vs. Basal.

balanced by the possibility of inducing important side effects. Therefore, the decision to give a prophylactic therapy to an individual patient must be preceded by an accurate evaluation of the benefits and the risks connected with the administration of the drug.

Nitrates have been shown to have a beneficial effect on portal hypertension because of their venular dilator activity,[1-6,17,18] and Angelico et al.[7] showed that the administration of Is-5-Mn for 1 year was able to reduce the incidence of first esophageal bleedings in cirrhotic patients to the same extent as propranolol administration. The risk that the long-term administration of Is-5-Mn might adversely affect renal blood flow and renal function by decreasing blood pressure and cardiac output was not accurately assessed in that study. However, such a side effect is conceivable, because Salmeron et al.[9] reported that a single oral dose of Is-5-Mn stimulates the renin-aldosterone axis and lowers renal blood flow and GFR in cirrhotics, especially in those with ascites. Other studies have evaluated the chronic renal effects of Is-5-Mn administered in combination with beta-blockers[11,12] and, therefore, it is difficult to separate out the effect of Is-5-Mn alone.

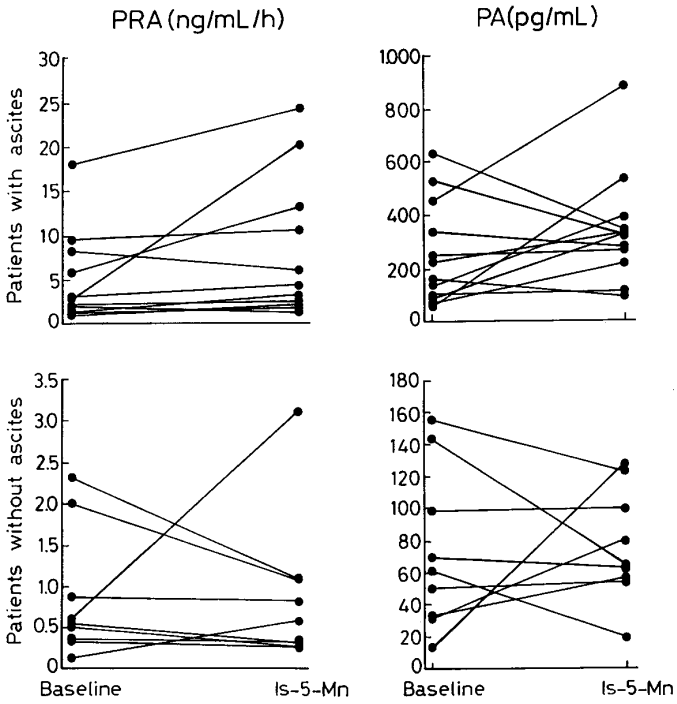

FIG. 2. Individual values of plasma renin activity and plasma aldosterone in cirrhotic patients with and without ascites under baseline conditions and after 90 days of therapy with isosorbide-5-mononitrate (40 mg, twice per day).

In the present study we investigated the effects of both acute and chronic administration of Is-5-Mn to cirrhotic patients with and without ascites. The results confirm that the acute administration of 20 mg of Is-5-Mn decreases GFR, but this occurred only in patients with ascites. Decreases of UV and of sodium and potassium excretion were observed in the global series of patients. These changes are probably because of the potent hemodynamic effects of the nitrate, which invariably induced a considerable fall of blood pressure. This is also confirmed by the levels of ANF, a sensitive index of central blood volume. ANF concentrations decreased after administering Is-5-Mn, and this decrease was statistically significant in patients with ascites. The decrease of plasma ANF can be explained by a decrease in right atrial pressure, the occurrence of which has been documented in previous studies.[5,9] Why the decrease of GFR occurred only in patients with ascites is unclear. Perhaps, the kidneys of patients with ascites are more vulnerable to hemodynamic changes than those of patients with compensated cirrhosis, or the hemodynamic changes caused by Is-5-Mn are greater in patients with ascites than in those without ascites. The changes of PRA seem to confirm both of these explanations, because it did not change in pa-

TABLE 4. Effects of Acute Administration of 20 mg Is-5-Mn on Blood Pressure, Renal Function, and Hormone Pattern Before and After 3 Months of Chronic Therapy With Is-5-Mn (40 mg Twice per Day) in Five Cirrhotic Patients

		Study 1		Rechallenge	
		Basal	Is-5-Mn	Basal	Is-5-Mn
MAP	(mm Hg)	95.5 ± 7.6	87.4 ± 5.8*	93.8 ± 6.4	86.8 ± 6.4*
HR	(beats/min)	65 ± 3	63 ± 3	65 ± 4	64 ± 4
GFR	(mL/min 1.73 m^2)	72 ± 12	67 ± 14	89 ± 8	73 ± 7
ERPF	(mL/min 1.73 m^2)	234 ± 55	210 ± 63	350 ± 111	496 ± 293
UV	(mL/min)	8.1 ± 1.4	6.9 ± 1.3	9.1 ± 2.5	8.6 ± 1.9
UNaV	(μEq/min)	211 ± 43	140 ± 34*	217 ± 52	172 ± 32
FENa	(%)	1.7 ± 0.6	1.2 ± 1.5	1.4 ± 0.3	1.38 ± 0.3
UKV	(μEq/min)	90 ± 13	57 ± 5	85 ± 28	55 ± 14
CH_20	(mL/min)	3.7 ± 1.2	2.9 ± 1	4.6 ± 1.6	4.9 ± 1.4
PRA	(ng/mL/h)	1.5 ± 0.5	1.3 ± 0.5	1.7 ± 0.7	2 ± 0.7
PA	(pg/mL)	100 ± 17	124 ± 29	143 ± 46	125 ± 32
ANF	(pg/mL)	119 ± 32	69 ± 18*	97 ± 9	56 ± 5*

* $P < .05$ vs. Basal.

tients without ascites, but increased in 4 of 11 patients with ascites, suggesting marked baroreceptor-mediated stimulation of renin release occurring only in some patients with ascites. Because we excluded azotemic patients from our study, it is possible that Is-5-Mn administration to cirrhotic patients with azotemia might cause even more severe kidney dysfunction than that observed in our subjects.

The long-term administration of Is-5-Mn caused less marked changes than a single short-term dose. After 90 days of treatment, in fact, the values of blood pressure were reduced only in patients with ascites and to a lesser extent than in the short-term study. Patients without ascites did not show alterations of kidney function nor of the hormonal pattern. In patients with ascites there was a significant reduction of sodium excretion but not of GFR and ERPF. In addition, none required increased doses of diuretic to control ascites. This suggests that the antinatriuretic effects of chronic Is-5-Mn therapy are mainly because of increased tubular reabsorption of filtered sodium and that this becomes evident only under water load conditions, as in our study. As for the hormonal pattern, it is worth noting that the decrease in ANF was not significant in either group of patients, and that in only four patients was PRA consistently increased at the end of treatment. These findings could be explained by a phenomenon of pharmacological tolerance, which is well known to occur on continuous administration of organic nitrates[19] and that can reduce the systemic and, probably, the renal effects of these drugs. The results observed in five patients who were rechallenged with 20 mg of Is-5-Mn at the end of the chronic therapy, however, exclude any important effect of tolerance, because blood pressure, GFR, and ERPF were affected by the drug to similar extents as in study 1. This is in agreement with the study of Garcia-Pagan et al.[6] who showed that long-term therapy with Is-5-Mn, administered twice a day, maintained its vascular effects. Therefore, the lack of an important impairment of the kidney function after long-term administration of Is-5-Mn, in spite of the acute renal effects of the drug, was most likely because of the intervals between drug administrations (12 hours), which made the systemic and renal effects of the drug transient. However, this draws attention to the time between the last administration of the drug and the evaluation of renal function. We chose an interval of 12 hours because we thought it important to investigate whether or not Is-5-Mn caused persistent rather than transient renal effects, because this is the important clinical issue.

In all, the results of the present study indicate that, although Is-5-Mn affects the renal function of cirrhotic patients in the short term, its long-term administration is well tolerated and does not cause any clinically important renal impairment. However, some patients with ascites can have a worsening of their state of effective hypovolemia, with a further impairment of their ability to excrete sodium and water. This is in accord with the clinical observation of Vorobioff et al.[10] that some cirrhotic patients treated with propranolol, when given additional isosorbide dinitrate, required larger doses of diuretics to control ascites.

In conclusion, the administration of Is-5-Mn to prevent the risk of bleeding from esophageal varices is a safe procedure for nonazotemic patients with compensated cirrhosis, because the beneficial effects override the minor side effects. Patients with ascites may also be treated with Is-5-Mn, but their cardiac and renal functions need to be closely monitored.

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