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Ornipressin in the Treatment of Functional Renal Failure in Decompensated Liver Cirrhosis

Effects on Renal Hemodynamics and Atrial Natriuretic Factor

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In 11 patients with decompensated cirrhosis and deteriorating renal function, the effect of the vasoconstrictor substance 8-ornithin vasopressin (ornipressin; POR 8; Sandoz, Basel, Switzerland) on renal function, hemodynamic parameters, and humoral mediators was studied. Ornipressin was infused at a dose of 6 IU/h over a period of 4 hours. During ornipressin infusion an improvement of renal function was achieved as indicated by significant increases in inulin clearance (+65%), paraaminohippuric acid clearance (+49%), urine volume (+45%), sodium excretion (+259%), and fractional elimination of sodium (+130%). The hyperdynamic circulation was reversed to a nearly normal circulatory state. The increase in systemic vascular resistance (+60%) coincided with a decrease of a previously elevated renal vascular resistance (−27%) and increase in renal blood flow (+44%). The renal fraction of the cardiac output increased from 2.3% to 4.7% ($P < 0.05$). A decline of the elevated plasma levels of noradrenaline (2.08–1.13 ng/mL; $P < 0.01$) and renin activity (27.6–14.2 ng · mL^{-1} · h^{-1}; $P < 0.01$) was achieved. The plasma concentration of the atrial natriuretic factor increased in most of the patients, but slightly decreased in 3 patients. The decrease of renal vascular resistance and the increase of renal blood flow and of the renal fraction of cardiac output play a key role in the beneficial effect of ornipressin on renal failure. These changes develop by an increase in mean arterial pressure, the reduction of the sympathetic activity, and probably of an extenuation of the splanchnic vasodilation. A significant contribution of atrial natriuretic factor is less likely. The present findings implicate that treatment with ornipressin represents an alternative approach to the management of functional renal failure in advanced liver cirrhosis.

Increasing evidence indicates that the use of vasoconstrictor substances represents a promising approach in the treatment of renal failure in advanced liver cirrhosis (1). An improvement of renal function has been achieved by administration of either α-sympathomimetic drugs (2–4) or the vasopressin analogues octapressin (5,6) and more recently 8-ornithin vasopressin (ornipressin) (7,8). A normalization of sodium and water excretion has also been achieved by central blood volume expansion with head-out water immersion in combination with a noradrenaline infusion (9,10).

Using a vasoconstrictor compound in advanced hepatic failure, one is confronted with the phenomenon of a pronounced arterial vasodilation in the systemic circulation that is counteracted by a profound vasoconstriction in the renal vasculature (11,12). The renal vasoconstriction is, at least partly, related to an increased sympathetic tone in the kidney, because the blockade of the lumbal part of the sympathetic nerves that innervate the kidney im-

Abbreviations used in this paper: ANF, atrial natriuretic factor; FENa, fractional elimination of sodium; PAH, paraaminohippuric acid.

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proved renal function in cirrhotic patients (13). The obvious paradox of using a vasoconstrictor compound in the treatment of renal dysfunction that coincides with a profound vasoconstriction of the renal vasculature needs further clarification. Peripheral arterial vasodilation, which appears to be most excessive in the splanchnic territories, has been postulated to play a key role in the development of the circulatory derangement and renal failure in advanced liver cirrhosis (12,14–17). An efficient treatment of this circulatory derangement therefore requires a vasoconstrictor substance with a preferential action in the splanchnic vascular bed. In this respect, vasopressin or its analogues with reduced antidiuretic activity might be of considerable advantage because vasopressin is a much more potent vasoconstrictor of iliac and mesenteric than of renal beds (18,19). In decompensated cirrhosis, ornipressin has been shown to increase creatinine clearance, urine volume, and sodium excretion and to normalize the hyperdynamic circulation (7). However, its effect on renal hemodynamics is less clear. A variable improvement of renal perfusion in cirrhotic patients was achieved using octapressin (5,6). Preliminary data also indicate an improvement of renal hemodynamics during ornipressin infusion (20).

To achieve a better insight into the mechanisms involved in the ameliorating effect of vasoconstrictor drugs on renal function in advanced liver disease we investigated the influence of ornipressin on various indices of renal function and renal hemodynamics in cirrhotic patients with functional renal failure. In addition, the influence of ornipressin on endogenous systems that have a considerable impact on renal function, namely the atrial natriuretic factor (ANF) as well as the renin-angiotensin and sympathetic nervous systems, was analyzed.

Patients and Methods

Patients

Eleven patients (3 women, 8 men) with decompensated alcoholic cirrhosis of the liver with severe impairment of renal function and spironolacton-resistant ascites entered the study. They had been admitted to the intensive care unit because of deteriorating renal function despite volume expansion. The mean age was 48 years (38–58 years). All patients had impaired liver function: serum cholinesterase <1.0 U/L (normal range, 2.2–3.8 U/L), prothrombin ratio <0.45 (of normal), bilirubin >2.5 mg/100 mg, and albumin <2.8 g/L. The impairment of renal function was indicated by a creatinine clearance below 40 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} body surface area. The fractional elimination of sodium (FENa) was below 1% and all patients had ascites. Hypovolaemia was excluded by a central venous pressure >5 mm Hg. Patients with severe imbalances of serum electrolytes did not participate in the study. The serum concentrations of electrolytes before the onset of ornipressin infusion were potassium, 4.1 ± 0.3 and sodium, 135 ± 3 mval.

All patients received spironolactone (100 mg twice daily PO) for more than 4 weeks before admission to the hospital. Because of deterioration of renal function the dose was increased to 200 mg IV twice daily, at least 5 days before the study and maintained during the study. None of the patients had received any additional diuretic therapy for at least 5 days. Nine patients improved during intensive care, two patients deteriorated, and finally died in coma. Liver cirrhosis was confirmed by biopsy or necropsy samples in all patients.

Protocol of the Study

The study was started at 8 AM at least 24 hours after admission of the patient to the intensive care unit. After a 2-hour preperiod, ornipressin (POR 8; Sandoz, Bale, Switzerland) was continuously infused at a dose of 6 IU/h via a central venous catheter over a period of 4 hours, using an infusion pump (Perfusor; Braun Melsungen, Melsungen, Germany). This was followed by an observation period of 2 hours (postperiod). During the study, parenteral nutrition adapted for liver failure was continued (infusion rate: 1 mL $\cdot$ kg^{-1} $\cdot$ h^{-1}, sodium 40 mmol/L).

The study was performed according the principles of the declaration of Helsinki, and informed consent was obtained in every case. The consent form had been reviewed and approved by the Ethical Committee of the Department of Internal Medicine. If the patient was unable to understand the nature of the procedures, the family members were specifically informed.

Clinical Tests

Hemodynamic monitoring was performed using a femoral artery catheter and a percutaneously inserted 7F flow-directed thermodilution pulmonary artery catheter (Gould SP 5507; Gould, Oxnard, CA). Cardiac output was estimated by the thermodilution technique with 10 ml of a 5% solution of dextrose in water at 0°C (Gould Cardiac Output Computer). All measurements were performed in triplicate and averaged. The intravascular pressures were calibrated against a mercury sphygmomanometer and were recorded by Gould transducer SP50 (with the midaxillary line as zero reference) and a Hewlett-Packard multichannel recorder (Hewlett-Packard, Waltham, MA). The values were averaged at the end of exspiration for three successive respiratory cycles. Mean pressures were derived by electronic integration. Systemic vascular resistance was calculated from a standard formula (21). Hemodynamic data were recorded before the infusion of ornipressin, 2 and 4 hours after the start of the infusion and 2 hours after the end of the infusion.

Urine was collected via a transurethral catheter in 2-hour periods for measurement of urine osmolality and sodium and creatinine concentrations. Serum osmolality and sodium and creatinine concentrations were measured before and at the end of ornipressin infusion. The concentration of

creatinine and sodium were determined by standard photometric methods (ACA, Wilmington, DE). The osmolality was measured by the freezing point method (Osmomat 030; Genotec, Berlin, Germany). Creatinine clearance, free water clearance and FENa were calculated using standard formulas (22).

Paraaminohippuric acid (PAH) and inulin clearance were determined according to standard methods in 8 patients. An IV loading dose of sodium PAH (Nephrotest; Lich, Hessen, Germany; 6 mg/kg) or polyfructosan (inulin; Inutest, Laevosan, Linz, Austria; 30 mg/kg) was followed by a continuous infusion at a rate of 30 mL/h (PAH, 22 mg/mL; polyfructosan, 40 mg/ml). Renal plasma flow and renal blood flow were calculated according to a standard formula (23). Renal fraction was determined by the ratio of cardiac output to renal blood flow. Filtration fraction was derived from the ratio of inulin clearance to renal plasma flow. Renal vascular resistance was calculated from the difference of mean arterial pressure and central venous pressure divided by the renal blood flow.

Biochemical Analyses

For analysis of the plasma level of noradrenaline, adrenaline and plasma renin activity arterial blood samples (femoral artery) in eight and nine patients, respectively, and for the determination of the ANF immunoreactivity, blood samples from the right atrium were collected in 10 patients before the start of the ornipressin infusion and 2 hours later into precooled heparinized tubes (for noradrenaline and adrenaline) and precooled tubes coated with sodium ethylenediaminetetraacetic acid (for ANF and plasma renin activity). Plasma was separated by centrifugation at +2°C and stored at −20°C until estimation.

Plasma levels of adrenaline and noradrenaline were analyzed after solvent extraction by high performance liquid chromatography with coulometric electrochemical detection (ESA Coulochem, Model 5100A; Bedford, MA). For the extraction of catecholamines from plasma (1–2 mL aliquots) the procedure described by Bauch et al. (24) with minor modifications was used. The concentration of tetraoctylammonium bromide in mixture B was reduced to 1.2 mmol/L. As an internal standard, α-methyldopamine was added to the plasma sample before extraction. Chromatographic separation was achieved on a Nucleosil 5 SA column (130 × 4.6 mm ID; Macherey–Nagel, Düren, Germany). The mobile phase contained 100 mmol/L sodium acetate, 60 mmol/L sodium hydroxide, 40 mmol/L citric acid, and 10% methanol. The final pH was adjusted to 5.2 and the mobile phase was pumped at a flow rate of 1 mL/min. Plasma renin activity and ANF were measured by radioimmunoassays (25,26).

Data Analysis

Data are expressed as mean values ± SEM. Statistical analyses were carried out by means of analysis of variance followed by Tukey's studentized range test. For comparing two pairs of measures, the paired Student's *t* test was applied. A significance level of $P < 0.05$ was chosen.

Results

Hemodynamic Changes

The effect of ornipressin on various hemodynamic parameters is summarized in Table 1. Before the onset of ornipressin infusion a hyperdynamic circulatory state, characteristic for liver failure (27–29), with increased cardiac output and decreased mean arterial pressure, was observed. These changes in systemic circulation were associated with a decrease in renal plasma flow and in renal fraction (proportion of cardiac output delivered to the kidney). During ornipressin infusion, the hypercirculatory state was reversed to an almost normal circulation accompanied by a significant increase in renal plasma flow and renal fraction. In addition, ornipressin caused a significant increase in pulmonary capillary wedge pressure, whereas the central venous pressure increased only slightly, without reaching the level of significance. The cardiovascular improvement presisted only as long as ornipressin was infused. In spite of a considerable increase of the lowered systemic vascular resistance from 545 ± 39 to 912 ± 130 dyne · s^{-1} · cm^5; $P < 0.02$) renal vascular resistance de-

Table 1. Hemodynamic Changes During Ornipressin Infusion

		Ornipressin			
	Preperiod	+2 hours	+4 hours	Postperiod	Control values
Heart rate (*beats/min*)	104 ± 4	75 ± 3[a]	76 ± 4[a]	92 ± 6	78 ± 4[b]
Pulmonary capillary wedge pressure (*mm Hg*)	11 ± 1	14 ± 1[a]	15 ± 1[a]	9 ± 1	12 ± 1[b]
Central venous pressure (*mm Hg*)	8 ± 1	10 ± 1	10 ± 1	8 ± 2	6 ± 1[b]
Mean arterial pressure (*mm Hg*)	81 ± 3	100 ± 4[a]	95 ± 4[a]	77 ± 4	91 ± 3[b]
Cardiac output (*L/min*)	10.8 ± 1.0	8.4 ± 0.7[a]	8.3 ± 0.8[a]	10.0 ± 0.8	6.6 ± 0.5[b]
Renal plasma flow (*mL/min*)	195 ± 40	290 ± 61[a]	273 ± 38[a]	207 ± 39	574 ± 35[c]
Renal fraction (of cardiac output) (%)	2.3 ± 0.4	4.7 ± 1.0[a]	4.5 ± 0.7[a]	3.0 ± 0.5	16 ± 2[c]

NOTE. n = 11.
[a]$P < 0.05$ vs. preperiod.
[b]Control values taken from Barrat-Boyes and Wood (57).
[c]Control values taken from Davies and Schock (58).

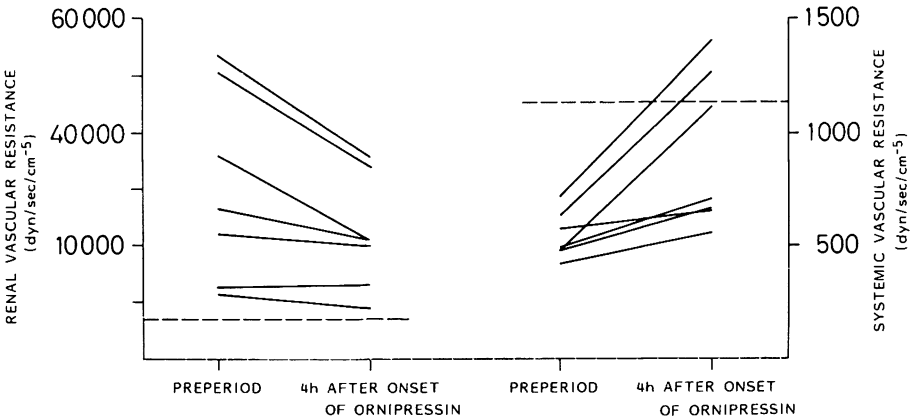

Figure 1. Changes in renal and systemic vascular resistance in response to ornipressin infusion. The normal upper range of renal vascular resistance and the normal lower range of systemic vascular resistance are indicated as *dotted lines*.

creased during ornipressin infusion from 30308 ± 6413 to 22153 ± 3801 dyne · s^{-1} · cm^5 ($P < 0.05$; Figure 1). The decrease of renal vascular resistance was most pronounced in the patients with the highest preinfusion resistance.

Changes in Renal Function

During the infusion of ornipressin a considerable improvement of renal function was achieved. The lowered creatinine clearance increased from 21 ± 3 to 32 ± 5 mL and 32 ± 5 mL · min^{-1} · 1.73 m^{-2} body surface area ($P < 0.05$), 2 and 4 hours after onset of ornipressin infusion, respectively.

The changes of various parameters for renal function are outlined in Figures 2 and 3. There was a significant increase in urine volume (from 1.0 ± 0.1 to 1.3 ± 0.2 and 1.6 ± 0.3 mL/min before and 2 and 4 hours after onset of ornipressin infusion, respectively), inulin clearance (18.6 ± 2.6 to 29.6 ± 3.8 and 31.6 ± 3.9 mL/min), PAH clearance (175 ± 36 to 261 ± 54 and 246 ± 34 mL/min). Free water clearance decreased significantly from −15 ± 4 to −32 ± 5 mL/h in the second 2 hour after onset of ornipressin infusion. In addition, a significant increase in FENa (0.46 ± 0.10 to 0.82 ± 0.16 and 1.3 ± 0.27%), sodium excretion (1.91 ± 0.65 to 5.2 ± 1.0 and 8.5 ± 2.8 mval/2h) and urine sodium concentration (16.6 ± 3.4 to 27.0 ± 6 and 36.6 ± 7.6 mval/L) occurred in re-

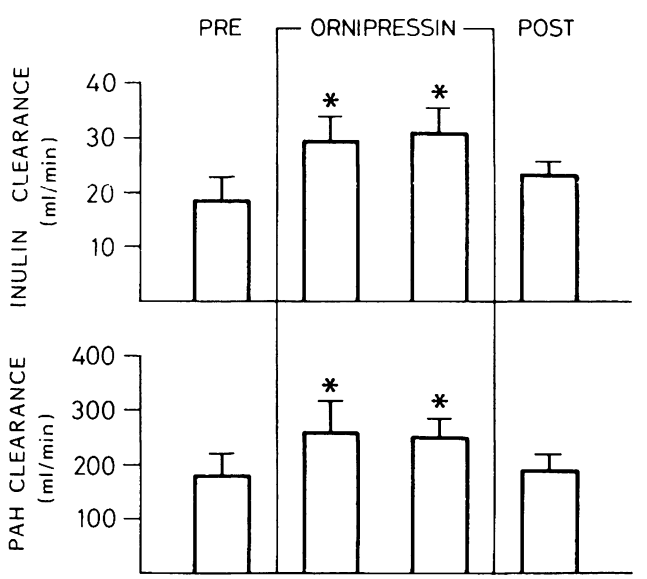

Figure 2. Effect of ornipressin infusion on PAH and inulin clearance. The clearances were measured from urine samples collected within 2 hours before, during, and after cessation of the ornipressin infusion. *$P < 0.05$ vs. preperiod (n = 8).

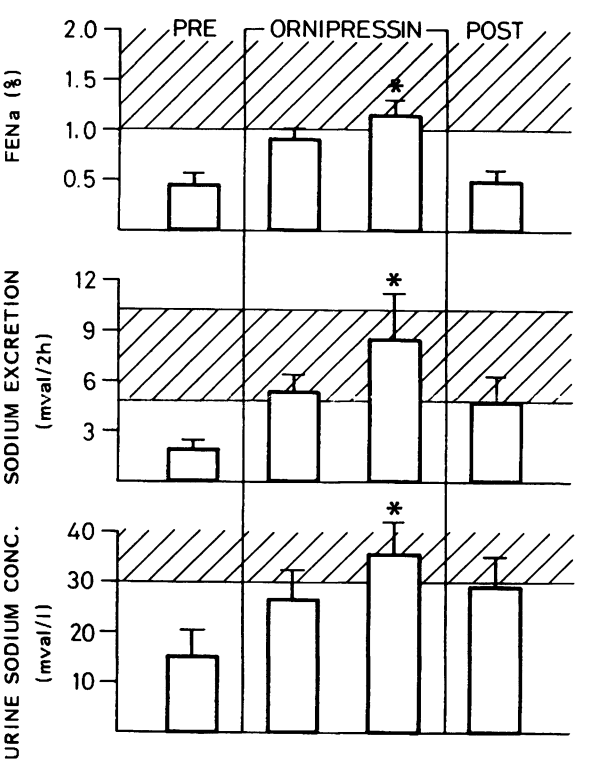

Figure 3. Effect of ornipressin infusion on urine sodium concentration, sodium excretion, and FENa. The parameters were measured or calculated from urine samples collected with 2 hours. The shaded areas indicate the normal range. *$P < 0.05$ vs. preperiod (n = 11).

sponse to ornipressin. After cessation of the infusion, renal function again deteriorated.

Changes in Plasma Levels of Catecholamines, Renin Activity, and ANF

The highly elevated plasma levels of noradrenaline and adrenaline decreased during the ornipressin administration [noradrenaline, from 2.08 ± 0.30 to 1.13 ± 0.24 ng/mL ($P < 0.01$); adrenaline, 0.86 ± 0.32 to 0.54 ± 0.19 ng/mL; $P < 0.05$]. The plasma renin activity declined from the initially high level of 27.6 ± 5.1 to 14.2 ± 4.0 ng · ml^{-1} · h^{-1} ($P < 0.01$). The atrial plasma level of ANF increased significantly from 33.5 ± 5.2 to 60.0 ± 15.0 fmol/mL ($P < 0.02$; Figure 4).

As indicated in Figure 4, the decrease in the levels of noradrenaline, adrenaline, and plasma renin activity occurred uniformly in all patients, whereas a variable response was observed concerning ANF. The atrial level of ANF increased considerably during ornipressin infusion in seven patients, but slightly decreased in three patients. However, these three patients exhibited a similar response to ornipressin as the 7 patients with an increase in ANF with respect to the hemodynamic changes, the improvement of the renal function, and the decrease in plasma noradrenaline and renin activity.

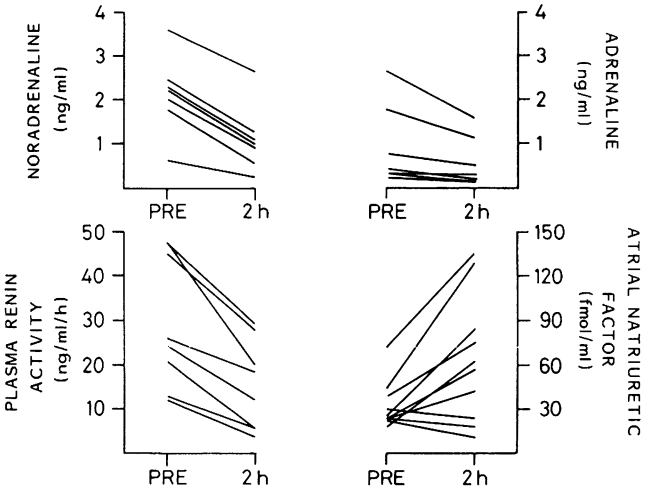

Figure 4. Individual changes in the arterial plasma levels of noradrenaline, adrenaline, and renin activity and in the atrial plasma level of ANF. Plasma samples were drawn immediately before and 2 hours after the onset of the ornipressin infusion. The mean levels of control subjects measured in our experimental conditions are noradrenaline, 0.26 ± 0.04 ng/mL; adrenaline, 0.05 ± 0.01 ng/mL; plasma renin activity, 1.58 ± 0.32 ng · mL^{-1} · h^{-1}. Control values for immunoreactive ANF in atrial plasma samples are not available for the antibody and experimental conditions used in the present investigation.

Discussion

The present investigation reinforces the beneficial effect of the vasopressin analogue ornipressin on renal dysfunction in patients with advanced liver cirrhosis. As described previously (7), creatinine clearance, urine volume, sodium excretion, and fractional elimination of sodium increased, whereas free water clearance decreased. In addition, we were able to demonstrate that glomerular filtration and renal blood flow improved considerably during the infusion of ornipressin. In line with these functional changes, an improvement of the renal hemodynamic situation was observed. The increase in systemic vascular resistance was counterbalanced by a decrease in renal vascular resistance. Subsequently, renal blood flow as well as the renal fraction of the cardiac output increased.

Various mechanisms may be involved in the beneficial effect of a vasoconstricting compound on renal function in advanced liver cirrhosis. The increase in mean arterial pressure during ornipressin infusion, at least partly, could be responsible for the improvement of renal function. However, not all changes in renal function can be explained sufficiently by the improvement in the systemic blood pressure. Data are available indicating that the increase of mean arterial pressure in cirrhotic patients during treatment with head-out water immersion and exogenous infusion of noradrenaline was not accompanied by significant changes in the clearance of creatinine, inulin, and PAH, whereas sodium and water excretion significantly increased (9). Therefore, additional mechanisms appear to be of importance. One of the striking results in our investigation was the stimulation of ANF release in the majority of the patients, accompanied by a decrease in the plasma levels of catecholamines and plasma renin activity. Release of ANF into circulation is mainly stimulated by manipulations known to increase atrial pressure, such as acute volume expansion, water immersion, and vasoconstrictor substances (30,31). In humans and rats, the administration of phenylephrine, vasopressin, or angiotensin II in hypertensive doses produce an immediate rise in ANF (32–34). Even increases in atrial pressure as small as 2 mm Hg are sufficient to stimulate ANF secretion (33). In the present study, central venous pressure increased by about 2 mm Hg, representing an adequate stimulus. Various stimuli have been shown to stimulate the release of ANF in advanced liver cirrhosis, including volume expansion after peritoneovenous shunting (35,36), head-out water immersion (37), and indirectly, large-volume paracentesis (38), but the extent of this release appears to be blunted (37). These findings indicate that in advanced liver cirrhosis the atrial pool of prohormone

and/or releasable ANF and/or its synthesis rate may be diminished. Consequently, a prolonged stimulation of ANF release, as in the case of a 2-hour infusion period of ornipressin, may result in an attenuated amount of releasable ANF and may explain the decrease of ANF in some of the patients. Actually, in these patients the atrial level of ANF was in the lower range already before the onset of ornipressin infusion. Furthermore, other mechanisms have to be considered which influence ANF plasma concentrations, such as enzymatic degradation and clearance of the peptide from the circulation (39).

Whether the increased amount of circulating ANF could have contributed to the increase in natriuresis still remains a crucial question. Several pharmacological studies point to a reduced responsiveness to exogenous ANF in cirrhosis with ascites in humans and rats (40–43). The blunted renal response to ANF seems to be related to the altered systemic hemodynamics of cirrhosis and excessive antagonism by antinatriuretic factors, such as the renin-angiotensin-aldosteron system. Because of its blood pressure lowering effect and hence further deterioration of the systemic hemodynamics, the therapeutic efficacy of exogenous ANF or a synthetic analogue has been shown to be limited in patients with cirrhosis complicated by renal dysfunction (40,41,43,44). The important role of arterial hypotension in the diminished renal response to ANF has been shown in rats with CCl_4-induced cirrhosis as well as in portal hypertensive rats, where the renal effects of ANF were enhanced on normalization of arterial pressure by either angiotensin II or ornipressin (42,45). Furthermore, the blunted natriuretic response to ANF in chronic bile-duct–ligated rats with cirrhosis and ascites has been reversed by bilateral renal denervation, indicating an involvement of increased renal sympathetic nerve activity in this phenomenon (46). Because a normalization of mean arterial pressure as well as an attenuation of the sympathetic nervous system activation was achieved during the infusion of ornipressin in the present study, the renal response to the increased plasma levels of endogenous ANF might have been preserved, and the increased release of ANF could have contributed to the enhanced natriuresis during ornipressin infusion. However, an impaired natriuretic response to ANF has been recently demonstrated in isolated perfused kidneys of rats with CCl_4-induced cirrhosis (47).

A predominant effect of ornipressin in functional renal failure in liver cirrhosis is the escape from extreme renal vasoconstriction. The decrease in renal vascular resistance can be at least partly explained by the reduction in sympathetic nervous system activity and renin release in response to ornipressin as indicated by the considerable decrease in the plasma levels of noradrenaline and adrenaline and plasma renin activity. On the other hand a participation of ANF in this phenomenon might be expected. ANF has been shown to be a potent and relatively specific renal vasodilator substance (48,49). The influence of this atrial peptide on renal hemodynamics seems to be unique as it causes a dilation of the blood vessels which supply the glomeruli and a vasoconstriction of the efferent arterioles (50) and, consequently, an increase of filtration fraction.

Recent findings point to the involvement of splanchnic vasodilation in the development of the functional renal failure in advanced cirrhosis. The systemic hyperdynamic circulatory status has been shown to be associated with a reduced flow to extrasplanchnic territories indicating a diversion of large fractions of the cardiac output from the vasoconstricted renal and femoral vascular beds to other vasodilated vascular beds, especially to the splanchnic area (16). The splanchnic vasodilation inspite of a considerably elevated sympathetic tone is probably related to the following phenomenon. During continued stimulation of sympathetic vasoconstrictor fibers to splanchnic vessels, an increase in intestinal blood flow occurs because of an autoregulatory escape (51). Therefore, the splanchnic vascular bed may not be sufficiently protected against the action of potent vasodilator compounds, which accumulate in liver failure (12,17). As potent vasoconstrictor substances in the splanchnic area (18), vasopressin and its analogues with preferential vasoconstrictor action have the potential to counteract the profound vasodilation in the splanchnic beds. In addition, during ornipressin infusion, the vasoconstriction in renal and femoral beds was probably attenuated by reducing the extreme activation of the sympathetic nervous system. Thereby, the blood flow was shifted from splanchnic territories to extrasplanchnic areas as underlined by the increase in the renal fraction of the cardiac output.

One of the main factors responsible for the efficacy of ornipressin in improving renal function appears to be the suppression of the increased activity of the sympathetic nervous and of the renin-angiotensin systems. This pronounced suppression can be at least partly explained by the increase in mean arterial pressure, thereby altering the arterial baroreceptor response. On the other hand, ANF may contribute to this suppression, because ANF is known to inhibit renin release (52,53) as well as sympatho-adrenal activity (54,55).

In summary, the present results suggest the following mechanisms to be involved in the beneficial effect of ornipressin on renal failure associated with advanced liver cirrhosis. The improvement of renal hemodynamics as indicated by a decrease of renal vascular resistance and an increase of renal blood

flow and of the renal fraction of cardiac output supposedly plays a key role. These changes appear to be linked to a shift of blood flow from splanchnic to extrasplanchnic territories, increase in mean arterial pressure, and to the suppression of the profound activation of the sympathetic nervous system and the renin-angiotensin axis. The contribution of ANF to this significant improvement is less defined. Because a variable response in the release of ANF occurred and the atrial plasma level of ANF even decreased in three patients, ANF is not necessarily a prerequisite for the observed changes.

The findings of the present investigation are of considerable clinical relevance. Treatment with ornipressin represents an alternative approach to the management of functional renal failure in advanced liver cirrhosis and might help to avoid or postpone the use of extracorporeal elimination techniques as an ultimate step. In cirrhotic patients, these procedures are afflicted with potential disadvantages, including dialysis-induced hypotension, increased risk of infection, worsening of coagulopathy, and changes in drug-protein binding (56). In addition, the use of ornipressin might be applied for optimizing the clinical condition of patients awaiting liver transplantation. This has been already demonstrated in a single patient (7). Further studies are in progress to evaluate the effect of long-term treatment with ornipressin.

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