DIAGNOSTIC AND THERAPEUTIC ADVANCES IN HEPATOLOGY

Carvedilol for Portal Hypertension in Patients with Cirrhosis

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Patient with Portal Hypertension and Esophageal Varices

A 48-year-old male with hepatitis C–related cirrhosis is found on endoscopy to have large esophageal varices with red signs. He has never previously had variceal bleeding, and there is no evidence of hepatic encephalopathy. He does have mild ascites. Comorbidity includes diabetes which has been present for many years and is well-controlled on a stable dose of insulin. He has no cardiopulmonary disease. The hemoglobin is 12.4 g/dL, white blood cell count is 6800/mm^3, and platelets are 112 $\times$ 10^9/L. Serum bilirubin is 1.8 mg/dL, creatinine is 1.2 mg/dL, international normalized ratio is 1.3, and the serum albumin is 3.5 g/dL. The electrocardiogram and chest x-ray are normal. The ultrasound examination does not show portal vein thrombosis or hepatocellular carcinoma.

What is the role of carvedilol in the prevention of variceal bleeding in this patient? How will the dose of carvedilol be adjusted and how is the patient to be monitored for adverse drug events? When would carvedilol be preferred over nadolol or propranolol? Would the approach be different if the patient was of Child-Pugh class C cirrhosis?

Abbreviations: EVL, endoscopic variceal ligation; HVPG, hepatic venous pressure gradient; RCT, randomized controlled trial; TIPS, transjugular intrahepatic portosystemic shunt.

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The Problem

Portal hypertension is an almost unavoidable complication of cirrhosis, and provides the driving force for most of its complications, such as esophageal and gastric varices, variceal bleeding, portal hypertensive gastropathy, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, thrombopenia, leukopenia and anemia, and portal-systemic encephalopathy.[1] Recent studies have shown that for these complications to develop, the portacaval pressure gradient—evaluated clinically by the hepatic venous pressure gradient (HVPG)—should increase above 10 mm Hg and should be above 12 mm Hg for variceal bleeding.[2,3] The prevalence of varices is about 40% in asymptomatic compensated patients.[2] Development of varices follows an incidence of approximately 6% per year. The incidence is nearly double in patients with a baseline HVPG >10 mm Hg, who therefore represent a high-risk group.[2] These patients are also at higher risk of developing decompensation (ascites, bleeding, jaundice, encephalopathy) and hepatocellular carcinoma.[4,5] Because of this, there is a great interest in strategies to revert portal hypertension, since these would prevent portal hypertension-related complications, clinical decompensation, and death. The benefit of reduction of HVPG has actually been proven for patients exhibiting a "good hemodynamic response" to nonselective beta-adrenergic blockers; i.e., those who exhibit a decrease in HVPG > 20% of baseline or to values below 12 mm Hg during continued therapy,[6,7] or who show a decrease in HVPG >10% of baseline 20 minutes after an intravenous infusion of propranolol.[8,9]

Besides the increased intravascular pressure, the risk of bleeding from varices is further influenced by other factors, such as the diameter of the varices and the thickness of the variceal wall.[10] These factors are interrelated by Laplace's law in the concept of wall tension (t), according to which:

t = variceal transmural pressure

$\times$ variceal radius/wall thickness

Variceal bleeding is thought to occur when variceal tension exceeds the elastic limit of the vessel.[11] This concept is relevant because it explains the higher risk of bleeding of patients with any of the following: large varices, red "wales" (areas of decreased thickness), advanced liver failure (Child-Pugh class B and C, which correlates with higher HVPG).[11,12] Current guidelines recommend providing prophylactic therapy to patients with varices who have any of these high-risk indicators.[13,14] In practice, this means that all patients with varices should be treated except those Child A patients with small varices without red color signs.

Recommended therapy for primary prophylaxis includes the administration of nonselective beta-blockers (mainly propranolol and nadolol) or endoscopic variceal ligation (EVL) with elastic bands.[13,14] Meta-analysis of the many studies devoted to this issue shows that EVL is more effective in preventing bleeding, without survival benefit.[1,15,16] However, a recent Cochrane review[15] questioned this conclusion on the basis that restricting the analysis to studies with good quality standards shows no difference in bleeding rates, on the fact that these studies have a short follow-up, and on its uncertain effects in patients with relatively small varices. Analysis according to size of trials also showed no differences in efficacy in trials including more than 100 patients,[1,17] indicating that the reported benefit from EVL over beta-blockers comes from small and/or low-quality studies. EVL cause fewer complications than beta-blockers, but as it has been pointed out, complications from beta-blockers are mild and subside after dose-reduction or drug discontinuation, whereas those of EVL often require hospitalization and may be lethal.[16] Because of this, it is wise to start therapy with beta-blockers and reserve EVL for patients with large varices who have contraindications for beta-blockers or who develop side-effects requiring its discontinuation. Patients treated with EVL need to have frequent follow-up endoscopies because recurrence of varices requiring retreatment occurs in more than 50% of the cases during the first year. Recommended schedule of follow-up endoscopy is at 1 month of last EVL session (to confirm eradication), 3 months later, and every 6 months thereafter.

Carvedilol

Carvedilol is a potent nonselective beta-blocker with mild anti-alpha 1 adrenergic activity (one-tenth of its beta-blocker activity). It was developed for the treatment of arterial hypertension and heart failure, and has U.S. Food and Drug Administration approval for both indications. Milligram for milligram, carvedilol is 2-4 times more potent than propranolol as a beta-receptor antagonist.[18] Carvedilol further has antioxidant activity, which may be of interest in patients with cirrhosis, but this possible benefit has not been studied.

Figure 1 summarizes the mechanism by which carvedilol decreases portal pressure in patients with cirrhosis. In short, as a nonselective beta-blocker carvedilol decreases heart rate and cardiac output and causes splanchnic vasoconstriction. This results in reduced portal blood inflow and in a fall in portal pressure. In addition, through its alpha 1 adrenoceptor blocking effect, carvedilol decreases the hepatic vascular tone and hepatic resistance, resulting in a further decrease in portal pressure.[1] However, the vasodilating activity of carvedilol may enhance arterial hypotension and sodium retention, a risk which is especially relevant in patients with advanced, decompensated cirrhosis.[19,20,21]

Drugs that inhibit cytochrome P450 2D6 activity (quinidine, paroxetine, fluoxetine, propafenone) may increase plasma concentrations of *R*-carvedilol (a stereoisomer with alpha- and beta-adrenergic blocking activity). In contrast, plasma concentrations of *S*-carvedilol (which has only beta-blocker activity) increase much less.[19] Thus, these drugs increase the risk of hypotension during carvedilol administration. Patients

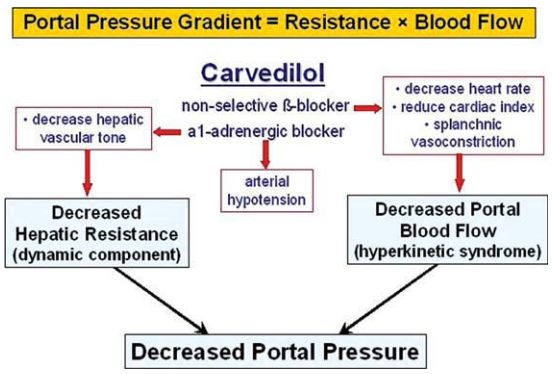

Fig. 1. Mechanism of the effects of carvedilol on portal pressure. Carvedilol is a potent nonselective beta-blocker, and as such, it decreases heart rate and cardiac index (blockade of beta-1 adrenergic receptors) and causes splanchnic vasoconstriction (blockade of beta-2 adrenergic receptors), which result in a reduced portal blood flow, and thereby in decreased portal pressure. This is the same mechanism of the portal pressure-reducing effect of propranolol or nadolol. In addition, carvedilol has mild anti-alpha 1 adrenergic activity, which results in decreased hepatic vascular tone and, hence, in a further reduction of portal pressure. However, the anti-alpha 1 adrenergic activity may result in arterial hypotension. Because of its combined effects, carvedilol is more powerful than propranolol or nadolol in decreasing portal pressure, but carries the potential risk of causing hypotension, which may be detrimental in patients with decompensated cirrhosis.

with genetic polymorphism of cytochrome P450 2DS are also at risk. Patients older than 65 years have a delayed clearance of carvedilol, as do patients with chronic liver disease.[19,21] Therefore, it is advised that carvedilol should be started at low doses (6.25 mg/day). If tolerated, the dose is increased stepwise up to a maximum of 25 mg twice daily (50 mg in patients weighing >85 kg).[19,21] Titration should be done slowly, increasing the dose at intervals of 1-2 weeks. The drug should be taken with food to slow the speed of absorption and reduce the likelihood of side effects.[19] The dose should not be increased in patients developing symptoms or with a systolic blood pressure <90 mm Hg or a heart rate <50 beats per minute (bpm).

There have been several studies on the use of carvedilol for portal hypertension in patients with cirrhosis.[19-28] Most of these studies assessed the effects of carvedilol on HVPG. The results show that carvedilol causes dose-related and marked decreases in HVPG (of about 20% from baseline), significantly greater than those caused by propranolol. Carvedilol causes a less marked reduction in cardiac index and azygos blood flow than propranolol, but a greater fall in arterial blood pressure (of about 10% with a 25 mg/day dose).[19] The effect on arterial blood pressure tends to be less pronounced on continued therapy.[20,28] Carvedilol does not decrease the glomerular filtration rate, but causes a significant increase in plasma volume, and about one-fourth of patients require an increase in the dose of diuretics (or to be started on diuretics).[20] Interestingly, patients with advanced liver failure (Child-Pugh class B or C) show greater decreases in HVPG than well-compensated patients, despite receiving lower doses.[19,20] This may be related to decreased carvedilol metabolism in patients with advanced liver failure.[21] Some studies suggest that relatively low doses of carvedilol (12.5 mg/day or 6.25 mg bid) retain a good portal pressure–reducing effect with less potential for hypotension, which may be relevant when treating decompensated patients with cirrhosis.[22,23]

Monitoring for Drug-Related Adverse Events

Side effects of carvedilol are similar to those of propranolol and nadolol, with the exception of a higher risk of hypotension and edema.[19,20,27] During titration, the patient should be specifically asked for drug-related adverse events (edema, dizziness, bradycardia, hypotension, nausea, blurred vision). The dose should not be increased in patients developing symptoms or with a systolic blood pressure <90 mm Hg or a heart rate <50 bpm. Body weight should be monitored because sodium retention is first manifested by weight gain; this may require low doses of a diuretic or an increase in dose if the patient was already on diuretics.[19] This occurred in about 25% of patients with cirrhosis in a well-controlled study.[20] In contrast, in a recent randomized controlled trial (RCT) of oral carvedilol (12.5 mg) versus EVL, the number of patients developing ascites or with increasing ascites was not higher in the carvedilol arm.[28] Patients with hypotension are at risk of reversible deterioration of renal function,[19] although this has not been reported in patients with cirrhosis.

Side-effects are more frequent at the start of therapy and usually respond rapidly to dose reduction or disappear with continued therapy. In heart failure studies, carvedilol had to be withdrawn because of intolerance or side effects in 5% of patients.[19] Figures in studies in patients with cirrhosis are 8%-13%.[19-28] As with all nonselective beta-blockers, carvedilol is contraindicated in patients with marked bradycardia, the sick sinus syndrome, and partial or complete heart block (unless a pacemaker is in place). Thus, an electrocardiogram is mandatory before starting therapy.[19,21] Carvedilol is also contraindicated in patients with asthma. Patients with insulin-dependent diabetes should be treated cautiously because carvedilol can mask the symptoms of hypoglycemia.

Areas of Uncertainty

The experience with the use of carvedilol for portal hypertension is limited. All but one published studies focused on the hemodynamic effects and safety of carvedilol, and the one prophylactic RCT included only 77 patients in the carvedilol arm.[28] Therefore, the clinical efficacy of the drug, its safety, and the frequency and severity of its side effects are far from well-characterized in this setting.

The prophylactic RCT of carvedilol versus EVL reported by Tripathi et al.[28] showed a benefit from carvedilol over EVL in terms of incidence of first bleeding (10% versus 23%), but no differences in mortality. This study is the only RCT of drug therapy showing a benefit over EVL, and as such is promising. However, the study has limitations,[17] the most important of which is that the study did not incorporate measurements of HVPG, so the apparent benefit from treatment could not be linked to its effect of lowering portal pressure. Moreover, because the study was not blinded, there is room for observer bias. In addition, there was an unusually long delay from randomization to first EVL session. Finally, the fact that decreasing

the number of bleeding episodes did not translate into decreased mortality is not intuitive and casts some doubt on the advantages of this treatment. Actually, the results of the per-protocol analysis did not confirm the lower risk of bleeding with carvedilol.[28] This suggests that part of the benefit was due to the very good results observed in the patients of the carvedilol arm and in part to some patients in the EVL arm bleeding before the first EVL session. On the other hand, the lack of differences in mortality may be partly due to the extensive use of transjugular intrahepatic portosystemic shunt (TIPS) for managing the bleeding episodes, because EVL patients required TIPS procedures significantly more often than those patients on carvedilol.[28] Side effects were frequent with carvedilol (50%) but were usually mild, and required discontinuation of the treatment in only 13%. By contrast, in the EVL arm, 12% of patients discontinued treatment because of intolerance, 30% (two-thirds of those achieving variceal eradication) had recurrent varices, 16% developed gastric varices, and 7% bled from banding ulcers. Although none of the EVL-related bleeding episodes was fatal, one patient required balloon tamponade and salvage TIPS.[28]

Even with the above limitations, the study is certainly promising and encourages further trials with carvedilol, including face-to-face studies versus propranolol and the use of carvedilol to maximize the fall in HVPG in propranolol nonresponders. Carvedilol should also be tested in situations with a higher risk of bleeding, such as prevention of recurrent variceal bleeding, because a good hemodynamic response in this setting is not only associated with decreased risk of rebleeding but also with decreased mortality.[6,29]

Recommendations

At present, there is not enough evidence to recommend the use of carvedilol for treating portal hypertension in cirrhosis outside of clinical trials. Having said that, there are two situations where carvedilol may be the right beta-blocker for a patient with cirrhosis and portal hypertension. The first is the patient that requires treatment for portal hypertension and has arterial hypertension as a comorbidity. In this setting, carvedilol is probably the ideal beta-blocker and could be regarded as a first choice. The second situation is the patient who fails to exhibit an adequate decrease of HVPG during treatment with propranolol or nadolol. Available pharmacological options in this setting are the association of a second drug (isosorbide mononitrate,[1,30] prazosin,[31] or simvastatin[32]) or to shift to carvedilol (if there are no contraindications and the patient is not hypotensive).[21] All the mentioned alternatives, except the association of simvastatin, carry the risk of causing hypotension, and the only one with which there is a large experience is with isosorbide mononitrate that can "rescue" about one-third of propranolol nonresponders.[1,30] In propranolol nonresponders, the target dose of carvedilol should probably be 12.5 mg twice a day if the patient is in Child-Pugh class A, and 6.25 mg twice a day (or 12.5 mg in a single dose) if he or she is in Child-Pugh class B or C.

The patient described at the beginning of this article is a decompensated individual with cirrhosis with a MELD (Model for End-Stage Liver Disease) score of 13 points and a Child-Pugh score of 7 points (class B), with high-risk varices that have never bled, but which require effective prophylactic treatment. He is diabetic under stable doses of insulin, which is not a contraindication for beta-blockers.[33] There are no other associated conditions that preclude the use of nonselective beta-blockers. Although he has mild ascites, creatinine is 1.2 mg/dL and therefore the patient has impending renal failure. In this situation, I would not recommend carvedilol, but to start therapy with nadolol at an initial dose of 20 mg per day, that will be increased by 20-mg steps every 3 days if tolerated and if the heart rate is >50 bpm and systolic blood pressure is >90 mm Hg. In case the patient develops severe side effects or intolerance to nadolol, I would recommend shifting treatment to EVL. If such a patient were treated at my hospital, I would certainly test the HVPG response to beta-blocker therapy. If the fall in HVPG was shown to be insufficient (it happens in 50% of patients), I would consider entering the patient in a trial of therapies aimed at maximizing the HVPG response. We do have ongoing cooperative studies on the use of carvedilol in propranolol or nadolol nonresponders (although as mentioned this would not be a choice in this particular patient), as well as on adding simvastatin to nadolol (which could be an option). We hope these studies will provide evidence to take adequate clinical decisions in patients facing these unanswered questions.

A 30-day supply in the United States for carvedilol 6.25 mg twice daily is approximately $15; the price for a 30-day supply of generic carvedilol 12.5 mg once daily is $7.80. The tablets are not scored and splitting is not possible. The sustained release preparation Coreg CR (GlaxoSmithKline) is available as 10 mg, 20 mg, 40 mg, and 80 mg capsules. Regardless of strength, the price for a 30-day supply of Coreg CR is $150. The price for a 30-day supply of Inderal LA

60 mg is $64; for propranolol 40 mg twice daily is $12; and for nadolol 80 mg is $52.

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