ADVANCES IN HEPATOLOGY

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Examining the New Definition of Hepatorenal Syndrome and the Role of Terlipressin

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G&H How common is hepatorenal syndrome, and what are its potential consequences?

RB Hepatorenal syndrome is the most serious complication of cirrhosis and portal hypertension and the complication that is most likely to lead to death in the short run. In the setting of cirrhosis and portal hypertension with ascites, up to 40% of patients with acute kidney injury who are admitted to the hospital have hepatorenal syndrome; thus, it is an important consideration in patients who present with deterioration in their renal function. The more severe the kidney injury, the more likely it is hepatorenal syndrome. In patients with hepatorenal syndrome, the likelihood of dying in the next 90 days is extremely high, which is why clinicians should recognize the condition to be a potential emergency that requires intervention.

G&H How and why has the definition of hepatorenal syndrome evolved?

RB It has long been recognized that hepatorenal syndrome is a functional renal failure, meaning that the kidney itself is normal and the condition is potentially reversible. However, owing to changes associated with cirrhosis and portal hypertension, the kidney is experiencing decreased blood flow and, at the same time, trying to maximally reabsorb water and salt from urine, resulting in very small amounts of highly concentrated urine. The definition of hepatorenal syndrome has evolved in part to match the definition of acute kidney injury used by nephrologists.

In addition, hepatologists wanted to identify patients with hepatorenal syndrome at an earlier stage to increase the likelihood that intervention can be successful. Patients with cirrhosis and ascites have worse renal function, measured by glomerular filtration rate, at any level of serum creatinine. Thus, prior definitions of hepatorenal syndrome using higher serum creatinine cutoffs (either serum creatinine doubling or >1.5 mg/dL) did not capture patients with an earlier stage of hepatorenal syndrome. The new definition uses a smaller increase in serum creatinine of 0.3 mg/dL or greater than 50% above the patient's baseline.

Additionally, the new definition attempts to make the diagnosis of hepatorenal syndrome easier, particularly if a patient is producing very little urine. The requirement for oliguria was removed (because urine output can be difficult to measure in the hospital at times), as was the requirement for low urine sodium.

G&H What are the advantages and challenges of adopting the new definition in terms of clinical trial design and clinical practice?

RB I believe that the new definition is quite good and certainly works. Previously, a fixed cutoff of 1.5 mg/dL was used for serum creatinine, which may or may not have represented any change from baseline if the patient had chronic kidney disease, or may have represented a large change if the patient had a baseline serum creatinine of, for example, 0.7 mg/dL. This was a heterogeneous measure. In contrast, using a 0.3 mg/dL increase in serum creatinine captures only patients whose serum creatinine

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has changed, which is advantageous. In the long run for clinical trial design, the new definition will allow for the identification of patients at an earlier stage, who are more likely to achieve a greater benefit from an intervention than patients with more advanced kidney dysfunction.

The challenge is that a 0.3 mg/dL increase in serum creatinine from baseline can be difficult to recognize in clinical practice and is not typically flagged for review or for being abnormal. In the absence of having a good baseline, it also becomes more difficult to identify patients with early hepatorenal syndrome. Clinicians may need to observe patients in the hospital to document that their serum creatinine is still rising in order to meet the new definition.

Certainly in clinical practice, better education of gastroenterologists, hepatologists, primary care physicians, and even nephrologists will be needed regarding the fact that patients with liver disease have a lower baseline serum creatinine in general; providers will have to pay more attention to small changes in serum creatinine so that they do not miss any patients with acute kidney injury at an earlier stage. For example, with the previous hepatorenal syndrome definition, a provider might have waited for serum creatinine to reach 2.0 mg/dL, which would have been a doubling of serum creatinine if the patient had started at 1.0 mg/dL. However, ideally, the provider would have noticed the patient at an earlier stage, which might not have been considered to be abnormal yet. Thus, better education will be needed or perhaps enhanced algorithms will need to be built into electronic data systems to recognize smaller changes from baseline, even if they have not yet exceeded the upper limit of normal.

G&H Are there any limitations to the new definition of hepatorenal syndrome?

RB The new definition does not include some clinical features of hepatorenal syndrome that are useful for practicing physicians to know. For example, although oliguria is not required in the new definition, patients with hepatorenal syndrome are oliguric because this condition is a functional renal failure marked by diminution in the production of glomerular filtrate and thus urine. Similarly, because hepatorenal syndrome is a state of low systemic vascular resistance, most patients will be relatively hypotensive, with a low systolic blood pressure and mean arterial pressure. These patients should have a sodium-avid kidney with low urine sodium unless they have developed superimposed acute tubular necrosis. These are helpful adjuncts for making a clinical diagnosis. For practicing physicians, knowing what hepatorenal syndrome looks like may help in making the diagnosis sooner and more accurately. However, I agree with not requiring these clinical signs and symptoms in the new hepatorenal syndrome definition.

G&H Could you discuss key recent data on the efficacy and safety of terlipressin in patients with hepatorenal syndrome?

RB Terlipressin (Terlivaz, Mallinckrodt) has been examined in multiple studies for decades, both in Europe and the United States; however, it was approved by the US Food and Drug Administration only this past September. Approval was based on the CONFIRM registrational trial, the results of which were published by Dr Florence Wong and colleagues in *The New England Journal of Medicine*. This study showed that terlipressin was twice as effective as placebo at reversing hepatorenal syndrome type 1, now known as hepatorenal syndrome–acute kidney injury, which is the more sudden and acute form of hepatorenal syndrome. Additionally, the study showed that the persistence of hepatorenal syndrome reversal was more likely with terlipressin than placebo. Finally, the need for renal replacement therapy or dialysis, both before and after liver transplant, was lower in patients treated with terlipressin. Clearly, the efficacy of terlipressin is well established.

However, there was an important safety signal, as the study found an increased risk of respiratory failure in patients treated with terlipressin. This led to an important safety warning in the label and the need to be very cautious with volume repletion in patients being treated with terlipressin, as overuse of albumin and overaggressive volume repletion will increase the risk of pulmonary edema and volume overload. It is important to avoid over-resuscitation with albumin, although the 2-day albumin challenge (1 g/kg/day) prior to the diagnosis of hepatorenal syndrome is still key. It is also important to monitor patients' pulmonary function with oxygen saturation prior to and during therapy and to stop therapy if patients develop worsening or new hypoxemia. Additionally, as with all vasoconstrictors, there were increased rates of abdominal pain compared with placebo, likely

owing to the intestinal ischemia that is well known with these drugs.

G&H What should be the current role of terlipressin in patients with hepatorenal syndrome?

RB Terlipressin is recommended as the first-line vasoconstrictor for hepatorenal syndrome in the US guidelines from the American College of Gastroenterology and the American Association for the Study of Liver Diseases as well as in guidelines from the European Association for the Study of the Liver. The guidelines are clear that once a patient presents with an acute kidney injury and does not respond to withdrawal of diuretics or the administration of an albumin challenge (1 g/kg/day for 2 days), terlipressin should be the first-line agent and albumin should be continued at a lower dose. Terlipressin should replace the use of midodrine plus octreotide outside of the intensive care unit (ICU). Midodrine plus octreotide was mainly being used because it could be administered outside an ICU; however, its efficacy has not been clearly established. In an ICU, noradrenaline can be used as an alternative to terlipressin, but it requires a central venous line and ICU monitoring in most instances. Thus, for patients who are still on a regular floor bed or in a step-down unit, where noradrenaline is not available, terlipressin has a clear advantage. In the ICU, the choice should be made based upon clinician comfort and perhaps cost. However, the only treatment option currently approved by the US Food and Drug Administration for hepatorenal syndrome type 1 (hepatorenal syndrome–acute kidney injury) is terlipressin, and it should be used as early as possible because its efficacy is substantially lower in patients who have high serum creatinine (>5 mg/dL) or high Model for End-Stage Liver Disease (MELD) scores.

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G&H Are there any other safety concerns or limitations regarding terlipressin treatment in this setting?

RB Most important, as mentioned before, is respiratory failure and the need to avoid volume overload. In my clinical practice, after I perform an albumin challenge, I tend to use 20 to 40 g of albumin per day during vasoconstrictor therapy. I titrate that amount, aiming for a serum albumin between 3 and 3.5 g/dL, although individual practice on ongoing albumin administration varies. I also try to avoid excessive use of crystalloid during this time. This is very important, particularly if the patient does not make a lot of urine on vasoconstrictor or terlipressin therapy; any excess fluid that is given increases the risk of pulmonary edema and respiratory compromise.

In addition, monitoring the patient's blood pressure or for any signs of ischemia, including abdominal pain, is critical. It is also important to follow the algorithm for stopping therapy in patients who do not respond to treatment at day 4 to avoid excess risk of adverse effects with a low likelihood of success.

G&H Are there any misconceptions in the medical community in this area?

RB One misconception is that hepatorenal syndrome is uniformly fatal and, as a result, there is no reason to administer any therapy. This is clearly not true. As seen in the CONFIRM trial, some cases of hepatorenal syndrome can be reversed. Terlipressin therapy can also be a bridge to transplant or liver recovery, if the latter is possible. People who develop hepatorenal syndrome have a high likelihood of developing recurrence, and that recurrence is associated with adverse consequences. Therefore, when I treat patients with hepatorenal syndrome, I am always thinking about what I am trying to bridge patients to. Generally, that is a liver transplant. If patients are not liver transplant candidates, they can only be bridged to an improvement in liver function. If their liver function does not improve and they are not a transplant candidate, the likelihood of long-term survival is very low, and palliative care should be discussed.

There has also been some concern that the use of terlipressin in patients with high MELD scores would have an adverse impact on their transplant candidacy by lowering their MELD scores and decreasing access to liver transplant. Although this may be true, strategies should be developed to mitigate this issue, perhaps by

giving patients the priority they would have had before starting terlipressin, as is done for dialysis. Nevertheless, it is important to know that the majority of patients with hepatorenal syndrome will not undergo liver transplant. Additionally, improvement in renal function pre- and posttransplant with terlipressin is beneficial to patients; it is known that the need for dialysis pre- and posttransplant is associated with worse outcomes. A high MELD score or a patient who is not a candidate for liver transplant should not be considered an absolute contraindication to terlipressin therapy. Clinicians should make treatment decisions in the best interest of the patient but recognize that adverse events of terlipressin, particularly respiratory adverse events, may make transplant difficult or even impossible. Decisions should be made very carefully in this group of patients.

G&H What are the next steps in research involving terlipressin?

RB There are several important next steps in research. One involves studies examining dosing. Some data from Europe have supported administering terlipressin as a continuous infusion rather than an intermittent bolus, the way it was in the US clinical trial. Titrated continuous infusion may be associated with fewer adverse effects. Terlipressin can also be used for other complications in portal hypertension, including variceal bleeding. Terlipressin may be more effective than octreotide when combined with variceal band ligation. There is also ongoing research on other vasopressin analogs that may offer potential advantages in terms of efficacy, ease of use, or side-effect profiles, but further research is needed. Although terlipressin is a welcome addition to our armamentarium for the life-threatening complication of hepatorenal syndrome, further research and development are needed for additional and better therapies for patients who do not respond to or are not candidates for terlipressin. Even more importantly, research is also needed for earlier recognition, intervention, and perhaps even avoidance of the development of hepatorenal syndrome, which would be the ultimate goal.

Disclosures

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Suggested Reading

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