Interest of the association clonidine-spironolactone in cirrhotic patients with ascites and activation of sympathetic nervous system

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Abstract

Background : **The aim of this study was to examine the effects of spironolactone, clonidine and the association of clonidine-spironolactone on renin-aldosterone and sympathetic systems, renal function, systemic hemodynamics and mobilization of ascites in 32 alcoholic cirrhotic patients with marked increase in sympathetic system.**

Methods : **Measurements were taken before and after an 8-day treatment with spironolactone (200 mg/day), after an 8-day treatment with clonidine (0.150 mg/day) and 10 days after adjunction of spironolactone (200 mg/day) to clonidine.**

Results : **Three patients abandoned the treatment or were excluded because lack of compliance. Spironolactone alone induced an increase in renin-aldosterone and sympathetic systems without any remarkable increase of natriuresis and body weight loss. Given for 8 days, clonidine alone induced a significant decrease in plasma norepinephrine associated with a significant increase in glomerular filtration rate without effect on natriuresis. In contrast, 10 days after adjunction of spironolactone to clonidine, plasma renin and aldosterone significantly decreased, natriuresis increased (from 7.4 ± 0.7 to 41.6 ± 3.2 mEq/24h) and body weight decreased (from 66.03 ± 2.3 to 63.5 ± 2.3 kg) without adverse effects.**

Conclusion : **In cirrhotic patients with ascites and marked activation of sympathetic nervous system, spironolactone (200 mg/day) is unable to mobilize ascites. In these patients, after 8 days, clonidine decreases sympathetic activity, increases glomerular filtration rate and after 18 days, decreases plasma renin and aldosterone concentrations allowing a better action of spironolactone. The association clonidine-spironolactone enhances natriuresis and body weight loss.** (Acta gastroenterol. belg., **2002**, 65, **1-5**).

Key words : norepinephrine, renin, aldosterone, glomerular filtration rate, ascites, clonidine, spironolactone.

Introduction

Ascites is one of the most frequent complications of cirrhosis. The appearance of ascites is the final consequence of a profound disturbance in systemic, splanchnic and hormonal function (1). The alterations in renal function consist in a decreased ability to excrete sodium and in a reduction of renal blood flow and glomerular filtration rate (2). The mechanisms of sodium retention and of functional renal failure are not yet fully understood : several studies have shown that peripheral arterial vasodilatation associated with portal hypertension may induce a reduction in effective blood volume and subsequently a permanent activation of antinatriuretic systems and of endogenous vasoconstrictive mechanisms (renin-aldosterone and sympathetic systems, vasopressin secretion (3)). The activated sympathetic nervous system stimulates renal α_2-adrenoreceptors and causes arterial vasoconstriction leading to a decrease in renal blood flow and glomerular filtration rate (4). Moreover, norepinephrine, induces an increase in reabsorption of sodium particularly in renal proximal tubules and enhances also renin, aldosterone and vasopressin secretion (5). Thus, the sympathetic nervous system contributes to renal hypoperfusion and sodium retention. We have recently shown that the degree of activation of renin-aldosteron and sympathetic systems influences diuretic response of ascites and patients with activation of the sympathetic response required high doses of diuretics (6). Consequently, sympathetic activity inhibition should improve renal function, decrease sodium retention and allow an easier action of diuretics in cirrhotic patients with ascites and hyperactivation of sympathetic system.

Clonidine, a centrally acting α_2-agonist, has been shown to have sympatholytic activity in patients with arterial hypertension or cirrhosis (7-10). In 4 patients with refractory ascites, we have shown that the association clonidine-spironolactone induced an increase in natriuresis and body weight loss (11).

The aim of this study was to examine the effects of spironolactone, clonidine and the association of clonidine-spironolactone on renin-aldosterone and sympathetic systems, renal function, systemic hemodynamics and mobilization of ascites in alcoholic cirrhotic patients with ascites.

Patients and methods

This study was approved by the Investigation and Ethics committee of the Centre Hospitalier Universitaire de Charleroi (Charleroi, Belgium). All patients gave informed consent before entering the study.

From March 97 to October 99, sixty-two alcoholic cirrhotic patients hospitalized for ascites were investigated. Thirty-two patients with an increase in sympathetic nervous activity (plasma norepinephrine > 300 pg/mL) were included in the study. Diagnosis of cirrhosis was based on liver histology in 16 patients and on clinical, laboratory and ultrasonographic data in the

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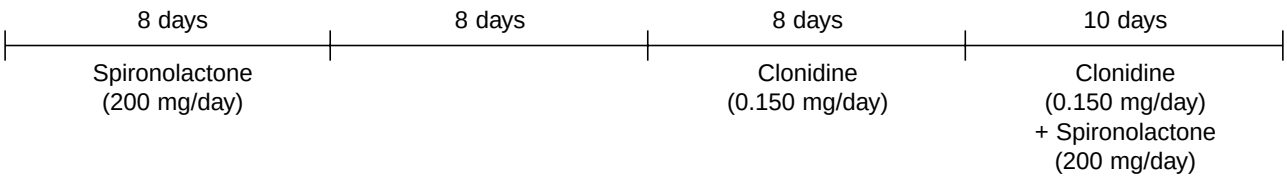

Fig. 1. — Design of the study

Table I. — **Characteristics of the 29 patients**

Age (y)	52.9 ± 1.7*
Sex (male/female)	19/10
Serum bilirubin (mg/dl)	1.8 ± 0.1
Serum albumin (g/L)	29 ± 0.3
Prothrombin time (%)	54 ± 0.1
Pugh's score	9 ± 0.3

*Mean ± SEM.

remaining 16 patients. Severity of cirrhosis was assessed according Pugh's classification (12). Ascites was present at clinical examination and confirmed by U.S. All patients stopped drinking alcohol for at least 2 weeks before entering the study. None of the patients had hepatic encephalopathy, gastrointestinal bleeding, bacterial infection, alcoholic hepatitis, hepatorenal syndrome or hepatocellular carcinoma. Patients were not included if they had severe condition as diabetes mellitus, chronic obstructive lung disease, ischemic cardiomyopathy or arterial hypertension. None of the patients was given vasoactive drugs or diuretics or underwent paracentesis. The main clinical characteristics and laboratory data of the patients are shown in table I.

During the study, patients were investigated in hospital. After 7 days on a 40 mEq sodium diet the 32 patients were treated during 8 days by spironolactone (200 mg daily, orally). Thereafter, spironolactone was stopped for 8 days. The 3rd week, the 32 patients were given clonidine (0.075 mg twice daily, orally). On the 25th day and for 10 days, the 32 cirrhotics received clonidine (0.075 mg twice daily, orally (Fig. 1)) associated with spironolactone (200 mg daily, orally). Hemodynamic parameters and hormonal measurements were performed under basal conditions, after an 8-day period of spironolactone administration, after an 8-day period of clonidine administration and after a 10-day period of combined treatment.

Mean arterial pressure (MAP) was calculated according to the formula MAP (mmHg) = (systolic + diastolic X 2) / 3. Heart rate was derived from continuous electrocardiographic monitoring.

After the patients had been lying down for at least 2 hours, blood samples were taken for measuring plasma concentrations of renin, aldosterone and norepinephrine. The samples were collected under ice in potassium ethylene-dramine-tetraacetate (EDTA) tubes, centrifuged at 4° C and the plasma was frozen at -30°C until assay.

Glomerular filtration rate was measured under basal condition, after an 8-day administration of spironolactone and after a 8-day administration of clonidine.

For 1 week and during the study, body weight and urine volume were measured daily. Urinary sodium excretion, blood urea nitrogen and serum concentrations of creatinine, sodium and potassium were determined every 3 days.

Laboratory measurements

Plasma renin concentrations were measured by a monoclonal antibody specific for human active renin (13). Normal values range from 7 to 76 µU/mL. The intra-assay coefficient of variation was 5.3% at 34 µU/mL and 2.7% at 29 µU/mL. Plasma aldosterone concentrations were measured using a radioimmunoassay method (14). Normal aldosterone levels range from 30 to 100 pg/mL. The intra-assay coefficient of variation was 6% at 221 pg/mL. Plasma norepinephrine concentrations were measured with high-performance liquid chromatography with electrochemical detection (15). Normal plasma norepinephrine levels range from 185 to 275 pg/mL. The intra-assay coefficient of variation was 4.3% at 1700 pg/mL. Oncotic pressure was measured by an oncometer BMT 912 (BMT Messtechnik CMBII, Berlin). Glomerular filtration rate was determined by chrome (51) clearance using methods previously described (16-17).

Statistical analysis

Results were expressed as mean ± SEM. Statistical comparisons were made using the non parametric Friedman chi^2 and Wilcoxon tests.

Results

Three patients abandoned the treatment just after the beginning of the investigations or were excluded because lack of compliance. Therefore, the present study included 29 patients.

The effects of spironolactone, clonidine and the association of clonidine-spironolactone on renin-aldosterone and sympathetic nervous systems are shown in table II. After 8 days, spironolactone induced a significant increase in plasma renin, aldosterone and norepinephrine concentrations. Given for 8 days, clonidine alone induced a significant decrease in plasma norepinephrine concentrations, which was maintained after adjunction

Table II. — **Effects of spironolactone (S), clonidine (C) and the association clonidine-spironolactone (C+S) on plasma norepinephrine, renin and aldosterone, glomerular filtration rate (GFR), systemic hemodynamics, plasma and urinary compositions and body weight**

	Baseline values	S	C	C + S	Friedman corrected chi^2
Norepinephrine (pg/mL)	856.4 ± 81.1	1050.3 ± 78.9[a]	499.8 ± 59.4[a]	437.3 ± 62.4[a]	$<10^{-4}$
Renin (µU/mL)	520.3 ± 68.8	673.5 ± 73.1[a]	776.4 ± 75.4[a]	312.3 ± 3.8[a]	$<10^{-4}$
Aldosterone (pg/mL)	826 ± 100	911 ± 106[a]	1033 ± 102[a]	433.2 ± 68.1[a]	$<10^{-4}$
GFR (mL/min)	61.1 ± 2.9	62.0 ± 3.1	75.4 ± 2.9[a]	–	$<10^{-4}$
Mean arterial pressure (mmHg)	101 ± 0.6	100 ± 0.6	92 ± 0.6[a]	103 ± 2.4	$<10^{-4}$
Heart rate (pulse/min)	87 ± 1.8	88 ± 2.7	78 ± 0.9[a]	88.5 ± 0.9	$<10^{-4}$
BUN (mg/dL)	26.8 ± 1.7	28.5 ± 2	29 ± 2	28.1 ± 2	N.S.
Serum creatinine (mg/L)	1	1	1	1	N.S.
Serum sodium (mEq/L)	129.4 ± 0.6	129.8 ± 0.5	131.7 ± 0.6	132 ± 0.5[a]	$<10^{-4}$
Serum potassium (mEq/L)	4.1 ± 0.07	4.3 ± 0.6	4 ± 0.05	4 ± 0.06	N.S.
Oncotic pressure (mm Hg)	19.2 ± 0.5	18.6 ± 0.4	19 ± 0.4	18.9 ± 0.5	N.S.
Urine volume (mL/24h)	412.5 ± 18	467.4 ± 17.2	484 ± 15[a]	800.5 ± 27.1[a,b]	$<10^{-4}$
UNaV (mEq/24h)	7.4 ± 0.7	16.1 ± 1.4[a]	8.2 ± 0.8	41.6 ± 3.2[a,b]	$<10^{-4}$
Body weight (kg)	66.03 ± 2.3	65.8 ± 2.3	66.2 ± 2.3	63.5 ± 2.3[a,b]	$<10^{-4}$

Means ± SEM
[a] Significantly different from baseline values ($p \leq 0.01$)
[b] Significantly different from the results obtained with spironolactone alone ($p \leq 0.01$)
BUN, blood urea nitrogen ; UNaV, urinary sodium excretion
N.S., no statistical significance.

of spironolactone. In addition, clonidine provoked a significant increase in plasma renin and aldosterone concentrations. However, 10 days of combined treatment resulted in a decrease of these circulating levels, reaching lower values than the baseline ones.

The effects of spironolactone, clonidine and the association of clonidine-spironolactone on glomerular filtration rate and systemic hemodynamics are shown in table II. After a 8-day period of administration of spironolactone, glomerular filtration rate and systemic hemodynamics were unchanged. Clonidine administration alone induced a significant increase in glomerular filtration rate and a significant decreases in mean arterial pressure and heart rate. After 10 days of combined treatment, these two parameters returned to baseline values.

The effects of spironolactone, clonidine and the association of clonidine-spironolactone on body weight, urinary and plasma compositions are shown in table II. After 8 days, spironolactone alone did not induce remarkable natriuresis (from 7.4 ± 0.7 to 16.1 ± 1.4 mEq/24h) or decrease in body weight (from 66 ± 2.3 to 65.8 ± 2.3 kg). After 8 days, clonidine alone induced a significant increase in diuresis but had no effect on natriuresis or body weight. Ten days after adjunction of spironolactone, natriuresis had significantly increased (from 7.4 ± 0.7 to 41.6 ± 3.2 mEq/24h) resulting in body weight reduction in all patients. The mean body weight decrease was 2.3 kg. Plasma compositions were unchanged except for a significant increase in natremia.

No adverse effect like hepatic encephalopathy, hyponatremia, hyperkaliemia, hypokaliemia or symptomatic orthostatic hypotension were observed.

Discussion

In the present study, all patients had advanced liver failure with ascites and increased sympathetic activity as indicated by elevated plasma norepinephrine concentrations associated with a decreased glomerular filtration rate and a low urinary sodium excretion. In these patients, 200 mg per day of spironolactone was unable to increase natriuresis and body weight loss.

The results show that clonidine alone induced a prolonged sympathetic-inhibition as indicated by the decrease in plasma norepinephrine concentrations and resulting in an increase in the initially decreased glomerular filtration rate. Esler *et al*. (9) have shown that clonidine induced reduction in renal norepinephrine concentration associated with a fall in renal vascular resistance. The fact that glomerular filtration rate increases after clonidine administration despite a concomitant fall in mean arterial pressure means that the decrease in renal vascular resistance results from preferential decrease in afferent arteriolar tone. These findings support the concept that the increased renal vascular resistance and the impaired glomerular filtration rate observed in patients with cirrhosis are a consequence of arteriolar vasoconstriction due to activated sympathetic nervous system. In addition, several studies in patients with arterial hypertension have shown that clonidine promoted the release of prostaglandins by the kidney (18). This mechanism could play a role in the increase of glomerular filtration rate induced by clonidine administration because prostaglandins act as local vasodilatator hormones of the kidney (19).

The effects of clonidine on systemic hemodynamics and on renin-aldosterone system were divided in two phases. In the first phase, after 8 days, clonidine alone induced a decrease in heart rate and mean arterial pressure as previously reported. Arterial pressure decreased due to a reduction in cardiac output (7), not compensated by reflex vasoconstriction. The decrease in arterial pressure worsened the vascular underfilling and induced an increase in plasma renin and aldosterone concentrations. During this phase, clonidine did not increase natriuresis despite an increase in glomerular filtration rate probably because it mainly induced an inhibition of sodium reabsorption in proximal tubules (4). Consequently, endogenous antinatriuretics, such as aldosterone, induce distal reabsorption of sodium and conceal natriuretic effect of clonidine. During this phase, clonidine treatment resulted in increase in diuresis. This aquaretic effect, already observed in previous studies, was due to a reduction of the antidiuretic action of vasopressin (20-22).

During the second phase, after an 18-day treatment by clonidine and 10 days after adjunction of spironolactone, arterial pressure and heart rate returned to baseline. The reason why clonidine did not induce chronic hemodynamic modifications are not explained. Roulot *et al*. (10) have shown the same results and have shown that clonidine pharmacokinetics were similar in cirrhotic patients and in normal subjects. Our findings suggest that compensatory mechanisms may protect cirrhotic patients against the arteriolar hypotensive effect of prolonged sympathetic withdrawal.

During this second phase, plasma renin and aldosterone concentrations were decreased and remained significantly lower as compared with baseline values. Spironolactone, a competitive antagonist of aldosterone cannot explain by itself these modifications ; indeed, other studies (23-25) and our results have shown that spironolactone leading to a decrease in effective blood volume, induces an increase in plasma renin and aldosterone concentrations. The reduction in plasma renin and aldosterone concentrations after a prolonged combined treatment by clonidine and spironolactone was probably the result of an inhibition of their secretions by clonidine after 18 days. Indeed, studies in patients with arterial hypertension have shown that clonidine depressed renin secretion in renal juxta-glomerular apparatus (26, 27). The decrease in plasma aldosterone is linked to the decrease in renin but could also be due to a direct sympathetic-inhibition of the adrenal glands or of ACTH secretion (28, 29). By decreasing the activity of the renin-aldosterone axis, clonidine increases the effectiveness of spironolactone (23). Indeed, by decreasing proximal reabsorption of sodium, clonidine increases the delivery of sodium to the distal nephron, therefore improving the distal natriuretic effect of spironolactone. Finally, the association of clonidine-spironolactone resulted in body weight loss and mobilization of ascites without adverse effects. These results must be confirmed by controlled studies.

Conclusion

In cirrhotic patients with ascites, spironolactone (200 mg/day) is frequently unable to mobilize ascites, when the sympathetic nervous system is severely activated. In these patients with resistance to spironolactone, clonidine appears to be a very promising therapy when used in combination with spironolactone. In our study, the association clonidine-spironolactone was able to induce natriuresis and body weight loss in all patients without side effects. Accordingly, this therapeutic association, important from a practical viewpoint, warrants further controlled studies.

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