The treatment of ascites

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Key words : hepatorenal syndrome, portasystemic shunt, transjugular intrahepatic, vasoconstrictor agents, liver cirrhosis, water, sodium, peritoneovenous shunt.

Introduction

The natural course of patients with cirrhosis is frequently complicated with ascites, which consists in the excessive accumulation of fluid in the peritoneal cavity. The development of ascites is closely related to complications such as dilutional hyponatremia, hepatorenal syndrome and spontaneous bacterial peritonitis, and is associated with poor prognosis (1) : the 1-year survival rate of patients admitted to the hospital for the treatment of an episode of ascites has been reported to be only of 56% (2).

The treatment of ascites has traditionally been based on the combination of a low-sodium diet and the administration of diuretics (3). However, this treatment is not entirely satisfactory because as much as 10 to 20% of patients with ascites develop refractory ascites, defined by either the absence of response to diuretic therapy or by the development of diuretic-induced complications that prevent the use of therapeutic doses of these drugs (table I) (4). Moreover, treatment with diuretics does not modify the hemodynamic abnormalities that characterise portal hypertension, so it has no influence on the most advanced clinical manifestations of these abnormalities, such as dilutional hyponatremia and hepatorenal syndrome. The present review will be focused on the alternative therapies to diuretics in the management of ascites. Additionally attention will be paid to the latest advances in the treatment of hepatorenal syndrome.

The treatment of ascites with paracentesis

In the last 10 years therapeutic paracentesis has progressively replaced diuretics as the treatment of choice in the management of tense ascites as a result of the publication of several randomized controlled trials (RCT) showing that large volume paracentesis (defined as the evacuation of ascitic fluid or more) followed by plasma volume expansion was more rapid and effective and associated with less complications than diuretics (5,6). Considering that paracentesis does not modify the pre-existing renal functional abnormalities of cirrhosis, once the ascites has been removed diuretics should be started immediately in order to avoid ascites reaccumulation. As showed by a recent RCT this strategy does not increase the risk of adverse effects on renal function (7).

Table I. — **Definition and diagnostic criteria of refractory ascites as proposed by the International Ascites Club**

Definitions
Refractory ascites. Ascites that cannot be mobilized or the early recurrence of which (i.e. after therapeutic paracentesis) cannot be satisfactorily prevented by medical therapy. The term "refractory ascites" includes two different subtypes : "Diuretic-resistant ascites" and "Diuretic-intractable ascites".
Diuretic-resistant ascites. Ascites that cannot be mobilized or the early recurrence of which cannot be prevented due to a lack of response to sodium restriction (50 mEq/day sodium diet) and diuretic treatment (mean loss of weight less than 200 g/day during the last four days of intensive diuretic therapy — spironolactone 400 mg/day and furosemide 160 mg/day — and urinary sodium excretion less than 50 mEq/day).
Diuretic-intractable ascites. Ascites that cannot be mobilized or the early recurrence of which cannot be prevented due to the development of diuretic-induced complications (*) that preclude the use of an effective diuretic dosage.

(*) Diuretic-induced complications : Diuretic-induced hepatic encephalopathy : development of hepatic encephalopathy in the absence of other precipitating factors. Diuretic-induced renal failure : increase in serum creatinine by greater than 100% to a value above 2 mg/dl in patients with ascites responding to diuretic treatment. Diuretic-induced hyponatremia : decrease in serum sodium concentration by greater than 10 mEq/L to a level lower than 125 mEq/L. Diuretic induced hypo or hyperkalemia : decrease of serum potassium concentration to less than 3 mEq/L or increase to more than 6.0 mEq/L despite appropriate measures to normalize potassium levels.
Reproduced from Arroyo *et al.* (4), with permission.

The most controversial issue on therapeutic paracentesis is whether or not this procedure should be performed in association with plasma volume expansion to prevent the effects of paracentesis on systemic hemodynamics. It is well known that large volume paracentesis is followed by an hyperactivation of the endogenous vasoconstrictor systems (8-11) in the absence of plasma volume depletion (12). The pathogenesis of these changes, which have been called post-paracentesis circulatory dysfunction (PPCD), is unknown. The removal of a large volume of ascites somehow triggers an exarcebation of the pre-existing splachnic vasodilatation (13,14). A recent study has shown that these hemodynamic changes are not reversible and have

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a negative impact on the evolution of the disease, leading to a higher rate of ascites reaccumulation, and to greater requirements of diuretic therapy. Most importantly, patients who develop PPCD have a shorter survival than those who do not (15). At present, the only effective method to prevent this complication is the administration of plasma expanders, especially albumin, wich has been shown to be more effective than dextran-70 or polygelin. Therefore, large-volume paracentesis should always be followed by the infusion of albumin (at the dose of 8 g per each litre of fluid removed). Controversy exists regarding the necessity of plasma volume expansion in paracentesis of less than 5 liters. No differences between albumin and other plasma expanders have been found in this setting, and thus the use of dextran-70 or polygeline, much more cheaper than albumin, seems acceptable (15). No data are available however on the consequences of performing such procedure without any plasma volume expansion.

Peritoneovenous shunt

Until the popularisation of paracentesis in the last decade, peritoneovenous shunting, introduced by Le Veen in 1974 (16), was the only treatment for patients developing refractory ascites. Numerous studies show that peritoneovenous shunting improves the circulatory dysfunction of cirrhotic patients as shown by a marked suppression of renin, aldosterone, norepinephrine and antidiuretic hormone and by increases in urine volume, free water excretion and even glomerular filtration rate (GFR) in some patients with functional renal failure (17-19). Despite these advantages, there are a large number of complications, the most important being the obstruction of the prosthesis, which occurs in more than 40% of cases in the first year and often requires reoperation. Other complications such as thrombosis of superior vena cava or peritoneal fibrosis may even preclude liver transplantation (20). Patients with the most severe forms of liver failure are particularly prone to complications after the placement of peritoneovenous shunt.

Peritoneovenous shunt has been compared to therapeutic paracentesis and shown to be superior in the control of refractory ascites, although no differences have been found in either the survival rate nor the total in-hospital time, the latter due to the high rate of shunt obstruction needing reoperation (21,22). As a result of these data PV shunt is now reserved for the treatment of refractory ascites in patients with poor liver function, not eligible for liver transplantation, or in whom therapeutic paracentesis are not practicable because of surgical scars.

TIPS in the treatment of refractory ascites

Since portal hypertension is the initial event in the pathogenesis of circulatory and renal dysfunction in patients with ascites, the relief of the increased portal pressure by a portocaval shunt could be a rational approach for the treatment of these patients. However, the applicability of major surgical procedures in patients with cirrhosis and ascites is very limited. The transjugular intrahepatic portosystemic shunt (TIPS) is a non surgical portocaval anastomosis that behaves as a side to side portocaval shunt (23), and can be performed in an angiography room within less than 2 h under local anaesthesia. Several pilot studies assessing TIPS in refractory ascites have been published in recent years (24-30). Most of them have shown that the insertion of TIPS is associated with an increase in cardiac output and a decrease in systemic vascular resistance. Together with these circulatory changes there is a marked suppression of plasma renin activity and aldosterone and norepinephrine concentrations. As expected, renal function improves, and there is an increase in sodium excretion and reduction in diuretic requirements. The main problems of TIPS are the development of hepatic encephalopathy (its incidence ranging in these patients between 50% and 75%) and the risk of impairing liver function. The maintenance of a portocaval pressure gradient below 12 mmHg has proven to protect effectively against the accumulation of ascites (31), but there is a high rate of shunt dysfunction that requires reintervention. Until now, only two RCT comparing TIPS with paracentesis in patients with refractory ascites have been published. In one study, although TIPS was highly effective in the control of refractory ascites, the paracentesis group had a significantly better survival than the TIPS group (32). In an interim analysis of another RCT, published in abstract form, no significant differences in survival were observed between the two groups (33). Both studies included a small number of patients. Larger controlled trials are required to determine whether TIPS improves the results obtained with paracentesis or peritoneovenous shunt in terms of quality of live and survival. As patients with refractory ascites constitute a non-homogeneous group, the identification of subgroups that would benefit from TIPS should be the principal aim of these trials (34).

Liver transplantation

Liver transplantation has become a standard therapy for patients with end-stage cirrhosis. Earlier recommendations suggested that the main indications for liver transplantation in patients with ascites were refractoriness, history of spontaneous bacterial peritonitis, and hepatorenal syndrome. However, since with these guidelines a significant proportion of patients may not reach the transplantation because of the short survival expectancy associated with these conditions, investigators have tried to define parameters with higher predictive value of survival. Consistently, instead of the usual variables considered in the Child-Pugh scale, parameters reflecting the degree of hemodynamic or renal dysfunc-

tion have been shown to be the best predictors of poor prognosis, including marked sodium retention, increased plasma renin activity and norepinephrine concentration, dilutional hyponatremia, arterial hypotension and reduced GFR (2,35). In a very recent report water excretion after a water load was the most valuable prediction of survival in cirrhotic patients with ascites (36).

The treatment of dilutional hyponatremia

At present no pharmacological therapy exists to dilutional hyponatremia other than water restriction. However, in cases of severe hyponatremia water restriction rarely corrects this disorder. On the other hand the administration of hypertonic saline solutions is not recommended because it invariably leads to further expansion of extracellular fluid volume and to the accumulation of ascites and edema. Recently, two new drugs have risen great expectation due to their capability of selectively increasing water excretion : antagonists of the V2 receptor of antidiuretic hormone and selective kappa opioid agonists (37). The former group of drugs antagonizes selectively the water-retaining effect of antidiuretic hormone in the cortical collecting duct. The latter inhibits antidiuretic hormone release from the neurohypophysis. Although up to now only preliminary studies are available, both compounds selectively increase water excretion in cirrhotic patients (38,39), and therefore could offer a novel therapeutic approach for the treatment of water retention and dilutional hyponatremia.

Hepatorenal syndrome

Hepatorenal syndrome (HRS) is a common and severe complication of cirrhosis characterised by an intense vasoconstriction of the renal circulation that leads to reduced renal blood flow and glomerular filtration rate. A consensus definition of HRS has been recently proposed and two different types have been described (4). Type I HRS is characterised by rapidly progressive reduction of renal function, as defined by a doubling of the initial serum creatinine to a level > 2.5 mg/dl, or a 50% reduction of the initial 24-hour creatinine clearance to a level lower than 20 ml/min in less than two weeks. Patients with this type of HRS usually die within two weeks (40). Type II HRS is characterised by a moderate and stable reduction of GFR and its main clinical consequence is diuretic resistant ascites. Survival in this second group is longer than that of patients with type I HRS but shorter than that of patients with ascites without renal failure. Although several diagnostic criteria of HRS have been defined (table II) (4) none of them has enough specificity to be considered as a definitive marker of this syndrome, and thus diagnosis is usually not straightforward.

A great variety of therapeutic modalities have been tried in patients with HRS. Unfortunately no RCTs regarding this subject have been undertaken and the results of most reports are discordant. Therefore there is still not a widely accepted attitude regarding the best approach.

Table II. — **International Ascites Club's Diagnostic Criteria of Hepatorenal Syndrome (*)**

Major criteria

1. Low glomerular filtration rate, as indicated by serum creatinine greater than 1.5 mg/dl or 24-h creatinine clearance lower than 40 ml/min.
2. Absence of shock, ongoing bacterial infection, fluid losses and current treatment with nephrotoxic drugs.
3. No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl or less or increase in creatinine clearance to 40 ml/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of a plasma expander.
4. Proteinuria lower than 500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.

Additional criteria

1. Urine volume lower than 500 ml/day.
2. Urine sodium lower than 10 mEq/L.
3. Urine osmolality greater than plasma osmolality.
4. Urine red blood cells less than 50 per high power field.
5. Serum sodium concentration lower than 130 mEq/L.

(*) All Major Criteria must be present for the diagnosis of Hepatorenal syndrome. Additional Criteria are not necessary for the diagnosis, but provide supportive evidence. Reproduced from Arroyo *et al.* (4), with permission.

Because HRS is a functional disorder pathogenetically related with the existence of an advanced liver disease, liver transplantation is theoretically the ideal treatment for patients with HRS as it allows solving both the diseased liver and kidney dysfunction. Immediately after transplantation a further impairment in renal function may be observed and a percentage of patients require haemodialysis and/or temporary cyclosporine withdrawal (41). Although patients transplanted with HRS have more complications, longer ICU and in-hospital stays, and higher in-hospital mortality rate than patients transplanted without HRS (42,43), normalisation of renal function is the rule, and only a reduced percentage of patients (between 1 and 7%) may progress to end-stage renal disease requiring long-term dialysis (41). Moreover, on a long-term basis, survival of transplanted patients with HRS at 1 year is only 10%, lower than that of patients without HRS (41). Combined liver-kidney transplant does not improve the results of isolated liver transplant (44).

The main problem regarding liver transplantation in the management of HRS is the extremely short survival of these patients, especially in HRS type I, in the setting of increasingly long waiting lists, which leads to a extremely reduced applicability. Therefore, the use of therapeutic methods to temporally improve renal function and act as a "bridge" to liver transplantation are of the utmost importance (45,46,47).

Peritoneovenous shunt was sporadically used in the past in the management of HRS as a means of attaining a persistent state of plasma volume expansion. How-

ever, despite isolated reports of reversal of HRS, controlled investigations failed to show an improvement in the survival of these patients (48).

Considering the great overactivation of the endogenous vasoactive systems that characterises HRS and the marked reduction in the activity of these systems shown in patients with refractory ascites after the placement of a TIPS, several groups have performed this procedure in HRS. Unfortunately very limited information is still available, but several reports including a few patients suggest that this procedure may improve and even solve HRS (46,49,50). In these patients renal function improvement does not occur immediately after the insertion of the stent, but it may take more than a month. In spite of this promising results there is a clear need for controlled studies before the use of TIPS in these patients can be finally recommended.

Hemodialysis and peritoneal dialysis have also been used in the management of patients with HRS. Although very sporadic case reports of renal function improvement have been published, all uncontrolled trials point to a extremely low — if any — effectiveness (51), as it is associated with a high incidence of severe side effects including arterial hypotension, coagulopathy and gastrointestinal hemorrhage.

Renal vasodilators have been used in patients with HRS in an attempt to reduce intrarenal vascular resistance, but either prostaglandins and analogues (52,53), or dopamine at non-pressor doses (54) have failed to improve renal function in these patients. Further studies are however needed regarding this point, as in a very recent case report the acute administration of the specific antagonist of endothelin-A receptors (BQ123) was associated with HRS improvement (55).

As renal hypoperfusion in HRS is thought to be related to the marked overactivation of the systemic vasoconstrictors, there is a rationale for the use of vasoconstrictor agents in an attempt to correct the decreased systemic vascular resistance typical of these patients. Supporting this hypothesis, the acute infusion of the vasopressin analogue ornipressin to patients with HRS was reported to improve the circulatory dysfunction by markedly suppressing the renin-angiotensin and sympathetic nervous systems. However, this was associated with an only slight increase in GFR (56), which was not furtherly improved after the combination of the former vasoconstrictor or norepinephrine with renal vasodilators (dopamine, prostacyclin) (57). The last step has been the combined administration of ornipressin plus plasma volume expansion with albumin which although did not improve GFR after a 3-day treatment period (45), was followed by a complete normalisation of all the endogenous vasoactive systems and a remarkable increase in renal function when the treatment was administered for 15 days (45). Moreover, after the discontinuation of the treatment patients maintained a relatively preserved renal function. Despite this extremely positive results, this treatment should be used with great caution, since in a significant number of patients it had to be discontinued due to ischemic complications. Certainly other types of vasoconstrictors, or the combination of systemic vasodilators, should be tried in order to overcome this severe side-effects of what is otherwise the most promising treatment of HRS at this moment.

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Treatment of ascites : Summary of the discussion

P. P. Michielsen

Introduction

The introductory talk of Prof. Arroyo largely covers the approach to tense ascites, refractory ascites, the use of therapeutic paracentesis, peritoneo-venous shunting and TIPS in these indications, as well as the approach to the hepatorenal syndrome and the possible use of aquaretic drugs. The summary of the subsequent discussion will be focused on the medical therapy of ascites, and the management of spontaneous bacterial peritonitis.

Choice of diuretics in the treatment of ascites

The aim of the medical treatment of ascites is the mobilization of intraabdominal fluid by creating a negative sodium balance. This is achieved by dietary sodium restriction and diuretics and will control 90% of cases of cirrhotic ascites. The diuretics most often used in the treatment of ascites in cirrhosis are the potassium sparing diuretic spironolactone and the loop diuretic furosemide. Two different diuretic schedules are used in cirrhosis. The first consists of the administration of increasing doses of spironolactone (every 3 days), adding furosemide in those patients not responding to the highest recommended dose of spironolactone (400 mg). The second consists of the simultaneous administration of furosemide and spironolactone from the beginning of the treatment, increasing the doses of both diuretics if no therapeutic response is achieved (to a maximum of 400 mg spironolactone and 160 mg furosemide). There are no studies comparing these two treatment schedules.

In the past, single-agent spironolactone was advocated (1). However, many patients with single-agent spironolactone develop hyperkalemia. Furthermore, it has been demonstrated that it takes approximately two weeks before onset of action of single-agent spironolactone (2). Single-agent furosemide has been shown to be less efficacious than single-agent spironolactone and to cause hypokalemia (3). Therefore, a combined diuretic therapy now is proposed.

When the baseline urinary sodium excretion is $>$ 10 mmol/l, spironolactone will often be sufficient ; when the excretion is very low, no response to spironolactone can be expected.

An alternative diuretic to spironolactone could be amiloride (10 mg amiloride = 100 mg spironolactone). In a randomized controlled trial, however, it was less effective than spironolactone ; it was only effective in patients with normal plasma aldosterone levels (4).

Torasemide, a new loop diuretic, induces higher natriuresis and diuresis than furosemide in cirrhotic patients (5). Its use has to await further controlled trials that justify the increased cost compared to furosemide.

Diuretic-induced renal failure

Diuretic-induced renal failure was defined as an increase in serum creatinine by greater than 100% to a value over 2 mg/dl in patients with ascites responding to diuretic treatment (6).

Diuretic-induced renal impairment has been estimated to occur in approximately 20% of hospitalized cirrhotic patients with ascites and is particularly common in patients without peripheral oedema. It occurs in patients well responding to diuretic treatment with loss of body weight and significant natriuresis. It is usually moderate and rapidly reversible following diuretic withdrawal. The goal of diuretic treatment should be to achieve a weight loss of ca 500 mg/d in patients without oedema. As the ascites has a limited rate of absorption of approximately 700-900 mild, if a diuresis greater than 900 mild is induced, the extra fluid will proceed from nonascitic extracellular fluids such as peripheral oedema and the intravascular space. Intravascular volume depletion and prerenal insufficiency will rarely occur as long as peripheral oedema is present ; however, once oedema disappears, the extra fluid will come from the intravascular space and complications secondary to volume depletion will develop (7). In patients who have massive oedema, there is no limit to the daily weight loss.

Hyponatremia and diuretics in cirrhotic ascites

Two situations can be distinguished.

1. Patients with severe spontaneous hyponatremia have impending hepatorenal syndrome, will most often not react to diuretic therapy, and have a very poor prognosis (8).

Autumn Meeting Belgian Association for the Study of the Liver Brussels, 12.12.1997. Summary of the discussion. Exp-erts : V. Arroyo, Barcelona. Moderators : J. Henrion, F. Nevens, P. Michielsen.
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2. Diuretic-induced hyponatremia is estimated to occur in 30% of hospitalized cirrhotic patients with ascites (6). It is defined as a decrease in serum sodium concentration by greater than 10 mmol/l to a level lower than 125 mmol/l. It is secondary to impairment of the already decreased renal ability to excrete free water : furosemide inhibits free water clearance directly, any type of diuretic by producing volume depletion may stimulate the release of ADH and decreases the delivery of filtrate to the diluting segment of the nephron (6).

It is seldom morbid, cirrhotics do not usually have symptoms from hyponatremia until sodium is < 110 mmol/l or unless the decline in sodium is very rapid. Attempts to rapidly correct hyponatremia can lead to more complications than the hyponatremia itself (9). Severe hyponatremia (< 120 mmol/l) warrants fluid restriction. Patients on the waiting list for liver transplantation are at risk of development of fatal demyelination due to dramatic perioperative increases (> 20 mmol/l) in serum sodium (10). In order to avoid this problem, fluid restrictions are necessary in hyponatremic transplant candidates keeping serum sodium > 120 mmol/l (11).

Use of clonidine in the treatment of refractory ascites

Clonidine is a central inhibitor of sympathetic nervous activity, which in low dose, not affecting blood pressure, is able to inhibit the hypersecretion of noradrenaline in decompensated cirrhosis (12). Recently, Lenaerts *et al.* (13) reported in 4 patients with refractory ascites that low-dose clonidine was able to diminish proximal sodium reabsorption, increasing the distal delivery of sodium. Addition of spironolactone, aldosterone antagonist, realized an increased natriuresis, allowing better control of the ascites.

Treatment of spontaneous bacterial peritonitis (SBP)

It is important that empiric antibiotic treatment is started immediately after performing ascitic fluid analysis when the diagnosis of SBP is clinically suspected or ascitic fluid neutrophils are > 250 cells per mm^3.

The use of ß-lactam antibiotics combined with aminoglycosids is now considered obsolete because of the modest results and the nephrotoxicity of aminoglycosids in cirrhotic patients (14). The third generation cephalosporin cefotaxime is now considered as first-choice antimicrobial agent in the treatment of SBP in cirrhotic patients (15). Treatment with 2 g cefotaxime given intravenously every 6, 8 or 12 h was equally effective (15,16). A short course of therapy (5 days) has been shown to be as effective as a long course of therapy (10 days) (18). Other antibiotics such as ceftriaxone (2 g per day) (19) or amoxicillin-clavulanic acid (20) are equally effective with resolution of the infection in approximately 85%. Aztreonam, only effective against gram-negative bacteria, is clearly less effective and not recommendable in the empirical treatment of SBP (21). Patients with uncomplicated, community-acquired SBP and who had not received antibiotics in the previous two weeks, with normal renal function, no encephalopathy, no shock, gastrointestinal bleeding or ileus, could be treated with oral quinolones as ofloxacin (400 mg bid), and might complete their treatment as outpatients if they show a good response to antibiotics (22).

Prophylaxis of SBP

Prophylaxis of SBP can be realized by selective intestinal decontamination of gram-negative bacteria with oral, poorly absorbable, quinolones.

A short-term (7 d) nosocomial prophylaxis with norfloxacin (400 mg bid) is advocated in hospitalized cirrhotic patients with gastrointestinal bleeding (23-25), or with low ascitic protein content (< 1 g/dl) (26). Long-term secondary prophylaxis with oral norfloxacin (400 mg/d) is advocated in patients with cirrhosis who previously had SBP (27). Long-term primary prophylaxis with oral norfloxacin (400 mg/d) in outpatients with cirrhosis and low ascitic protein can be considered (28), the benefits must be weighed against the risk of induction of bacterial resistance. Alternative antibiotics to norfloxacin for long-term prophylaxis are ciprofloxacin (oral dose 750 mg weekly) (29) and trimethoprim-sulphamethoxazole (orally 5 times a week) (30).

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