ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Terlipressin for the Treatment of Hepatorenal Syndrome

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G&H Can you describe the pathophysiology of the hepatorenal syndrome?

TB Hepatorenal syndrome is a complication of the portal hypertension that occurs in patients with cirrhosis. Historically, it had been theorized that hepatorenal syndrome is caused by active renal vasoconstriction. However, treatment with vasodilators results in transient improvement in kidney function that is not sustained with the cessation of treatment. More recently, it has been confirmed that these patients also develop a form of the hyperdynamic circulation where they are vasodilated peripherally and in the splanchnic bed. This causes a misdirection of the blood away from the kidney, largely into the splanchnic bed, and the kidneys respond to this seeming shortage of blood as they would in cases of shock, with the production of excess renin-angiotensin and retention of sodium, which causes renal vasoconstriction and ascites. Fatality associated with hepatorenal syndrome is very high, with median time to death of 2–6 weeks in patients with type 1 disease. As an important overall determinant of survival in liver disease, renal function also factors heavily into the Model for End-stage Liver Disease score that prioritizes patients for transplant candidacy.

G&H What is the rationale for the use of terlipressin in these patients?

TB With the understanding of the role of the hyperdynamic circulatory state, it has been theorized that an agent that could lessen the vasodilation in the splanchnic bed would, in turn, improve kidney function. Terlipressin is an analog of the vasoconstrictor vasopressin, which is used to treat bleeding esophageal varices, another sequelae of portal hypertension. The problem with vasopressin is that it is a very potent vasoconstrictor, which, if administered via a peripheral vein, can cause tissue necrosis as well as cardiac and intestinal ischemia. Terlipressin, a prodrug of vasopressin, is converted into vasopressin in the tissue, but it is a much safer drug with fewer side effects. It has been found in uncontrolled trials that when terlipressin is given in combination with albumin, which expands the blood volume, renal function in patients with hepatorenal syndrome is improved.

G&H Can you describe the findings of the latest studies of terlipressin for hepatorenal syndrome?

TB Two randomized, controlled trials have been completed, one largely in the United States (112 patients at 35 sites), with a few patients in Russia and Germany, the other in Spain (46 patients in 9 sites). Both compared terlipressin plus albumin to albumin alone in the treatment of type 1 hepatorenal syndrome. The results of both studies have been presented in abstract form within the past year, and full papers have been submitted for publication. Both studies showed that terlipressin improves renal function in these patients.

No significant overall survival benefit was shown in either study. This was because the number of patients enrolled was not large enough to show a survival benefit. There was a survival benefit demonstrated within the subgroup of patients who responded to therapy versus those who did not, regardless of which therapy (albumin alone or albumin plus terlipressin) elicited a response. Approximately twice as many patients responded to terlipressin as responded to albumin alone. These results show a proof of concept that giving a vasoconstrictor to reduce vasodilatation in the splanchnic bed redistributes the blood back to the kidney and improves kidney function.

G&H Is future research with terlipressin expected to provide more definitive proof of survival benefit?

TB Hepatorenal syndrome is a rare disorder with a rapid course where patients die very quickly, which makes study enrollment extremely challenging. We calculated that an enrollment of 800 patients would be necessary to power a study for statistical significance in terms of survival benefit. It is unlikely that we will ever be able to conduct a trial on this scale, simply due to the rarity and natural course of the disease. The current data are slated for submission to the US Food and Drug Administration as is, with the hope of obtaining approval for terlipressin as a treatment for hepatorenal syndrome.

G&H Do these findings indicate new directions for future research?

TB These findings, and the proof of concept that they provide, change the paradigm in terms of research and treatment of portal hypertension. With the understanding of the hyperdynamic circulation as the potential root of cirrhosis-related complications, new approaches can be investigated for treatment of cardiac complications as well as the hypotensive state associated with end-stage liver disease. Overall, hypotension is very common in patients with liver disease. When they get to the end stage of disease, they often die a hypotensive death. They are also very susceptible to septic shock. This raises the question of whether terlipressin can be used to manage shock in the broader population of cirrhotic patients. Limited studies showing some benefit in this condition have already been conducted.

G&H How do you envision terlipressin providing benefit in the scenario of patients undergoing liver transplantation?

TB Terlipressin could potentially provide significant benefit in the arena of transplantation. Overall outcomes of transplant in patients in renal failure are not good. If renal failure can be effectively treated before transplantation, so that patients are not on dialysis at the time of the procedure, outcomes will be better.

Although renal complications of cirrhosis are reversible after transplant, the longer a patient is on dialysis, the worse their overall outcome is likely to be and the greater their chance of ultimately requiring liver-kidney transplant. Thus, preventing these patients from progressing to dialysis is key, particularly as patients with acute renal disease and a serum creatinine measure of greater than 6–7 mg/dL do not appear to benefit from terlipressin therapy. In order for this therapy to be effective, transplant candidates with hepatorenal syndrome need to be identified earlier and treated before they require dialysis.

G&H How can future monitoring of cirrhotic patients be improved to optimize terlipressin therapy?

TB Improved monitoring is important, but in addition, gastroenterologists and hepatologists need to be very careful in diagnosing this disorder, as most cirrhotic patients with renal failure do not have hepatorenal syndrome. Septic shock is a far more common cause of renal dysfunction in these patients. In this regard, doctors can potentially err in using terlipressin inappropriately for the wrong condition. In cases of suspected hepatorenal syndrome, a urinalysis should be conducted by a nephrologist to determine whether there are granular casts or white cells in the urine. If either of these is present, the patient most likely does not have hepatorenal syndrome. Urinalysis is a cheap, simple test, but in this particular instance, the analysis needs to be done by an experienced nephrologist who can confirm that no other process is at work in causing renal failure. Educating all involved clinicians in the proper diagnosis of hepatorenal syndrome will be key in the proper use of terlipressin, if the drug is ultimately approved for use in this condition.

Suggested Reading

Martin-Liahi M, Pepin MN, Guevara M, Torre A, Monescillo A, et al. Randomized comparative study of terlipressin and albumin vs albumin alone in patients with cirrhosis and hepatorenal syndrome. Abstract presented at the 42nd Annual Meeting of the European Association for the Study of the Liver; April 11-15, 2007; Barcelona, Spain.

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