

ADVANCES IN HEPATOLOGY

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The Use of Nonselective Beta Blockers for Treatment of Portal Hypertension



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G&H What are the various stages of portal hypertension?

GG-T Portal hypertension, which simply refers to an increase in portal pressure, can occur in different stages based upon its severity. In compensated cirrhosis with mild portal hypertension, the portal pressure (as measured by the hepatic venous pressure gradient) is between 6 and 10 mm Hg. In compensated cirrhosis with clinically significant portal hypertension, the portal pressure (as determined by the hepatic venous pressure gradient) exceeds 10 mm Hg. In patients with decompensated cirrhosis, the portal pressure (as measured by the hepatic venous pressure gradient) exceeds 12 mm Hg, and a pressure greater than 16 mm Hg portends a poor survival.

G&H What is the cause of portal hypertension?

GG-T The most common cause is cirrhosis. In fact, cirrhosis is defined by the presence of portal hypertension; if a patient with chronic liver disease has portal hypertension, he or she has cirrhosis. In cirrhosis, portal hypertension results from an increased intrahepatic resistance and from increased blood flow into the portal venous system. Distortion of the liver architecture by fibrous tissue and regenerative nodules leads to an increase in resistance. However, at the same time, there is an increase in flow from the gut into the portal system because there is splanchnic vasodilatation—that is, the arterioles that feed the gut are dilated.

G&H What are the consequences of portal hypertension?

GG-T The most important consequences are those that constitute decompensation of cirrhosis, such as ascites, variceal hemorrhage, and encephalopathy. Once decompensation occurs, the mortality of patients with cirrhosis is significantly increased. The median survival of a patient without complications of portal hypertension is greater than 12 years, whereas in the decompensated patient, it is below 2 years.

G&H Which nonselective beta blockers are usually used to treat portal hypertension?

GG-T The nonselective beta blockers most commonly used in these patients are propranolol and nadolol. Another option is carvedilol, which is a nonselective beta blocker that also has an alpha-adrenergic vasodilating effect and causes a more marked reduction in portal pressure than traditional nonselective beta blockers. All nonselective beta blockers, including carvedilol, act by causing splanchnic vasoconstriction, thereby decreasing portal blood flow. Carvedilol has the added advantage that it may cause intrahepatic vasodilation inside the liver, therefore decreasing resistance.

G&H According to the studies conducted thus far, how effective are nonselective beta blockers in this setting?

GG-T They are very effective at different stages of cirrhosis. In patients who have high-risk varices (ie, varices that are likely to bleed), nonselective beta blockers significantly decrease the incidence of first variceal hemorrhage. In patients who have already bled from varices, nonselective

beta blockers prevent recurring variceal hemorrhage when used in conjunction with endoscopic ligation. The most important component of this therapeutic combination is the nonselective beta blocker. Recent data suggest that in patients with very compensated cirrhosis (ie, patients who have clinically significant portal hypertension but no or small varices), nonselective beta blockers can prevent clinical decompensation. Thus, nonselective beta blockers are effective at most stages of cirrhosis, from the patient with clinically significant portal hypertension who has no or small varices to the patient who has recovered from variceal hemorrhage.

G&H How can response to these agents be measured?

GG-T The hepatic venous pressure gradient can be measured before and after initiating nonselective beta blockers, and reductions in this pressure gradient have been predictive of good outcomes. Reducing the portal pressure by more than 20% from baseline or to a level below 12 mm Hg significantly decreases the risk of bleeding (or rebleeding) and also decreases the risk of developing other complications of portal hypertension such as ascites. However, measurement via the hepatic venous pressure gradient is invasive and is not routinely performed, so response to nonselective beta blockers is assessed by heart rate.

It should also be noted that the benefits of nonselective beta blockers may go beyond their portal pressure-reducing effects. For example, nonselective beta blockers may be anti-inflammatory and may reduce flow to varices without necessarily reducing portal pressure.

G&H Are there any significant risks associated with these agents?

GG-T A controversy has arisen because nonselective beta blockers also decrease cardiac output. Patients with cirrhosis and refractory ascites may be very dependent upon cardiac output to maintain an adequate arterial blood pressure. By potentially reducing the cardiac output, nonselective beta blockers may lead to a decrease in kidney perfusion and to hepatorenal syndrome, a condition with a high mortality. A study from France by Sersté and colleagues showed that, in patients with refractory ascites, those on nonselective beta blockers at the time of presentation died more than patients who were not on these agents. A subsequent study did not confirm the higher mortality of nonselective beta blockers in patients with refractory ascites but showed a higher mortality in patients with spontaneous bacterial peritonitis (an infection of ascitic fluid) who were on nonselective beta blockers at the time of presentation.

Notably, in both of these studies, the mean arterial pressure of the patients on nonselective beta blockers was significantly lower than in patients who were not on these agents. This suggests that the detrimental effect of these agents may be observed particularly in patients in whom the mean arterial pressure decreases. Thus, the mean arterial pressure cannot be allowed to decrease too much in a patient with cirrhosis taking nonselective beta blockers.

G&H Should these study findings affect the use of nonselective beta blockers in patients with portal hypertension?

GG-T Findings from these 2 trials led some physicians to discontinue nonselective beta blockers in patients with high-risk varices and even in those who had bled from varices, including patients who did not even have ascites. It is important to keep in mind that these were both small studies that did not match patients by severity of liver disease and did not assess the continued use (or not) of nonselective beta blockers during follow-up.

Importantly, since these trial results have been published, there have been numerous studies that have shown either that beta blockers are associated with lower mortality in patients with refractory ascites or that there is no difference in mortality. A meta-analysis of available studies concluded that the use of nonselective beta blockers is not associated with a significant increase in all-cause mortality in patients with cirrhosis and ascites or refractory ascites. Notably, in studies that showed no harmful effect, or a beneficial effect, with the use of nonselective beta blockers, the mean arterial pressure was not significantly different between beta blocker users and nonusers. Thus, it appears that beta blockers will be deleterious only if they are associated with a decrease in mean arterial pressure. Higher doses will be associated with a larger decrease in mean arterial pressure and have been shown to be the ones that are deleterious.

These findings are reflected in the new guidance for the management of portal hypertension. While in patients without ascites, maximum doses are 320 mg/day for propranolol (160 mg twice daily) and 160 mg once a day for nadolol, in patients with ascites (refractory or not) maximum doses are now capped at 160 mg/day for propranolol (80 mg twice daily) and at 80 mg once a day for nadolol.

G&H When are nonselective beta blockers contraindicated?

GG-T There are several compelling contraindications such as asthma, chronic obstructive pulmonary disease

with significant reversibility, and heart block. These occur in approximately 15% of patients with cirrhosis. Another 15% cannot tolerate even minimal doses of nonselective beta blockers because of side effects.

There are also instances when the use of nonselective beta blockers should be temporarily stopped. This is the case of patients who experience a decrease in systolic blood pressure to below 90 mm Hg, who develop acute kidney injury, and/or who develop hyponatremia that usually occurs in the setting of an acute event such as infection. In these cases, the dose of nonselective beta blockers should be reduced or discontinued, and once the acute event has resolved, the drug can be restarted. There is no reason to discontinue a nonselective beta blocker when a patient is tolerating it well and is stable on it, regardless of whether the patient has ascites and whether the ascites is refractory.

G&H If nonselective beta blockers are not an option, how should portal hypertension be treated?

GG-T For primary prophylaxis (ie, for patients who have never bled and have large varices), endoscopic ligation can be used. However, this treatment is a local therapy that obliterates varices and has no effect on portal pressure; therefore, it will not have any effect in delaying the development of other complications of portal hypertension such as ascites, as has been observed with nonselective beta blockers.

Treatment for recurrent variceal hemorrhage is more complicated. For patients who have bled, the standard therapy is endoscopic ligation plus nonselective beta blockers, and, as previously mentioned, the key element of this combination is the drug. If a patient cannot tolerate nonselective beta blockers, he or she is left with endoscopic ligation alone. However, one meta-analysis showed that in patients with Child class B and C (who often have ascites), endoscopic ligation alone to prevent recurrent variceal hemorrhage was associated with a significantly higher mortality compared to combination therapy. Therefore, in this setting, doctors should consider transjugular intrahepatic portosystemic shunts sooner rather than later.

G&H Are any promising treatments currently being investigated?

GG-T There are many treatment approaches currently being studied that involve intrahepatic resistance. One of the most promising is the use of statins such as simvastatin, which act by improving endothelial dysfunction inside the liver, causing vasodilation so that resistance decreases. A randomized, controlled trial of patients who have bled from varices showed that adding simvastatin to endoscopic ligation and nonselective beta blockers is associated with lower mortality.

G&H Are there any other important research needs in this area?

GG-T As previously mentioned, it is known that reducing portal pressure by 20% from baseline or to levels below 12 mm Hg protects patients from many of the complications of cirrhosis. The challenge is that response to traditional nonselective beta blockers occurs in only approximately 35% to 50% of patients. Research is needed to determine which therapy or combinations of therapy would increase the number of hemodynamic responders.

Dr Garcia-Tsao has no relevant conflicts of interest to disclose.

Suggested Reading

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