Long-Term Effect of Nadolol or Nadolol Plus Isosorbide-5-Mononitrate on Renal Function and Ascites Formation in Patients With Cirrhosis

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The association beta-blockers plus nitrates has been reported to impair renal function and renal sodium handling, leading to increased risk of development of ascites, or worsening of a preexisting ascites, or increase in the requirements of diuretic agents. In 81 patients with cirrhosis and esophageal varices, participating in a multicenter controlled clinical trial of prophylaxis of variceal bleeding comparing nadolol (NAD) plus isosorbide-5-mononitrate (I5M) with NAD alone, renal function, presence of ascites, and diuretic requirements were assessed at inclusion and after 6 months of follow-up. No significant variation in s-urea or s-creatinine was observed in either group. Three patients in the nadolol group and two in the NAD plus I5M developed ascites at 6 months (P = .70), and a need to increase diuretic regimen was observed in four and three patients, respectively (P = .76). Decrease in heart rate and in mean arterial pressure was similar in the two groups. There was a significant correlation between increase in s-creatinine and decrease in mean arterial pressure in the whole series (P = .015). Only in patients treated with the association was there a significant larger proportion of patients ascitic who became anascitic, than of patients anascitic who became ascitic (P = .03). In patients treated with the association, there was a significantly larger decrease in hepatic venous pressure gradient (P = .05). It is concluded that patients treated with the association NAD plus I5M are not at increased risk of developing renal dysfunction or worsening of ascites compared with patients treated with NAD alone. Therefore, the presence of ascites should not be considered a contraindication to the use of this association in patients with cirrhosis and portal hypertension. (HEPATOLOGY 1995;22:808-813.)

The association of beta-blockers and vasodilators was shown to be superior to beta-blockers alone in decreasing portal pressure in cirrhosis[1-3] and in decreasing the number of patients who were nonresponders to treatment.[4] Therefore, it is under evaluation as a suitable option for improving the effectiveness of beta-blockers in the prevention of variceal bleeding.[5] Recently, Salmeron et al[6] observed impairment in renal water and sodium metabolism after acute administration of nitrates, and Vorobioff et al[2] reported that long-term administration of the association propranolol plus isosorbide-dinitrate for 1 or 2 months had detrimental effects on renal function, because it provoked increases in serum creatinine levels, and a tendency to develop ascites or to worsen preexisting ascites, which then required an increase in the dose of administered diuretics in more than half of the patients. Similar patients taking propranolol alone or receiving no treatment at all did not experience any change in renal function and ascites formation. However, these results have not been confirmed.

In December 1991, we started a multicenter randomized clinical trial comparing the beta-blocking agent nadolol (NAD) with the association NAD plus isosorbide-5-mononitrate (I5M) in the prophylaxis of first variceal bleeding in patients with cirrhosis and esophageal varices. Since December 1993, a large group of patients have been followed for at least 6 months, and a complete clinical and biochemical evaluation was planned after 6 months of treatment. We had the opportunity of analyzing possible deleterious effects of the association NAD plus I5M on renal function, and the

Abbreviations: NAD, nadolol; I5M, isosorbide-5-mononitrate; HVPG, hepatic venous pressure gradient.

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TABLE 1. Clinical Characteristics of the Two Treatment Groups

Characteristics	NAD	NAD + I5M
Age (yr)	58 ± 10	61 ± 7
Sex (M/F)	26/19	24/12
Etiology (alcoholic/nonalcoholic)	22/23	20/16
S-bilirubin (μmol/L)	32 ± 19	34 ± 19
S-albumin (g/L)	37 ± 9	35 ± 7
Prothrombin time (%)	63 ± 16	58 ± 12
Child-Pugh score	7.2 ± 1.9	7.9 ± 1.6
Administered dose of nadolol	71 ± 32 mg	69 ± 25 mg
Administered dose of isosorbide-5-mononitrate	—	34 ± 19 mg
Noncompliance	4	3

occurrence or worsening of ascites in patients with cirrhosis of various degrees of severity, and to compare these effects with those of a randomized group of patients treated with NAD alone.

PATIENTS AND METHODS

From December 1991 to June 1993, 96 patients with cirrhosis and esophageal varices were enrolled in a multicenter randomized clinical trial comparing NAD with NAD + I5M in the prophylaxis of first variceal bleeding. An interim analysis of the trial was reported as an abstract.[5] The protocol conformed with the guidelines of the Declaration of Helsinki and was approved by the competent Ethics Authorities. Inclusion criteria were as follows: (1) clinical diagnosis of cirrhosis of any cause; (2) age between 18 and 70 years; (3) presence of esophageal varices classified as F2 or F3 according to Beppu et al[7] or F1 with presence of red color signs; (4) consent to the study. Exclusion criteria were (1) previous variceal bleeding; (2) previous treatment with beta-blockers or sclerotherapy; (3) Child-Pugh score exceeding 11; (4) presence of tumors in any site; (5) inability to follow scheduled controls; (6) contraindications to beta-blockers or nitroderivatives.

The study was designed as a single-blind, multicenter randomized study, with stratification according to centers. Randomization was performed with opaque sealed envelopes prepared by the coordinating center. Patients were treated either with NAD alone, at a dose reducing resting heart rate by approximately 25% (40 to 160 mg/day in single daily administration), or with the association NAD + I5M. For this purpose, first NAD was given at increasing doses until a 25% decrease in heart rate was obtained, then I5M was added starting with 10 mg twice daily, and increased to 20 mg twice daily unless symptomatic hypotension (systolic blood pressure ≤85 mm Hg) or severe headache occurred. To ensure blindness of patients, patients treated with nadolol alone received a placebo tablet in addition. According to the randomization procedure, 50 patients were assigned to the NAD group, and 46 to the NAD + I5M group. Groups were comparable for all investigated characteristics (Table 1). Patients were followed at monthly intervals during the first 3 months, then every 3 months. Compliance was assessed by measuring heart rate and asking the patients how often they did not take the medication. Patients reporting a lack of assumption of treatment for more than 5% of prescribed pills, or showing lack of decrease in heart rate in more than one control, were considered noncompliant. After 6 months, a complete clinical and biochemical evaluation and an endoscopic examination were performed.

Of the 96 patients enrolled, 6 were lost to follow-up before the sixth month of treatment (after 1, 1, 2, 2, 3, 4 months of treatment, respectively); 2 died of causes unrelated to liver disease (one of myocardial infarction, one of car accident), 7 were withdrawn from treatment for different reasons (3 for variceal bleeding, 4 for side effects). Five patients with side effects related to I5M administration but without side effects related to NAD were switched to NAD treatment according to the protocol. Therefore, 81 patients were available for the evaluation of renal function after 6 months of treatment. End points divided according to the treatments are given in Table 2.

Because a sizeable cohort of patients have been currently followed for longer periods, the occurrence of the main end point (occurrence or worsening of ascites) was also evaluated as a cumulative percentage of patients free of the complication, using Kaplan-Meier curves,[8] which were compared by the log rank test.[9]

The course of portal hypertension was indirectly assessed from esophageal varices, which were classified at 6-month intervals according to the Beppu's classification.[7] In 5 and 6 patients treated with NAD and NAD + I5M, respectively, hepatic venous pressure gradient was measured after 1 month of chronic administration of the treatment, using hepatic vein catheterization, according to a procedure described elsewhere.[10]

Statistical Analysis. Data are given as mean ± SD. Differences in continuous variables were evaluated by two-way analysis of variance with repeated measurements. This allowed the simultaneous estimation of the effect of the treatments (F between treatments), of the 6 months of time of treatment (F within treatments), and possible differences in the effect of the 6 months of treatment between the two groups (F of the interaction term). Differences in frequencies were tested by corrected χ^2 and McNemar test,[11] when appli-

TABLE 2. End Points of Investigated Subjects Within 6 Months of Inclusion

End Point	Group: NAD	Group: NAD + I5M	
Died			
Of liver-related causes	0	0	
Of nonhepatic causes	1	1	
Withdrawn from treatment			
For variceal bleeding	2	1	
For side effects related to beta-blockers	3	1	
For side effects related to nitrates	0	5	(switched to NAD)
Lost to follow-up	4	2	
Total patients with end point within 6 months	10	10	(including 5 switched)
Randomized	50	46	
Patients with data available	40	41	
Switched to NAD	+5	−5	
Actually treated with the treatment	45	36	

NOTE. Treatment received: comparison of 45 vs. 36 patients. Intention to treat: comparison of 40 patients of group N vs. 41 patients of group N + I.

TABLE 3. Variations in Heart Rate and Mean Arterial Pressure in the Two Treatment Groups

Group	NAD	NAD + I5M
Heart rate before treatment	79 ± 9	80 ± 7
Heart rate after 6 months	58 ± 5	61 ± 7
Between treatment groups: $F = 2.12$; $P = .15$		
Within treatment groups: $F = 431$; $P < .0001$		
Interaction term: $F = 0.76$; $P = .39$		
Mean arterial pressure before treatment	99 ± 10	101 ± 10
Mean arterial pressure after 6 months	94 ± 11	94 ± 9
Between treatment groups: $F = 0.18$; $P = .68$		
Within treatment groups: $F = 35.36$; $P < .0001$		
Interaction term: $F = 1.17$; $P = .28$		

cable. P values less than .05 were considered significant. Statistical analysis was carried out using the BMDP statistical package (programs 2V and 4F).[12]

Because the main objective of the study was searching for a possible deleterious effect of the association NAD + I5M on renal function, the principal analysis was performed according to the treatments received by the patients. In a second phase, because a comparison of treatment strategies was also considered of value, analysis was also performed according to the intention-to-treat principle.

RESULTS

Significant decreases in heart rate and in mean arterial pressure after 6 months of treatment were observed in both groups, without differences among them (Table 3). Mean arterial pressure decreased by a mean of 4.6 ± 10.1% in patients treated with NAD, and by a mean of 5.2 ± 13.8% in patients treated with NAD + I5M. No significant change in s-creatinine or s-urea was observed after 6 months in any group (Figs. 1 and 2). In particular, marked increase in s-creatinine was only observed in one patient of each group, and marked increase in s-urea was observed in two patients treated with NAD and one treated with NAD + I5M.

Ascites occurrence and severity were not different between the two groups at the time of inclusion, or at 6 months of treatment, as described in Table 4. In particular, three and two patients developed ascites in the NAD and NAD + I5M groups, respectively, and a need of increasing the diuretic regimen was observed in four and three patients, respectively. Conversely, a decrease in diuretic regimen was reported in five patients treated with NAD and 10 patients treated with the association. Considering the individual patients in the NAD group, of the 14 patients who had ascites at the time of inclusion, 6 were anascitic after 6 months of treatment, and of the 31 patients without ascites at inclusion, 3 had ascites after 6 months (McNemar test: = 1.00; $P = .32$); at variance, in the NAD + I5M group, of the 17 patients with ascites at inclusion, 9 became anascitic after 6 months of treatment, and of the 19 patients without ascites at inclusion, only 2 had ascites at 6 months (McNemar test = 4.46; $P = .03$). This implies that only in the NAD + I5M group were there significantly more patients ascitic who became anascitic than patients anascitic who became ascitic.

According to Kaplan-Meier plot and Mantel-Cox test, the probability of being free of ascites (if nonascitic at inclusion) or of worsening of ascites (if ascitic at inclusion) was nearly identical in patients treated with NAD or NAD + I5M (log rank test = 0.006; $P = .94$; Fig. 3).

Of the seven patients (three in the NAD group and four in the NAD + I5M group) who after 6 months had abnormal values of s-creatinine, 2 (29%) had developed important hypotension, and the remainder had no decrease in mean arterial pressure or a decrease around the mean value of the whole group. Similarly, of the four patients who had abnormal values of s-urea after 6 months of treatment, one (25%) had developed im-

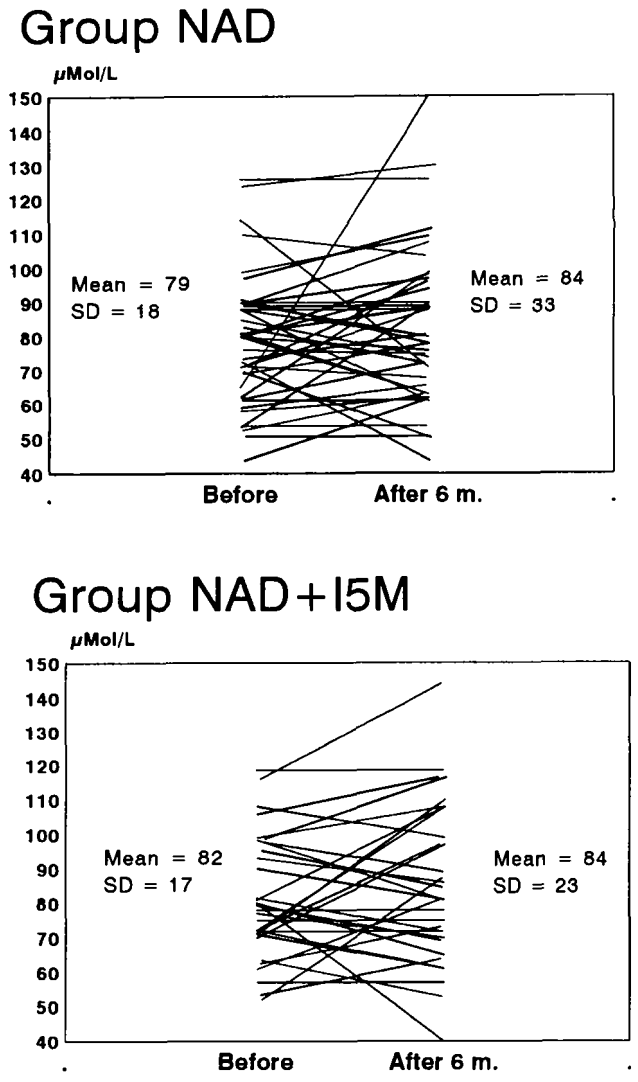

FIG. 1. Variations in s-creatinine in patients receiving nadolol (NAD) or nadolol plus isosorbide-5-mononitrate (NAD + I5M). No significant difference among treatments ($F = .12$; $P = .72$) or among times ($F = 1.14$; $P = .28$). No significant interaction effect ($F = .14$; $P = .71$).

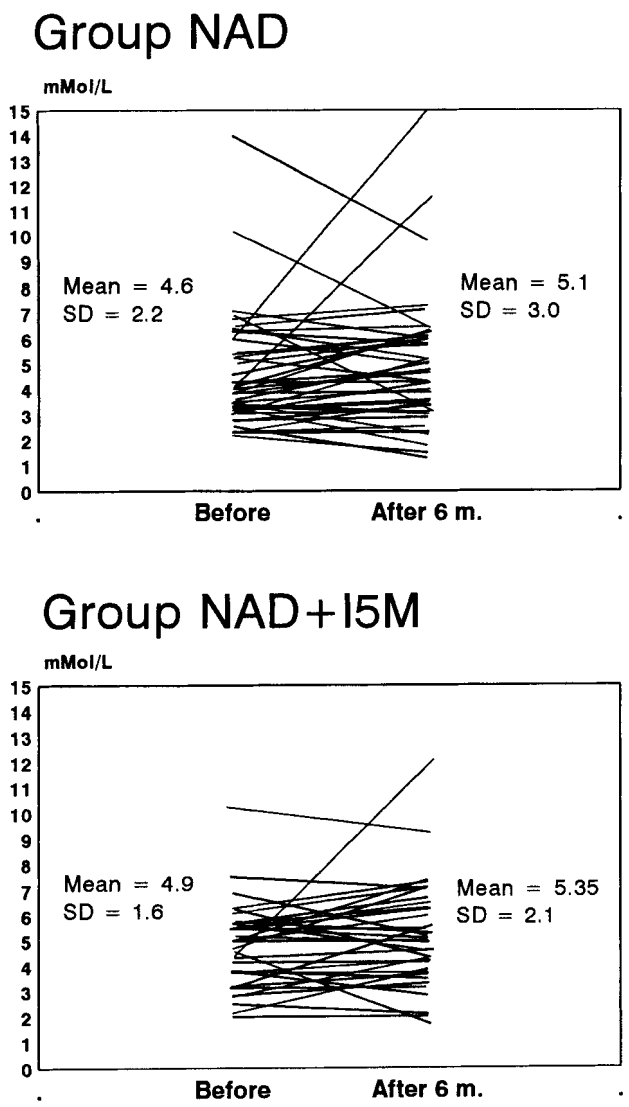

FIG. 2. Variations in s-urea in patients receiving nadolol (NAD) or nadolol plus isosorbide-5-mononitrate (NAD + I5M). No significant difference among treatments ($F = .28$; $P = .60$) or among times ($F = 3.35$; $P = .07$). No significant interaction effect ($F = .01$; $P = .98$).

portant hypotension. A significant inverse correlation was found between changes in s-creatinine and changes in mean arterial pressure ($r = -.27$; $P = .015$) (Fig. 4), whereas the correlation between changes in s-urea and in mean arterial pressure was not significant ($r = -.20$; $P = .075$).

Results did not change when analysis was performed according to the intention-to-treat principle.

In patients treated with NAD, esophageal varices' size decreased in 11 (24%), remained unchanged in 33 (73%), and increased in 1 (2%). In patients treated with NAD + I5M, esophageal varices' size decreased in 11 (31%), remained unchanged in 24 (66%), and worsened in 1 (3%) ($\chi^2 = 0.42$; $P = .80$). Hepatic venous pressure gradient in the five patients treated with NAD decreased from 20.2 ± 5.8 to 17.0 ± 4.2 mm Hg (mean decrease = 15%), and in the six treated with NAD + I5M from 20.3 ± 3.5 to 14.3 ± 1.9 mm Hg (mean decrease = 30%). According to the analysis of variance, there was no difference in baseline values (between-factor $F = 0.50$; $P = .49$), but both treatments were effective in decreasing hepatic venous pressure gradient (HVPG) (within-factor $F = 37.3$; $P = .0002$). The interaction term, which assesses the difference of the effects of the two treatments, was also significant ($F = 4.86$; $P = .05$), indicating that the association was more effective in decreasing HVPG than NAD alone. Comparison of percent variations showed a significantly larger decrease in HVPG in patients treated with NAD + I5M compared with those treated with NAD alone ($t = 2.42$; $P = .04$). Three of five patients treated with NAD, but none of the six patients treated

TABLE 4. Changes in Ascites (A) Characteristics During Follow-up of Patients Treated With Nadolol (NAD) or Nadolol Plus Isosorbide-5-Mononitrate (NAD + I5M)

Characteristics	Group NAD (n = 45)		Group NAD + I5M (n = 36)		P*
	No.	%	No.	%	
Presence of A at inclusion	14	31	17	47	.21
With A at 6 months	8	18	8	22	.84
With transient A	4	9	1	3	.22
Absence of A at inclusion	31	69	19	53	.21
With A at 6 months	3	7	2	6	.70
With transient A	1	2	0	0	.80
Requiring increase in diuretics	4	9	3	8	.76
Requiring decrease in diuretics	5	11	10	28	.10

* P according to Yeates-corrected χ^2.

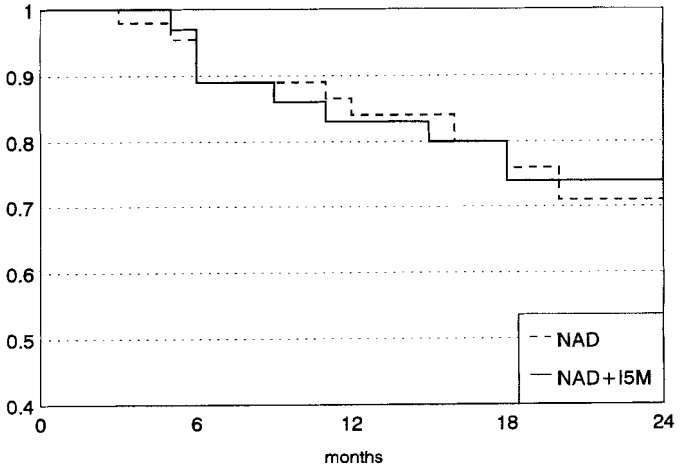

FIG. 3. Cumulative probability of being free of ascites (if nonascitic at inclusion) or of needing increase in diuretic administration (if ascitic at inclusion) in patients receiving nadolol (NAD) or the association nadolol plus isosorbide-5-mononitrate (NAD + I5M). No significant difference according to log rank test ($P = .94$).

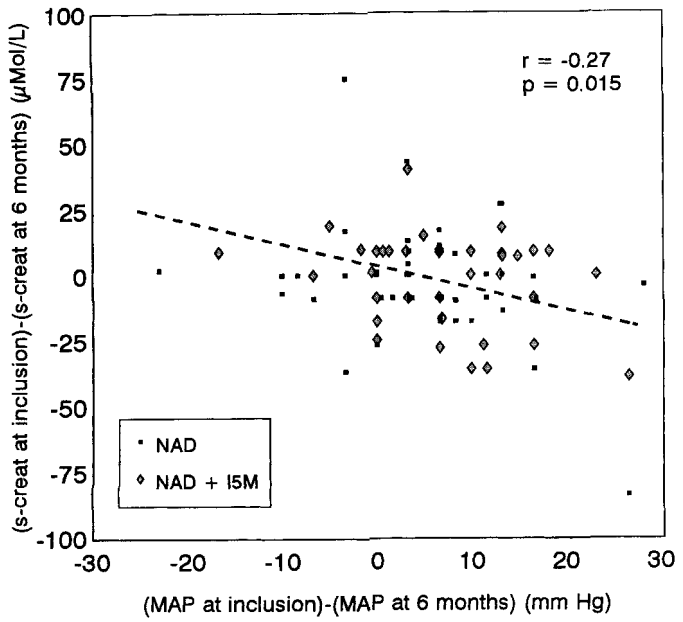

FIG. 4. Significant correlation between changes in s-creatinine and changes in mean arterial pressure (MAP) after 6 months of treatment.

with NAD + I5M, showed a decrease in HVPG lower than 20% (Fig. 5).

DISCUSSION

The main result of the current study is that cirrhotic patients treated with NAD + I5M are not exposed to an increased risk of renal failure or of development or worsening of ascites compared with patients treated with NAD alone; in fact, patients treated with the association showed a very similar trend, or, to a limited extent, had a tendency to a better sodium homeostasis.

The association beta-blockers plus nitrates was shown to be hemodynamically superior to beta-blockers alone in decreasing portal pressure,[1-3] and in reducing the rate of nonresponse to treatment according to hemodynamic criteria.[4] For these reasons, this association is under evaluation as a prophylactic treatment of patients with esophageal varices.[5]

A detrimental effect of nitrates on renal function and sodium homeostasis in cirrhotics was first suggested by Salmeròn et al,[6] who studied the acute effect of I5M administration. However, in the first study on the long-term hemodynamic effect of the association beta-blockers plus nitrates, Garcia-Pagan[4] was unable to document any change in renal function after 3 months of treatment. Recently, in a long-term study of 28 patients chronically treated with propranolol plus isosorbide dinitrate and 16 patients treated with propranolol alone or without any treatment, Vorobioff et al[2] observed that the association provoked a significant (although not clinically relevant) increase in s-creatinine, and a marked increase in the risk of developing ascites or of worsening a preexisting ascites, whereas the treatment with propranolol alone or the lack of treatment was not associated with any of these alterations, and suggested that ascitic patients should be considered unsuitable for treatment with the association beta-blockers plus nitrates.

The current report supplies different results, because s-creatinine and s-urea remained unchanged and within the normal range in almost all subjects for the 6-month period of the study, and patients treated with the association did not experience a worsening of their sodium homeostasis; in fact, only in this group of patients was there a significant trend of ascitic patients to become anascitic, and a marginally larger decrease in the use of diuretics was observed. Differences in the study subjects and in the duration of treatments may have contributed to this discrepancy. Difference in the drugs administered may also have played an important role, because nadolol, at variance of propranolol, was shown to increase or at least not decrease renal perfusion, possibly because of a dopaminergic effect.[13-15] I5M may also be less hypotensive than isosorbide dinitrate because of its long-lasting effect and the lack of abrupt decrease in arterial pressure, which characterizes the effect of isosorbide-dinitrate in portal hypertension.[16,17] An additional factor may explain the difference in results. It was stressed in a recent editorial by Henriksen and Ring-Larsen[18] that development of hypotension may be dangerous for patients with advanced cirrhosis, because their renal perfusion pressure may be insufficient to keep blood flow autoregulated.[19-21] Indeed, in the Vorobioff et al's study,[2] patients treated with the association experienced a decrease in mean arterial pressure, averaging 14 mm Hg. On the contrary, in the current series, mean decrease in mean arterial pressure was lower, and the decrease induced by the association was marginally larger than that induced by NAD alone. The observation that there was a significant correlation between decrease in mean arterial pressure

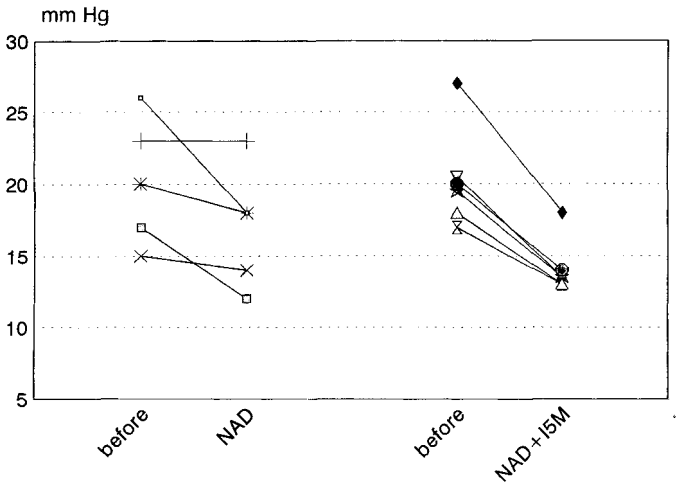

FIG. 5. Individual values of hepatic venous pressure gradient in 5 patients chronically treated with nadolol (mean decrease = 15%), and in 6 patients chronically treated with the association nadolol plus isosorbide-5-mononitrate (mean decrease = 30%) (P = .04).

and increase in s-creatinine in the whole series, irrespective of the treatment received, emphasizes the role of hypotension in impairing renal function. However, the fact that these effects occurred with the same frequency in patients who received NAD or NAD + I5M suggests that great attention should be paid to renal function if a patient develops hypotension, whatever the treatment regimen administered. For this reason, the association NAD + I5M seems particularly interesting among the possible associations of beta-blockers and nitroderivatives, because it provokes only a minor decrease in arterial blood pressure.

The current report offers a clue of a possible beneficial effect of the association on sodium homeostasis, because in the group treated with NAD + I5M we observed that it was more likely that patients with ascites became anascitic during treatment than patients anascitic became ascitic, whereas the same trend was not apparent in patients treated with NAD alone. In addition, there was a trend to a larger number of patients treated with the association who requested decrease in diuretic regimen compared with patients treated with NAD alone. These effects cannot be clearly explained on the basis of available evidence, but the fact that this observation is derived from a randomized study stresses its value. The larger decrease in portal pressure reported in subjects treated with the association[1-3] might be, at least in part, responsible for this effect. In the current series, a significantly larger effect of the association in decreasing HVPG was apparent, mean percent decrease in patients treated with the association being twice that of patients treated with NAD alone. In addition, only in the group of patients treated with NAD alone were there subjects who should be classified as nonresponders according to hemodynamic parameters. Also, the endoscopic evaluation showed a trend to a more favorable course of esophageal varices in patients treated with the association, although the difference did not reach statistical significance.

In conclusion, patients with cirrhosis and esophageal varices without end-stage liver disease treated with the association NAD + I5M are not at increased risk of developing renal dysfunction or worsening of ascites than patients treated with NAD alone. Therefore, the presence of ascites should not be considered a contraindication to the use of this association in these subjects.

Addendum: While the paper was under editorial process, a paper appeared that showed a lack of deleterious effects on renal function or ascites in patients treated with propranolol plus I5M compared with matched historical groups treated with propranolol or sclerotherapy.[22] Results are in agreement with ours. At variance with the current report, in that study patients were treated for prevention of variceal rebleeding, and ascites was present at inclusion in 60% of the patients.

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