Pharmacologic Management of Portal Hypertension

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KEYWORDS

• Chronic liver disease • Portal pressure • Hepatic resistance • Splanchnic blood flow • Drug therapy

KEY POINTS

- Drugs for portal hypertension should decrease portal pressure without adverse effects on the systemic circulation and liver function.
- Targets of pharmacologic treatment of portal hypertension include increased hepatic resistance, increased splanchnic blood flow, and hyperdynamic circulation.
- Nonselective β-blockers (NSBBs) are the mainstay of chronic oral treatment of portal hypertension, whereas terlipressin and somatostatin/somatostatin analogues are used parenterally in acute variceal bleeding and hepatorenal syndrome.
- Carvedilol is a new and increasingly used NSBB with anti-α-1 adrenergic activity that has greater portal pressure decreasing effect than standard NSBBs.
- Most drugs currently under investigation are aimed at reducing hepatic resistance (hepatic vascular tone) and include statins, antioxidants, RAAS inhibitors, as well as antifibrotic stategies (structural changes).

INTRODUCTION

Portal hypertension (PH) is a frequent and severe clinical syndrome, which almost invariably complicates liver cirrhosis and is responsible for most of its clinical consequences, such as gastroesophageal varices, ascites, hepatorenal syndrome, hepatic encephalopathy, bacteremia, and hypersplenism.[1] Longitudinal studies assessing clinical-hemodynamic correlations have demonstrated that, in patients with cirrhosis, all the complications of PH do not appear until portal pressure, estimated by its clinical equivalent the hepatic venous pressure gradient (HVPG), increases to greater than 10 mm Hg.[2] This threshold value therefore defines clinically significant portal hypertension (CSPH), whereas subclinical PH is defined by HVPG between 6 and 9 mm Hg.[2]

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The aim of therapy in patients with PH is to decrease portal pressure, because elevated portal pressure is the driving force of all the clinical consequences of the syndrome.

In pragmatic terms the goal of therapy in subclinical PH should be to avoid CSPH, whereas asymptomatic patients with CSPH should be treated to decrease portal pressure below the threshold of 10 mm Hg, as CSPH markedly increases the risk of clinical complications ("decompensation"). In compensated patients without varices, there is evidence that even a small reduction in HVPG ($\geq$10% of baseline value) is beneficial, decreasing the rate of varices formation.[3] In patients with symptomatic PH, therapy should be more aggressive, aimed at decreasing portal pressure ideally to less than 12 mm Hg or, in patients not achieving this goal, a $\geq$20% decrease in HVPG versus pretreatment value, as this decreases the risk of both bleeding/rebleeding from varices, developing clinical decompensation, and reduces mortality.[4]

Drugs for PH should be able to decrease portal pressure without decreasing mean arterial pressure, which could worsen hyperdynamic circulation and increase the risk of renal failure. In addition, pharmacologic treatments should be ideally able to maintain or even improve effective liver perfusion, because this may improve liver function.

DRUGS USED IN CLINICAL PRACTICE

Most drugs used in clinical practice are splanchnic vasoconstrictors, acting by reducing splanchnic blood flow and hyperkinetic circulation (**Fig. 1**). **Box 1** summarizes the most commonly used drugs, further described herein.

Vasopressin Derivatives

Terlipressin (triglycyl lysine vasopressin) is a synthetic analogue of vasopressin with longer biologic activity and better safety profile[5–8] that is indicated for the treatment of acute variceal bleeding (AVB) and of type 1 hepatorenal syndrome (HRS).

Its effects encompass a marked vasoconstriction of the splanchnic circulation, an increase in arterial blood pressure and systemic vascular resistance, and a decrease in cardiac output. Altogether these induce a rapid and prolonged decrease in portal pressure of about 20% after a single injection.[7] The effects are maintained up to 4 hours, allowing its administration as intermittent intravenous injections, although continuous intravenous infusion is also possible.[8–10] In adults (>40 kg of body weight) the recommended dose for variceal bleeding is 2 mg every 4 hours for the first 24 to 48 hours, followed by 1 mg every 4 hours for 2 to 5 days.[11–13] In patients with HRS terlipressin is used in combination with albumin infusion at an initial dose of 0.5 to 1 mg intravenously every 4 hours, which is increased up to 3 mg every 4 hours if there is no response[14]; therapy is maintained up to 14 days. In HRS continuous intravenous infusion (beginning from 3 mg/d) might be beneficial, reducing daily dose and severity of adverse events.[15]

The most common side effects associated with the use of terlipressin are abdominal pain and increased blood pressure that reverse after drug withdrawal. In the setting of AVB, serious side effects such as peripheral, intestinal, or myocardial ischemia occur in less than 3% of the patients.[12] In patients with HRS included in 2 recent randomized controlled trials (RCT), treatment-related serious adverse events, mostly cardiovascular and leading to treatment discontinuation, were observed in 9% to 22% of patients.[16,17] Given the risk of ischemic and arrhythmic complications, terlipressin should not be used in patients with a history of ischemic heart or cerebral disease limb or gut vascular disease,[18] and caution should be used in elderly and/or hypertensive subjects. Hyponatremia, in some cases symptomatic, can arise during treatment[19] and reverses after drug discontinuation. Interestingly, terlipressin-associated