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Review

The Rational Use of Diuretics in the Management of Cirrhotic Ascites in Japan

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Abstract

In cirrhosis, portal hypertension and hypoalbuminemia (due to decreased albumin synthetic capacity) and hormonal imbalance (due to increased renin-angiotensin-aldosterone and vasopressin systems) cause fluid retention and electrolyte abnormalities. Diuretics are indispensable for the control of body fluid volume in liver cirrhosis, and aldosterone antagonists and loop diuretics have been widely used. In Japan, tolvaptan, a vasopressin V2 receptor antagonist, became available in September of 2013, expanding treatment options. This drug has been reported to be effective in improving hyponatremia and ascites in combination with aldosterone antagonists and loop diuretics without markedly affecting renal function. Excessive diuretic use should be avoided because it can cause deterioration of renal function, which influences the vital prognosis of liver cirrhosis. Therefore, it is important to choose appropriate diuretics to protect renal function.

Keywords

Cirrhotic ascites; aldosterone antagonists; loop diuretics; vasopressin V2 receptor antagonist

1. Introduction

Cirrhosis is the terminal manifestation of chronic liver injury, characterized by symptoms of hepatic failure such as jaundice, ascites, and hepatic encephalopathy, as well as esophagogastric varices caused by portal hypertension due to hepatic fibrosis. The treatment may be for the condition itself (use of direct acting antiviral drugs for the hepatitis C virus) or for complications such as ascites and hepatic encephalopathy.

Ascites refers to the condition in which fluid accumulates beyond the physiological limit in the peritoneal cavity, and it is one of the important complications of liver cirrhosis. Diuretics are the mainstay of treatment, and at present, aldosterone antagonists, loop diuretics, and vasopressin V2 receptor antagonists are used in Japan. These diuretics act on different nephron segments. In liver cirrhosis, it is reported that the vital prognosis deteriorates in complicated cases of acute kidney injury (AKI) [1], cases with high serum creatinine levels [2], and cases with low serum sodium (Na) levels [3]. The appropriate use of diuretics is important. This article reviews the pathogenesis of ascites, and the mechanism of action, characteristics, and use of these diuretics.

2. Pathophysiology of Cirrhotic Ascites

Ascites due to cirrhosis is caused by a combination of several factors, including systemic circulatory, renal, and hepatic factors (Figure 1).

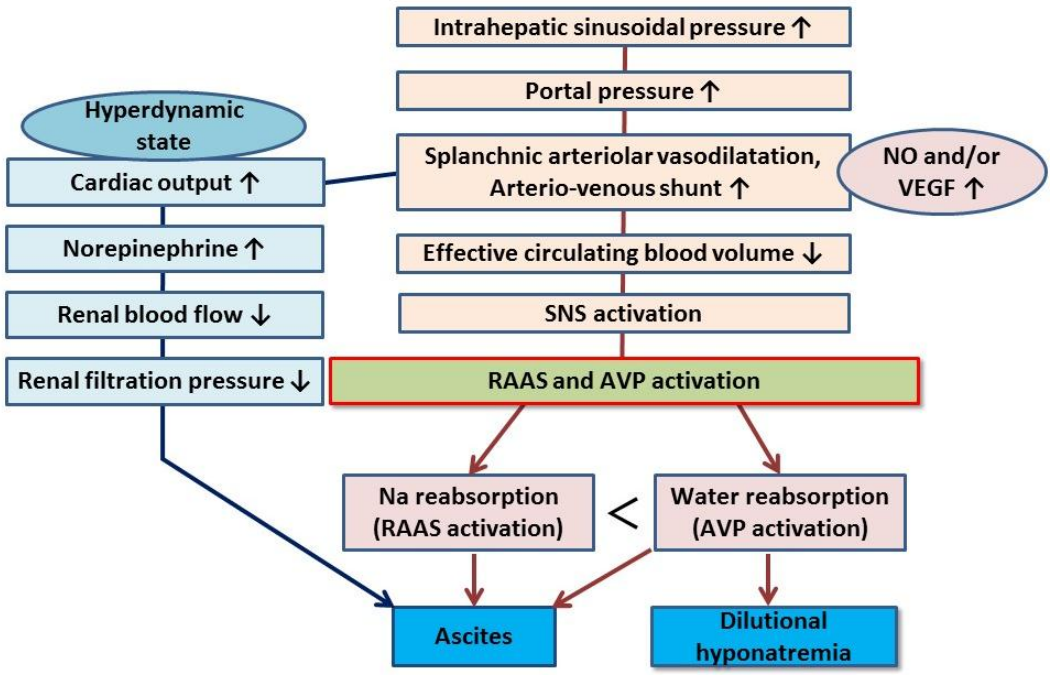

Figure 1 Pathophysiology of hepatic ascites.

Hepatic ascites is caused by systemic, renal, and hepatic factors among others, mutually influencing each other.

Abbreviations: NO; nitric oxide, VEGF; vascular endothelial growth factor, SNS; sympathetic nervous system, RAAS; renin-angiotensin-aldosterone system, AVP; arginine vasopressin (adapted from [25])

In cirrhosis, compression of the hepatic venous or portal branches impairs hepatic venous outflow, causing increased intrahepatic sinusoidal pressure, portal hypertension, and peripheral branch permeability. In addition, vasodilators such as nitric oxide and vascular endothelial growth factor are increased, and peripheral blood vessels dilate and form shunts over time. On the other hand, lowering of the protein synthesis ability lowers intravascular colloid osmotic pressure due to hypoalbuminemia. This results in the lowering of the effective circulating volume of blood and activation of the sympathetic nervous system. Activation of the renin-angiotensin-aldosterone system (RAAS) and the arginine-vasopressin (AVP) leads to the reabsorption of Na and water, respectively. This results in the retention of ascites. The water content of the body is determined by the movement of Na and water, but the change in the movement of water is greater than that of Na. In cirrhosis, cardiac output increases (hyperdynamic state) and norepinephrine increases to induce peripheral vasodilation. As a result, renal blood flow and renal filtration pressure decrease, contributing to ascites retention.

3. Aldosterone Antagonists (Spironolactone and Potassium Canrenoate)

This is the first choice diuretic in accordance with the pathophysiology of fluid retention in liver cirrhosis [4]. The collecting tubule, where the drug acts, moves Na ions into the cell through the Na channels on the luminal side of the epithelial cell, causing a negative potential difference in the lumen, and creating an electrical gradient that allows the secretion of potassium (K) from the cell into the lumen. The drug inhibits Na reabsorption by regulating the ability and number of the Na channels to open on the luminal side of the epithelial cells. Na reabsorption at this site is 2% to 3% of the glomerular filtered Na content and is less diuretic than loop diuretics. A small amount of ascites may be controllable with spironolactone alone, but if it is ineffective, a combination therapy with loop diuretics or vasopressin V2 receptor antagonists is recommended. Potassium canrenoate is used when oral diuretics are ineffective. Inhibition of Na reabsorption by the drug may cause hyperkalemia because it indirectly inhibits K release. Renal dysfunction is frequently combined in cirrhotic ascites [5], and regular follow-up of the serum K level is necessary. The drug also has a high affinity for the androgen and progesterone receptors, and long-term use may cause gynecomastia, mastalgia, and menstrual abnormalities.

4. Loop Diuretics (Furosemide)

The ascending limb of Henle's loop, on which the drug acts, is impermeable to water but highly permeable to Na and chloride (Cl), which are actively reabsorbed from the lumen into the cells through the Na-K-2Cl cotransporter on the luminal side of epithelial cells. The drug inhibits reabsorption of Na and Cl by inhibiting the Na-K-2Cl cotransporter. Na reabsorption at this site is as much as 20% to 25% of the glomerular filtered Na content and thus exerts a strong diuretic effect. In terms of fluid retention in cirrhosis, the efficacy rate when used alone has been reported to be approximately 50% [6]. It is usually used in combination when the aldosterone antagonist is ineffective.

The drug is largely bound to albumin in the blood, and when it reaches the capillary around the proximal tubule, the organic anion transporter removes albumin, secretes it into the lumen, and is transported to the ascending limb of the loop of Henle to exert diuretic action. Thus, furosemide is not effective under a low serum albumin condition.

Adverse effects include electrolyte abnormalities such as hypokalemia, hyperuricemia, glucose tolerance abnormality, and hearing loss. Importantly, liver cirrhosis is the deterioration of renal function and hyponatremia caused by long-term overdose of drugs [7], which also influences the vital outcome of the disease, as described earlier.

5. Vasopressin V2 Receptor Antagonist (Tolvaptan)

Because the ascending limb of Henle's loop and the distal tubule are not permeable to water, the urine reaches the collecting tubule in a diluted state. Vasopressin binds to the vasopressin V2 receptor on the vascular side of the epithelial cells of the collecting tubule, and the cAMP-dependent movement of water channels aquaporin 2 (AQP-2) to the luminal side of the epithelial cells leading to water reabsorption and concentration of urine. Tolvaptan is a selective vasopressin V2 receptor antagonist that binds more potently than vasopressin, and binding to the V2 receptor returns AQP-2 to epithelial cells, inhibiting water reabsorption and increasing urine output [8]. The drug is used in combination with spironolactone and/or furosemide and has the following characteristics:

1) Reduced effect on renal function

A single-dose cross-over study in patients with congestive heart failure reported that the drug did not reduce renal blood flow or glomerular filtration rate [9]. In the Phase 3 study in Japan, the drug had no adverse effect on serum creatinine levels [10].

2) Diuretic effect is not affected by serum albumin levels

In a post hoc analysis summarizing four Japanese clinical studies on hepatic ascites, the drug was found to have diuretic effects (weight loss and urine output gain) independent of serum albumin levels [11]. As noted above, furosemide may act from the luminal side of the tubule, whereas the drug may act on the vasopressin V2 receptors on the vascular side of epithelial cells.

In addition, an improvement in the effect of lowering serum Na concentration can be expected, which often is noted when existing diuretics such as spironolactone or furosemide are used [10]. Adverse effects may require appropriate serum Na levels and hydration because they may cause dehydration and hypernatremia if they develop profoundly and fluid restriction continues. As serious hepatic dysfunction may occur from the early stage of the drug administration, liver function tests should be performed frequently during the first two weeks of administration and as needed thereafter.

The assessment of the therapeutic effects of the drug is a 1.5kg reduction in body weight per week and a reduction in symptoms of edema, abdominal fullness, and dyspnea [12]. Basically, high pre-dose urine osmolality, and a decrease in urine osmolality 4 hours after use when the blood concentration peaks, are crucial to consider the effects of the drug. Urinary osmolality of > 352 mOsm/L in the morning before initiation and decrease in urine osmolality of at least 26% in the first 4 to 6 hours has been reported as responses in patients with decompensated heart failure [13].

Recently, several retrospective studies have analyzed the prognostic effect of tolvaptan in patients with decompensated cirrhosis [14-16]. Their results revealed that the survival of tolvaptan users or responders was significantly higher than that of nonusers or non-responders. Future prospective studies are essential to verify the effect of tolvaptan on the prognosis of patients with decompensated cirrhosis.

6. How to Use Diuretics for Hepatic Ascites in Japan

The treatment principle of hepatic ascites is to administer diuretics and recommend bed rest, water restriction, and mild salt restriction (5–7g/day) to a certain degree that does not cause anorexia. However, because excessive rest promotes a decrease in muscle mass, patients should be instructed to exercise aerobically for about 30 min at a time. The American Association for the Study of Liver Diseases (AASLD) recommends that one of the first-line treatments for hepatic ascites is extreme salt restriction (2g/day) [17]. However, extreme salt restriction not only leads to protein malnutrition due to anorexia, but also increases the rate of renal dysfunction and hyponatremia associated with diuretics [18]. The European Association for the Study of the Liver (EASL) currently recommends moderate salt restriction (4.6–6.9g/day) [19]. In cirrhotic ascites, renal dysfunction such as lowering of glomerular filtration rate and renal plasma flow rate already occurs [5]; therefore, it is important to prevent further damage to the liver when treating ascites. The importance of branched-chain amino acid-containing nutrient supplementation for refractory ascites has been reported [20], and should be used as the principal treatment.

The EASL guidelines recommend oral spironolactone as the first-line treatment for hepatic ascites, with the addition of furosemide if treatment fails [19], whereas the AASLD guidelines recommend the usual regimen of a single morning dose of oral spironolactone and furosemide [17]. A common feature of the AASLD and EASL guidelines is the maximum dose of oral spironolactone and furosemide of 400mg/day and 160mg/day, respectively; however, these doses of diuretics were found to cause dehydration and hyponatremia in Japanese patients.

Currently, we recommend the use of diuretics as shown in Figure 2. Spironolactone is the first-line drug for small ascites. It takes three to four days until the effect is manifested, but it is effective in 50% to 90% of cases [6]. If dose escalation to 50 mg/day is ineffective, furosemide is administered concurrently. The drug exerts a more rapid and potent diuretic effect than spironolactone; however, because overdose leads to a variety of complications, such as those described in the earlier sections, and to a decrease in the efficacy of tolvaptan [21], the dose may be increased to only 20 mg/day and, if ineffective, may be combined with tolvaptan after hospitalization.

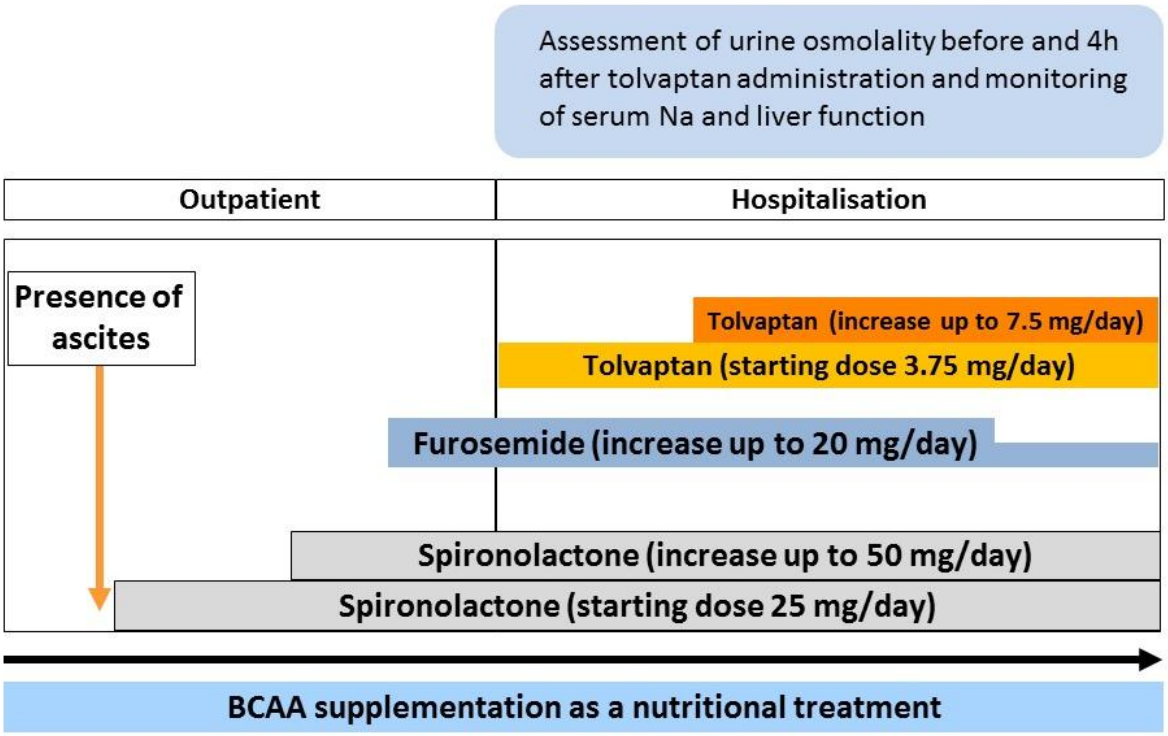

Figure 2 Diuretic treatment based on evidence-based clinical practice guidelines for liver cirrhosis 2015 - from outpatient setting to inpatient hospitalization.

If ascites is poorly controlled when the dose of spironolactone is increased to 50 mg/day and the dose of furosemide increased to 20 mg/day in the outpatient setting, start with 3.75 mg/day of tolvaptan in the hospital. If tolvaptan is ineffective for about 3 to 5 days, the dose is increased up to 7.5 mg/day. If tolvaptan is effective, the dose of furosemide is reduced without reducing the tolvaptan dose. It is important to introduce tolvaptan before renal function deteriorates though overdose of the pre-existing diuretics.
Abbreviations: BCAA; branched-chain amino acids. Adapted from [25].

Tolvaptan administration begins at 3.75 mg/day and includes the measurement of urine osmolality before and 4 hours after initiation, and the checking of serum Na levels and liver function. In cases of decreased urine osmolality, the treatment is considered responsive and continued. If urine osmolality is decreased for about three to five days but no weight loss is observed, the dose is increased to 7.5 mg/day (maximum dose for hepatic ascites). There are several possibilities when maximal dose escalation is ineffective (unchanged urine output or ascites/body weight). If renal blood flow is decreased due to increased abdominal pressure, abdominal paracentesis or Cell-free and Concentrated Ascites Reinfusion Therapy (CART) is performed. Intravenous administration of the human serum albumin infusion is carried out if renal blood flow is lowered because of intravascular dehydration. Decreased interstitial osmolality of the kidney medulla occurs with high-dose and long-term use of furosemide, which may be beneficial when the dose of furosemide is reduced [22]. If it is judged to be effective, control of ascites is done by reducing the furosemide dose without reducing the dose of tolvaptan to protect renal function.

The intravenous administration of potassium canrenoate and loop diuretics is implemented when the improvement of hepatic ascites is not observed with oral diuretics. If diuretics are ineffective and serum albumin level is less than 2.5 g/dL, albumin infusion therapy should be considered with the goal of 3.0 g/dL to increase the efficacy of loop diuretics. Albumin increases plasma colloid osmotic pressure and effective circulating volume of plasma, resulting increment of urine volume, and the inhibitory effect of the RAAS is also expected. Ascites resistant to diuretics may be treated by large volume paracentesis, CART, peritoneal venous shunts, and transjugular intrahepatic portosystemic shunts. Some of these procedures can cause serious complications; therefore, it is important to evaluate the patient's condition appropriately. Details on these procedures are not included in this paper.

7. Conclusion

The treatment of hepatic ascites hitherto has involved the excessive use of pre-existing diuretics such as aldosterone antagonists and/or loop diuretics, and dehydration and AKI was induced. Repeated AKI is known to lead to chronic kidney disease and may affect the prognosis of patients with cirrhosis [23]. If tolvaptan is introduced before the overdose of those pre-existing diuretics, it may contribute to the long-term survival of decompensated cirrhotic patients with the aim of preventing AKI. Although the assessment of the safety and effect of long-term administration of tolvaptan is still inadequate [24], future studies will improve our understanding of these diuretics and validate the need to choose these diuretics appropriately to improve prognosis and the quality of life of cirrhotic patients.

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Author Contributions

MT and ST contributed to the literature review, drafting and editing of the manuscript.

Competing Interests

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