The Role of Medical Therapy for Variceal Bleeding

Abdul Q. Bhutta, MD[a,b], Guadalupe Garcia-Tsao, MD[c,d,*]

KEYWORDS

• Cirrhosis • Variceal hemorrhage • Drug therapy • Pharmacologic bases
• Nonselective β-blockers • Octreotide • Terlipressin • Somatostatin

KEY POINTS

- Variceal hemorrhage is a complication of cirrhosis that is mostly due to portal hypertension.
- Pharmacologic therapy for portal hypertension consists of splanchnic vasoconstrictors that decrease portal venous inflow or intrahepatic vasodilators that decrease intrahepatic resistance.
- Pharmacologic therapy for acute variceal hemorrhage consists of intravenous vasoconstrictors and antibiotics.
- Pharmacologic therapy to prevent recurrent variceal hemorrhage is based mainly on the use of nonselective β-blockers with or without nitrates.

INTRODUCTION

Acute variceal hemorrhage (AVH) is a medical emergency, and one of the complications of portal hypertension that define the development of decompensated cirrhosis. Approximately half of the patients with cirrhosis have gastroesophageal varices and one-third of all patients with varices will develop AVH, a complication that still carries a mortality of up to 15% to 20% despite all recent medical advances.[1] This review summarizes the current standard pharmacologic management of AVH in the context of cirrhosis-related portal hypertension. Discussed is not only treatment of the acute

Grant Support: NIH P-30DK 034989.
[a] Department of Internal Medicine, Yale University, 330 Cedar St, Boardman 110 P.O. Box 208056, New Haven, CT 06520-8056, USA; [b] Section of Hospital Medicine, Yale-New Haven Hospital, 20 York Street, CB-2041, New Haven, CT 06520, USA; [c] Section of Digestive Diseases, Yale University School of Medicine, 333 Cedar St, 1080 LMP, P.O. Box 208019, New Haven, CT 06520-8019, USA; [d] Section of Digestive Diseases, VA-CT Healthcare System, 950 Campbell Avenue, West Haven, CT 06516, USA
* Corresponding author. Section of Digestive Diseases, Yale University School of Medicine, 333 Cedar Street–1080 LMP, P.O. Box 208019, New Haven, CT 06520-8019.
E-mail address: guadalupe.garcia-tsao@yale.edu

Gastrointest Endoscopy Clin N Am 25 (2015) 479–490
http://dx.doi.org/10.1016/j.giec.2015.03.001 giendo.theclinics.com
1052-5157/15/$ – see front matter

episode of variceal hemorrhage but also the prevention of recurrent variceal hemorrhage, which is an integral part of the management of any patient with AVH. The recommendations made are mostly based on evidence in literature that has been summarized and prioritized at consensus conferences.[2–4]

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION

An understanding of pathophysiology of portal hypertension is important to understand the basis for the pharmacologic management of variceal hemorrhage. An increase in intrahepatic resistance is the initial mechanism of portal hypertension. Intrahepatic resistance results mainly from progressive architectural distortion (a fixed component), but one-third is due to intrahepatic vasoconstriction secondary to endothelial dysfunction with a deficiency in nitric oxide (NO) being the predominant abnormality.[5] As intrahepatic resistance increases, portal flow is diverted through portosystemic collaterals that develop through pre-existing vessels that would normally drain blood into the portal vein and probably also through vessels that are newly formed (neoangiogenesis through an increase in vascular endothelial growth factor).[6,7] Despite diversion of blood through collaterals and some attenuation of portal pressure, increased portal venous inflow sustains and progressively worsens portal hypertension. Portal inflow results from splanchnic vasodilatation, and the main contributor is an increase in NO. Therefore, in cirrhosis, NO is low in the intrahepatic circulation (vasoconstricted) but elevated in the splanchnic circulation (vasodilated).[8,9]

In patients with cirrhosis, mostly of an alcoholic or viral cause, indirect measurement of portal pressure by hepatic vein catheterization and determination of the hepatic venous pressure gradient (HVPG) has been shown to be the best predictor of different stages in the development of varices and variceal hemorrhage.[10] Normal HVPG is 3 to 5 mm Hg. An HVPG between 5 and 9.5 mm Hg indicates the presence of a silent stage of portal hypertension. Once the HVPG reaches and surpasses a threshold of 10 mm Hg (the so-called clinically significant portal hypertension), patients are at a higher risk of developing varices[10] and cirrhosis decompensation.[11] Almost all patients with gastroesophageal varices have reached an HVPG threshold of at least 12 mm Hg.[1,3] In patients who present with AVH, a threshold of greater than 20 mm Hg identifies those with a higher risk for treatment failure and death.[12,13] Conversely, decreases in HVPG are predictive of favorable outcomes. A decrease greater than 10% from baseline identifies a subgroup of patients without varices that is less likely to develop varices over time[10] and identifies a subgroup of patients with large varices that is less likely to develop variceal hemorrhage.[14] Patients with a history of variceal hemorrhage, a decrease in HVPG to less than 12 mm Hg, or a decrease greater than 20% from baseline (the so-called HVPG responders), are at a significantly reduced risk of recurrent variceal hemorrhage and show improved survival.[1,13,15]

Therefore, reduction in portal pressure is the main goal of therapy in patients with variceal hemorrhage. Targets of pharmacologic therapy consist of drugs that will reduce portal pressure by decreasing portal venous inflow or by decreasing intrahepatic resistance. In the following section, drugs used in the treatment of AVH and in the prevention of recurrent variceal hemorrhage are described.

DRUGS USED IN THE TREATMENT OF ACUTE VARICEAL HEMORRHAGE BY MECHANISM OF ACTION

Drugs That Act by Decreasing Portal Flow

Splanchnic vasoconstrictors decrease portal flow by constricting arterioles that feed the intestine and thereby reduce blood flow into the portal vein. Intravenous