Treatment of Ascites

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Bed Rest and Low-Sodium Diet

The assumption of an upright posture by patients with cirrhosis and ascites is associated with a striking activation of the renin-angiotensin system and the sympathetic nervous system, a reduction of GFR, and an enhancement of tubular sodium reabsorption [1]. Therefore, from a theoretical point of view, bed rest could be useful for the treatment of ascites, particularly in patients who do not respond satisfactorily to diuretics.

Low-sodium diet (40-60 mEq/day) is another useful measure for the treatment of cirrhotics with ascites. Approximately 20% of these patients may decrease their ascites only by reducing the sodium content in their diet. In the remaining cases, sodium restriction diminishes the diuretic requirements. An important cause of diuretic-resistant ascites is inadequate sodium restriction. This should be suspected in any patient whose ascites does not decrease despite a good natriuretic response to diuretics. Once ascites has disappeared, many cirrhotics continue to require a strict sodium diet and diuretics. Others, however, can be maintained free of ascites with moderate sodium restriction and low doses of diuretics. Finally, it is not infrequent to observe patients who spontaneously recover their ability to excrete sodium normally. Therefore, the long-term management of cirrhotics with ascites varies markedly from patient to patient, and every effort should be made to adjust sodium intake and diuretic dosage to individual requirements at each moment during the course of the disease.

Diuretics

Loop diuretics, in particular furosemide, and distal diuretics, especially spironolactone, are the commonest drugs in the treatment of cirrhotics with ascites.

Loop diuretics exert their primary action in the ascending limb of the loop of Henle. They are the most powerful diuretics used in clinical practice today. High dosage can increase sodium excretion to 30% of the filtered sodium. This high natriuretic potency can be attributed to two features. First, between 20% and 50% of the filtered sodium is reabsorbed in the loop of Henle, representing a major substrate for the action of diuretics. Second, in the absence of hyperaldosteronism, the distal and collecting tubules, which are downstream from the loop of Henle, have a limited capacity for sodium reabsorption and are incapable of mitigating the diuresis induced by loop diuretics. These agents circulate in blood strongly bound to plasma proteins. At the proximal tubule, they are actively secreted into the tubular lumen by the organic acid transport pathway from which they are carried with the luminal fluid to the ascending limb.
of the loop of Henle. Therefore, the active fraction of loop diuretics is that which reaches the tubular lumen. The natriuretic action of loop diuretics is mainly related to their inhibitory effect on a specific cotransport system, the $\text{Na}^+2\text{Cl}^-\text{K}^+$ carrier, in the luminal membrane of the ascending limb cells. Loop diuretics increase the renal synthesis of prostaglandins, which are powerful natriuretic substances [2]. Therefore, prostaglandins may also be involved in the natriuretic effect of these drugs. In fact, prostaglandin inhibition reduces the natriuretic activity of loop diuretics [2].

Spironolactone has a much lower natriuretic potency than loop diuretics. It can increase sodium excretion to 2% of the filtered sodium. Spironolactone inhibits sodium reabsorption in the distal and collecting tubules by antagonizing the tubular effect of aldosterone and is therefore particularly effective in patients with hyperaldosteronism. The therapeutic dosage of spironolactone depends on the plasma aldosterone concentration [3]. Patients with moderately increased aldosterone levels require low doses of the drug (100–150 mg/day). However, as much as 500 mg/day may be required to antagonize the tubular effect of aldosterone in cases of marked hyperaldosteronism.

Contrary to what would be expected on the basis of their intrinsic natriuretic potency, spironolactone is more effective than loop diuretics in nonazotemic patients with cirrhosis and ascites. The administration of a loop diuretic alone is followed by a satisfactory diuretic response in only 50% of these patients [3]. In contrast, spironolactone is effective in most cirrhotics without renal failure [3, 4]. This apparently paradoxical observation could be explained by considering the site of action of these agents and the mechanism of sodium retention in cirrhosis. Cirrhotics with ascites usually present a marked hyperaldosteronism and tend to retain sodium avidly in the distal nephron. On the other hand, loop diuretics inhibit sodium reabsorption in the ascending limb of the loop of Henle but have no effect in the distal nephron. Therefore, it is possible that loop diuretics fail to increase sodium excretion in many of these patients because most of the sodium not reabsorbed in the loop of Henle by the action of these agents is subsequently taken up along the distal nephron by the action of aldosterone. In fact, in one of these studies, patients not responding to furosemide were those with higher plasma aldosterone levels [3]. The most rational treatment of cirrhotics with ascites is therefore the administration of spironolactone alone or associated with a loop diuretic. A therapeutic schedule used in many centers starts with 40 mg/day furosemide and 100 mg/day spironolactone. If there is no response, the dosage is increased stepwise to 160 mg/day furosemide and 400 mg/day spironolactone. Patients not responding to this program should be considered as having diuretic-resistant ascites.

The response to diuretics in patients with cirrhosis and ascites can be predicted on the basis of renal function [1]. Patients with normal BUN and serum creatinine concentration usually respond to standard doses of these agents. By contrast, cirrhotics with impaired GFR do not respond to diuretics or require very high doses of these drugs. This different behavior is probably related to differences in intrarenal sodium handling. In nonazotemic cirrhotics the main cause of sodium retention is increased distal sodium reabsorption, a process that can be reversed with the diuretics currently available. By contrast, the predominant mechanisms of sodium retention in patients with impaired renal hemodynamics are decreased sodium filtration and enhanced sodium reabsorption in the proximal tubule. An additional mechanism contributing to the poor response to diuretics in patients with azotemia may be impaired tubular secretion of these agents.