Nephrol Dial Transplant (2005) 20: 1623–1629
doi:10.1093/ndt/gfh871
Advance Access publication 10 May 2005

Original Article

Nephrology Dialysis Transplantation

Renal effects of treatment with diuretics, octreotide or both, in non-azotemic cirrhotic patients with ascites

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Abstract

Background. Diuretic-induced hyperreninaemia is associated with renal dysfunction in cirrhotic patients with ascites, and in turn prevents the use of high doses of diuretics. Furthermore, ample evidence suggests that octreotide can inhibit the activation of the renin–aldosterone axis. The present study investigated the renal effects of the addition of octreotide to furosemide and spironolactone in the treatment of non-azotemic cirrhotic patients with ascites.

Methods. We studied 20 patients treated with furosemide and spironolactone. Of them, 10 (Group 1) discontinued diuretic treatment for 7 days. Thereafter, for 5 days each patient received subcutaneous octreotide 300 μg b.i.d., in 10 patients (Group 2) in addition to their usual diuretics. We collected data on the patients while they received diuretics (both groups), after discontinuation of diuretics (Group 1), and after octreotide administration (both groups).

Results. We observed a trend to increase creatinine clearance and a significant reduction in plasma active renin and plasma aldosterone after the discontinuation of diuretics. The subsequent introduction of octreotide reduced glomerular filtration rate, although it significantly decreased plasma active renin and plasma aldosterone. In contrast, the addition of octreotide to diuretic treatment significantly increased glomerular filtration rate, urine volume and sodium excretion. The magnitudes of the decreases in plasma-active renin and aldosterone produced by the combination of octreotide and diuretics were similar to those produced by octreotide alone or by the discontinuation of diuretics.

Conclusions. Octreotide alone does not improve renal function in cirrhotic patients with ascites. On the contrary, adding it to diuretic treatment increases glomerular filtration rate and sodium and water excretion, mainly through the suppression of an activated renin–aldosterone axis.

Keywords: ascites; cirrhosis; diuretic treatment; octreotide; renal function

Introduction

Dietary sodium restriction and a dual-diuretic regimen with furosemide and spironolactone have been shown to be effective in the management of ascites in the majority of cirrhotic patients with ascites [1]. In addition, diuretic-related plasma volume depletion has been associated with the amelioration of the hyperdynamic circulation in cirrhosis [2,3]. However, 10–20% of patients with ascites either do not respond to diuretic therapy or develop diuretic-induced complications, which prevent the use of high doses of these drugs [1]. Renal impairment, a common complication of diuretic therapy, is most often attributable to volume depletion [4,5], and it is usually reversible after diuretic withdrawal [4]. Indeed, a diuretic-induced decrease in plasma volume stimulates the release of renin and aldosterone [3,5], and the increase in circulating angiotensin II (AT II) that follows impairs renal perfusion [5], preventing the efficient transport of diuretics to their sites of action. In addition, AT II has a direct sodium-retaining effect due to the presence in the proximal tubule of a large number of AT II receptors that are much more sensitive to AT II than the receptors in the renal efferent arterioles [6]. Plasma volume depletion also mediates the activation of other neurohumoral systems, such as the sympathetic nervous system (SNS) and antidiuretic hormone (ADH), which produce renal vasoconstriction and increased reabsorption of sodium and water [1].

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On the other hand, the administration of the long acting somatostatin analogue, octreotide, has been associated with splanchnic vasoconstriction [7], mainly through the inhibition of glucagon release [8]. In addition, somatostatin and octreotide have been reported to inhibit the release of renin and aldosterone in cirrhosis through a direct effect on specific somatostatin-binding sites in renin-producing cells [9,10] and adrenal zona glomerulosa cells [11,12]. Rosenthal *et al.* [13] suggest that in man the inhibition of furosemide-induced hyperreninaemia by somatostatin possibly involves a decrease in cyclic adenosine 3′,5′-monophosphate levels, which mediates the secretion of renin. Somatostatin also significantly checks the increase in plasma renin activity following β-adrenergic stimulation in healthy volunteers [14] or in patients with renovascular hypertension [15]. Similarly, octreotide attenuates the increase of plasma renin activity induced by tilting the head up [16]. In addition, the aldosterone release stimulated by AT II is decreased by the administration of somatostatin [11,17] or octreotide [12]. Decreases in renin and aldosterone levels were demonstrated after octreotide administration in rats with portal hypertension [18] and in cirrhotic patients [19,20], suggesting that octreotide may regulate AT II and aldosterone secretion in patients with cirrhosis.

On the basis of the above observations, we undertook the present study to evaluate the renal effects of the addition of octreotide to diuretic treatment with furosemide and spironolactone in non-azotemic cirrhotic patients with ascites.

Subjects and methods

Patients and study design

We studied 20 patients with cirrhosis and ascites who were admitted consecutively in our department. The study was performed with the subjects' written consent and in compliance with the declaration of Helsinki and the approval of the local Ethical Committee. The diagnosis of cirrhosis was histologically proven in nine patients; in the others it was based on clinical, laboratory and ultrasonographic findings. The presence of ascites was confirmed by ultrasonography or paracentesis. At the inception of the study, all patients were clinically stable, and all were being treated with varying doses of both furosemide and spironolactone. The doses of the diuretics had been the same for at least 1 month prior to their inclusion in the study. The patients were taking the diuretic pills at exactly the same times each day (8:00 am and 8:00 pm) during the 10 days prior to entering the study and during it.

The inclusion criteria were: (i) absence of gastrointestinal bleeding, hepatic encephalopathy or infection in the 2 weeks preceding the study or during it; (ii) absence of refractory ascites or of hepatorenal syndrome, according to the criteria recently proposed [21]; (iii) no treatment with other drugs (other than diuretics) known to affect systemic and renal haemodynamics or renal function, within the 5 days before inclusion; (iv) absence of diabetes, organic nephropathy, cardiopathy, arterial hypertension; (v) absence of hepatocellular carcinoma or portal vein thrombosis; and (vi) willingness to participate in the study. All patients were on restricted sodium intake (80 mmol/day) for at least 7 days prior to inclusion in the study.

Table 1. Protocol of the study

Measurements	Group 1[a] and Group 2[b]		
	Day 1	Day 9[c]	Day 14[c]
Systemic haemodynamics	X	X	X
Body weight, and blood and urine tests[d]	X	X	X
Creatinine clearance	X	X	
Glomerular filtration rate		X	X
Endogenous vasoactive systems	X	X	X

[a]Octreotide given 300 μg b.i.d. SC (at 8:00 am and 8:00 pm) from day 9 to day 14. Diuretic treatment was discontinued from day 2 to day 8.
[b]Octreotide given 300 μg b.i.d. SC (at 8:00 am and 8:00 pm) from day 9 to day 14, with diuretic treatment maintained throughout the study.
[c]First daily doses of octreotide and diuretics were not given. First daily doses of octreotide and diuretics were administered at 12:30 pm, after the evaluation of GFR.
[d]Including serum urea, serum creatinine, serum sodium concentration, 24 h urinary sodium and creatinine excretion, 24 h urine volume and urinary flow rate.

After inclusion in the study, 10 patients were randomly assigned to discontinue diuretic treatment for 7 days (Group 1), to minimize the effects of spironolactone on renal function [22]. Thereafter, all 20 patients received subcutaneous (SC) octreotide, 300 μg b.i.d. for 5 days. The patients in Group 1 were evaluated while receiving diuretics, after interruption of diuretics and after octreotide administration, as outlined in Table 1. The other 10 patients (Group 2) were maintained on their usual diuretic regimens throughout the study and were evaluated twice on diuretics, so that the spontaneous variations of these parameters in a 7 day time frame were assessed, and 5 days after the addition of octreotide. The individuals making the measurements were blinded as to the treatment groups to which patients belonged. All patients fasted and rested in bed at least for 8 h before each haemodynamic evaluation.

Systemic haemodynamic evaluation

Systemic haemodynamic study was performed between 8:00 am and 8:15 am. Arterial blood pressure (BP) was measured with a standard mercury sphygmomanometer. Mean arterial pressure (MAP) was defined to equal diastolic BP + [systolic BP − diastolic BP]/3. Cardiac output (CO) was evaluated by a duplex-Doppler apparatus (Toshiba Sonolayer SSA 270; Tokyo, Japan) according to the mitral inflow method. The ratio of MAP to CO was used as an index of systemic vascular resistance (SVR).

Renal function studies

Urine was collected for 24 h before each examination day and urine volume was recorded. At the 8.00 am end-point of the 24 h urine collection blood samples were obtained.

We determined 24 h urinary sodium and creatinine excretion, serum urea (sUre), serum creatinine (sCre) and serum sodium (sNa). Creatinine clearance (Ccre) was calculated using the conventional formula.

To evaluate glomerular filtration rate (GFR), the patients were given 250 ml of tap water at 8:00 am (to induce an adequate urinary flow), while plastic cannulas were inserted into the antecubital veins of both arms, two cannulas per patient, one per arm, to sample blood and administer tracers. After a 30 min equilibration period, urine was obtained by spontaneous voiding and discarded. At 8:30 am, we started infusing a 5% solution of D-glucose in water at a rate of 2 ml/min to sustain diuresis until the completion of each renal haemodynamic study. Immediately after the infusion was started, 1 mCi Tc^{99m}-diethylenetriaminetetraacetic acid (DTPA) was rapidly injected intravenously. The Tc^{99m}-DTPA was prepared carefully according to the manufacturer's specification 30 min before use. GFR was determined by collecting blood samples at 120, 180 and 240 min after the injection of Tc^{99m}-DTPA and by calculating its rate of disappearance from plasma [23]. All blood and urine measurements were made in our hospital with standard laboratory methods.

Endogenous vasoactive systems

Plasma active renin (PAR) and plasma aldosterone (PA) were measured by immuno-chemi-luminometric assays using specific monoclonal antibodies (Nichols Institute Diagnostics, San Clemente, USA). Radioimmunoassay was used for the measurement of plasma glucagon (Euro-Diagostica AB, Malmo, Sweden). The serum concentration of serum nitrite and nitrate (NOx) (combined nitrite and nitrate concentrations) was measured using a colorimetric assay kit based on a simple two-step process, whose first step is the conversion of nitrate to nitrite using nitrate reductase (two reagents), and the second step is the addition of the Griess reagents, which convert nitrite into a deep purple azo compound (Alexis Biochemical, Laufelfingen, Switzerland).

Statistical analysis

We used Statistica 6.0 for statistical analysis. The Wilcoxon matched pairs test was used to compare variations within the same group, and the Mann–Whitney U-test to evaluate differences between groups. Results are expressed as medians and ranges or medians and percentiles. In all cases, the chosen level of significance was $P < 0.05$.

Results

The baseline clinical and laboratory characteristics of the 20 patients are summarized in Table 2. Creatinine excretion confirmed that urine collections were complete. All patients completed the study.

A trend toward decreased MAP ($P = 0.05$) and a modest but significant decrease in SVR ($P = 0.04$) was observed in the patients who discontinued diuretic treatment (Table 3). The withdrawal of diuretics had no effect on sNa, sUre and sCre. In contrast, we observed a trend toward increased Ccre ($P = 0.05$) in conjunction with a significant decrease in urinary volume (UV) ($P = 0.009$) and urine sodium (UNaV) ($P = 0.005$), and a significant increase in body weight (BW) ($P = 0.005$) after the discontinuation of diuretic treatment. These changes were associated with significant decreases in PAR and PA ($P = 0.01$ and $P = 0.04$, respectively), whereas no significant alterations were detected in the values of plasma glucagon and serum NOx.

Table 2. Baseline clinical and laboratory characteristics at the time of enrolment into the study of cirrhotic patients with ascites treated with octreotide alone after the discontinuation of diuretics (Group 1) or with a combination of octreotide and diuretics (Group 2)

	Group 1 ($n = 10$)	Group 2 ($n = 10$)
Age (years)	55 (39–72)	58 (45–75)
Sex (male/female)	6/4	4/6
Etiology of cirrhosis (alcohol/HBV/HCV)	5/2/3	4/4/2
Child-Pugh class (B/C)	5/5	4/6
Alanine transaminase (U/l)	39 (30–72)	45 (28–97)
Prothrombin time (INR)	1.33 (1.01–1.85)	1.28 (1.05–1.78)
Serum bilirubin (mg/dl)	2.8 (1.1–7.4)	2.6 (1–6.5)
Serum albumin (g/dl)	2.7 (2.2–3.8)	2.6 (2.2–3.4)
Spironolactone (mg/day)	125 (50–300)	125 (50–250)
Furosemide (mg/day)	50 (20–120)	60 (40–100)

Data are expressed as medians and ranges.

The administration of octreotide after the discontinuation of diuretic treatment caused a significant increase in CO ($P = 0.03$) and cardiac index (CI) ($P = 0.03$), without modification of MAP, heart rate (HR) and SVR (Table 3). Octreotide alone induced a significant decrease in GFR ($P = 0.03$); other parameters of renal function were not significantly changed, although we observed a trend toward a decreased UNaV ($P = 0.06$) (Figure 1) associated with a trend toward an increased BW ($P = 0.06$). Of note, GFR calculated based on measured Ccre was overestimated by 28% ($P = 0.04$) on day 9 of the study. We noted significant reductions in PAR ($P = 0.03$), PA ($P = 0.03$) and plasma glucagon ($P = 0.02$) levels after octreotide administration.

No significant difference was found in any parameter between day 1 and day 9 of diuretic treatment of Group 2 (Table 4). The addition of octreotide to the diuretics did not significantly affect MAP, while a significant decrease in HR ($P = 0.009$), CO ($P = 0.02$) and CI ($P = 0.03$), and a significant increase in SVR ($P = 0.04$) was observed. This combined treatment significantly increased GFR ($P = 0.03$), which was overestimated up to 23% ($P = 0.04$) by Ccre on day 9 of the study, and produced a significant increase in UV ($P = 0.03$) and UNaV ($P = 0.01$), and a significant decrease in BW ($P = 0.01$). No significant changes were detected in other parameters of renal function. Significant decreases in PAR ($P = 0.02$), PA ($P = 0.02$) and plasma glucagon levels ($P = 0.01$) were noted after the addition of octreotide to diuretics, whereas serum NOx levels were not changed. The magnitudes of the decreases of PAR and PA produced by octreotide

Table 3. Effects of the discontinuation of diuretics and giving octreotide alone on systemic haemodynamics, renal function, weight and endogenous vasoactive systems in cirrhotic patients with ascites (Group 1 results)

	Diuretic treatment[a] (day 1)	7 days after discontinuation of diuretics	5 days after octreotide initiation	P^b	P^c
Systemic haemodynamics					
MAP (mmHg)	85.8 (83.3, 92.5)	80 (77, 86.3)	81.8 (73.7, 85)	0.05	0.2
HR (b.p.m.)	72 (68, 88)	74 (64, 88)	72 (68, 76)	0.4	0.5
CO (l/min)	6.5 (4.9, 7.2)	6.2 (5.5, 6.4)	6.7 (6.1, 7)	0.8	0.03
CI (l/min/m^2 BSA)	3.75 (2.77, 3.83)	3.38 (3.31, 3.49)	3.79 (3.48, 4.08)	0.7	0.03
SVR (dynes × s/cm^5)	1421 (1256, 1588)	1275 (1194, 1382)	1205 (1088, 1315)	0.04	0.5
Renal function and body weight					
Ccre (ml/min)	84 (72, 109)	91 (84, 119)		0.05	
GFR (ml/min)		79 (63, 110)	72 (59, 97)		0.03
sNa (mmol/l)	135 (131, 139)	136 (130, 138)	135 (131, 137)	0.5	0.3
sUre (mg/dl)	36 (24, 47)	36 (32, 39)	38 (28, 44)	0.6	0.4
sCre (mg/dl)	0.9 (0.7, 1)	0.8 (0.7, 1)	0.8 (0.8, 1.1)	0.2	0.4
UV (ml/min)	1.5 (0.93, 1.52)	0.89 (0.68, 0.9)	0.76 (0.65, 0.82)	0.009	0.3
UNaV (μEq/min)	91.3 (55, 153)	29.5 (25, 52.2)	18.5 (14, 42.6)	0.005	0.06
BW (kg)	73 (66.1, 78.5)	74.2 (68.2, 80.5)	75.2 (70, 79)	0.005	0.06
Endogenous vasoactive systems					
PAR (μU/ml)	244 (133, 1394)	109 (76, 810)	47 (17, 360)	0.01	0.03
PA (ng/dl)	50 (36, 144)	40 (21, 82)	19 (12, 21)	0.04	0.03
Glucagon (pmol/l)	77 (58, 113)	88 (63, 115)	55 (42, 92)	0.7	0.02
NOx (μmol/l)	69 (58, 78)	73 (51, 78)	68 (50, 72)	0.5	0.3

MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; CI, cardiac index; SVR, systemic vascular resistance; Ccre, creatinine clearance; GFR, glomerular filtration rate; sNa, serum sodium; sUre, serum urea; sCre, serum creatinine; UV, urine volume; UNaV, urine sodium; BW, body weight; PAR, plasma active renin; PA, plasma aldosterone; NOx, serurm nitrite and nitrate. Data are expressed as medians and percentiles (25th percentile, 75th percentile).
[a]Furosemide and spironolactone.
[b]Discontinuation of diuretics *vs* diuretic treatment.
[c]Octreotide *vs* discontinuation of diuretics.

plus diuretics were similar to those produced by octreotide alone or by the discontinuation of diuretics (Table 5).

Discussion

In accordance with the results in previous reports [2,3], the present study shows that diuretic treatment may improve, at least partially, systemic haemodynamics in cirrhotic patients with ascites, as indicated by the tendency of MAP to decrease and the significant decrease in SVR after the discontinuation of diuretics. Although this effect seems paradoxical, it might involve diuretic-induced plasma volume depletion [3,5], for plasma volume expansion in cirrhosis has been associated with low arterial resistance [2]. In addition, diuretics can activate powerful vasoconstrictors, such as some components of the renin–angiotensin system, SNS and ADH, leading to increases in arterial pressure and systemic vascular resistance [3]. A direct vasoconstrictive effect of spironolactone on splanchnic circulation has also been suggested [24]. As was expected, the discontinuation of diuretic therapy induced a decrease in UV and UNaV and an increase in BW [1]. In contrast, Ccre showed a tendency toward increase, in conjunction with a decrease in PAR and PA, indicating that renal perfusion during diuretic treatment is reduced [3,5]. Interestingly, using Ccre measurements to derive GFR overestimated GFR, confirming that the former is a poor marker of renal function in decompensated cirrhotic patients [25].

The administration of octreotide after the discontinuation of diuretics had no effect on MAP, HR and SVR while it induced a modest but significant increase in CO. Indeed, in previous studies, cirrhotic patients with ascites who received octreotide alone did not show systemic haemodynamic improvement [19,20]. This might be related to the inhibitory effect of octreotide on the renin–angiotensin system, which is activated to compensate for the hypotensive effect of arterial vasodilation in cirrhosis. The reduction in glucagon levels may have prevented more pronounced adverse systemic haemodynamic effects by reversing arterial hyporeactivity to endogenous vasoconstrictors [7].

In the present study, octreotide alone did not improve renal function, which supports previous observations [19,20]. In fact, a significant decrease in GFR associated with non-significant decreases in UV and UNaV were demonstrated. The renal effects of octreotide might be linked with the impairment of systemic haemodynamics. Another possible mechanism could involve the octreotide-induced suppresion of RAAS. The activation of RAAS in cirrhotic patients has been associated with sodium retention and the development of ascites [1]. However, the AT II-related preferential vasoconstriction of the efferent arterioles assists in the maintenance of GFR at near constant values despite a reduction in renal perfusion

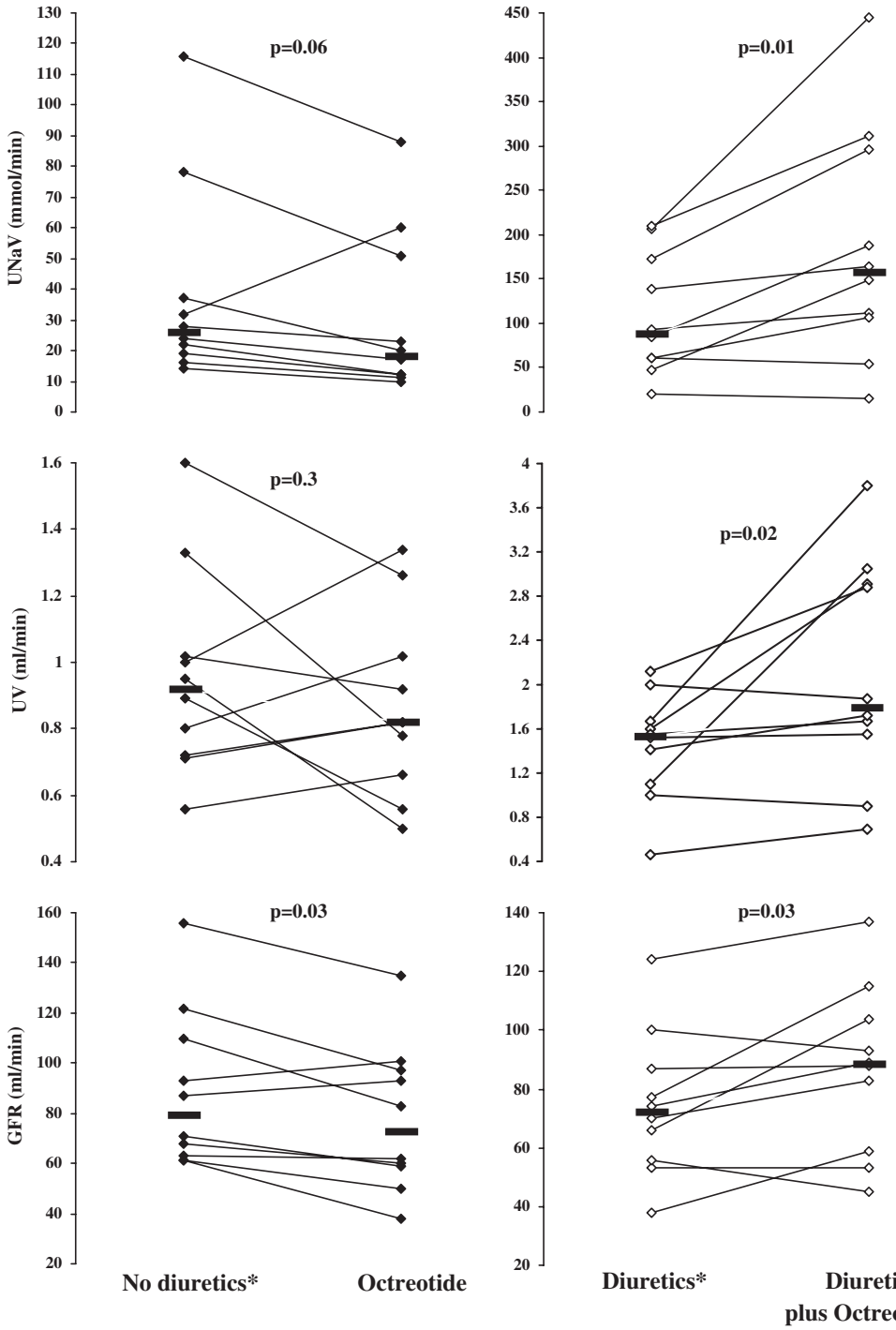

Fig. 1. Individual data on the effects of octreotide alone or the addition of octreotide to diuretics on 24 h urinary sodium excretion (UNaV), urine volume (UV) and glomerular filtration rate (GFR) in cirrhotic patients with ascites. The horizontal bars represent medians; *day 9 of the study.

pressure [26]. Indeed, it has already been reported that the inappropriate inhibition of the renin–aldosterone axis by chronic octreotide administration results in decreases in GFR and filtration fraction despite increased renal blood flow [20]. On the other hand, the reduction in AT II and aldosterone levels may counterbalance the sodium-retaining effects of octreotide-related renal haemodynamic alterations.

The association of octreotide to diuretic treatment had a beneficial effect on systemic haemodynamics, as indicated by the decrease in CO and HR, and the increase in SVR. Additionally, our data demonstrate that adding octreotide-induced decreases in renin and aldosterone levels, the magnitudes of which were comparable with the magnitudes of the increases in these hormones produced by diuretic treatment.

Table 4. Effects of diuretic treatment and treatment with octreotide and diuretics combined on systemic haemodynamics, renal function, weight and endogenous vasoactive systems in cirrhotic patients with ascites (Group 2 results)

	Diuretic treatment[a] (day 1)	Diuretic treatment (day 9)	5 days after addition of octreotide	P^b	P^c
Systemic haemodynamics					
MAP (mmHg)	88.4 (81.4, 96.6)	90 (84.2, 94.6)	94.2 (85.3, 100.1)	NS	0.9
HR (b.p.m.)	75 (72, 88)	78 (72, 84)	70 (62, 74)	NS	0.009
CO (l/min)	7 (6.2, 8.1)	6.8 (6.2, 7.9)	5.7 (5.1, 6.5)	NS	0.02
CI (l/min/m^2 BSA)	3.76 (3.39, 4)	3.7 (3.37, 4.1)	3.31 (2.87, 3.57)	NS	0.03
SVR (dynes × s/cm^5)	1297 (1201, 1496)	1248 (1189, 1467)	1551 (1478, 1802)	NS	0.04
Renal function and body weight					
Ccre (ml/min)	86 (75, 103)	88 (76, 110)			
GFR (ml/min)		72 (56, 87)	88.5 (59, 104)	NS	0.03
sNa (mmol/l)	135 (133, 138)	134 (133, 137)	136 (133, 137)	NS	0.4
sUre (mg/dl)	33 (18, 43)	31 (21, 39)	31 (28, 33)	NS	0.4
sCre (mg/dl)	0.9 (0.8, 1)	0.9 (0.9, 1)	0.8 (0.8, 1.1)	NS	0.2
UV (ml/min)	1.5 (1.04, 1.9)	1.53 (1.1, 1.67)	1.79 (1.55, 2.91)	NS	0.03
UNaV (μEq/min)	79.5 (55, 180)	83.8 (60.1, 205)	175 (147, 310)	NS	0.01
BW (kg)	76.8 (66, 82.2)	76.9 (66.1, 82.6)	76.1 (65.4, 80.6)	NS	0.01
Endogenous vasoactive systems					
PAR (μU/ml)	254 (133, 740)	268 (150, 765)	148 (70, 383)	NS	0.02
PA (ng/dl)	64 (16, 161)	61 (20, 175)	37 (16, 48)	NS	0.02
Glucagon (pmol/l)	86 (67, 126)	90 (70, 135)	58 (41, 106)	NS	0.01
NOx (μmol/l)	65 (58, 73)	63 (56, 75)	68 (54, 73)	NS	0.9

MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; CI, cardiac index; SVR, systemic vascular resistance; Ccre, creatinine clearance; GFR, glomerular filtration rate; sNa, serum sodium; sUre, serum urea; sCre, serum creatinine; UV, urine volume; UNaV, urine sodium; BW, body weight; PAR, plasma active renin; PA, plasma aldosterone; NOx, serurm nitrite and nitrate. Data are expressed as medians and percentiles (25th percentile, 75th percentile).
[a]Furosemide and spironolactone.
[b]Diuretic treatment on day 1 *vs* diuretic treatment on day 9.
[c]Octreotide plus diuretics *vs* diuretic treatment.

Table 5. Treatment-induced changes in vasoactive systems

Changes of (%)	Discontinuation of diuretics	Octreotide alone	Octreotide plus diuretics	P^a	P^b	P^c
PAR (μU/ml)	−54 (−83, −31)	−64 (−84, −17)	−51 (−76, −27)	0.4	0.7	0.4
PA (ng/dl)	−18 (−58, −0.3)	−29 (−48, −0.4)	−23 (−40, −8.7)	0.6	0.3	0.4

PAR, plasma active renin, PA, plasma aldosterone. Data are expressed as medians and percentiles (25th percentile, 75th percentile). Negative changes indicate a decrease.
[a]Octreotide alone *vs* discontinuation of diuretics.
[b]Octreotide plus diuretics *vs* discontinuation of diuretics.
[c]Octreotide plus diuretics *vs* octreotide alone.

Therefore, the addition of octreotide did not affect the basal stimulation of RAAS in cirrhotic patients with ascites, while the vasoconstrictive effect of endogenous vasoconstrictors and spironolactone may have been augmented by the decrease of glucagon levels. The octreotide-induced inhibition of diuretic-related hyperreninaemia was associated with an increase in renal perfusion as shown by the increase in GFR. In addition, the partial improvement in systemic haemodynamics may have contributed to the enhancement of renal function through the suppression of other neurohumoral systems (including SNS and ADH), while an additional, although insignificant, decrease in the activity of RAAS was demonstrated in the octreotide plus diuretics group, compared with the octreotide-only group.

The enhancement of sodium excretion by the combination of octreotide and diuretics resulted from the increase in GFR, the decrease in aldosterone levels, and the expected decrease in AT II. The observed increase in water excretion must be attributed to increased natriuresis and, possibly, to a decrease in ADH levels, as it has been suggested that octreotide *per se* has an antidiuretic effect [27]. The reduction in BW is indicative of a decrease in plasma volume, which in turn may have contributed to the improvement of systemic haemodynamics.

In conclusion, octreotide alone does not improve renal function in cirrhotic patients with ascites. The addition of octreotide to diuretic treatment ameliorates renal function, mainly by suppressing the diuretic-related component of the activation of RAAS, resulting in increased sodium and water excretion. To assess the value of this therapeutic approach, further studies are needed with a larger number of patients, including patients with

diuretic-related renal dysfunction or with ascites refractory to diuretic treatment.

Conflict of interest statement. None declared.

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Received for publication: 29.11.04
Accepted in revised form: 2.2.05