Variceal Bleeding: Pharmacological Therapy

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Key Words

Portal hypertension · Beta-adrenergic blockers · Cirrhosis

Abstract

The complications of portal hypertension are totally prevented if hepatic venous pressure gradient is decreased below 12 mm Hg. Besides, if this target is not achieved, a 20% decrease in portal pressure from baseline levels offers an almost total protection from variceal bleeding. This sets the rationale for drug therapy to reduce portal pressure in portal hypertension. Pharmacological therapy to decrease portal pressure includes vasoconstrictors to decrease portal blood inflow, vasodilators to decrease hepatic resistance, and combination therapy. Oral agents, such as β -adrenergic blockers and organic nitrates, are used for long-term prevention of variceal bleeding, while parenteral agents, such as somatostatin (and analogues) and terlipressin, are used for the treatment of acute variceal bleeding.

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Rational Basis of Drug Therapy for Portal Hypertension

Portal hypertension, i.e. an increase in portal pressure above a critical threshold, is the major cause of complications and is thus clinically significant. This very important concept has been strongly substantiated in recent years. Hepatic venous pressure gradient (HVPG) [1], which accurately reflects portal pressure in the majority of liver diseases [2, 3], is the most commonly used method to assess portal pressure in clinical practice. Varices do not develop until the HVPG increases to 10–12 mm Hg, and the HVPG should be of at least 12 mm Hg for the appearance of other complications, such as variceal bleeding and ascites [4–6]. Implicit in this concept is that preventing the HVPG to increase above these values, will prevent the development of the complications of portal hypertension. The question that follows is if by reducing the HVPG below these thresholds, complications of portal hypertension could be prevented. Indeed longitudinal studies have demonstrated that if HVPG decreases below 12 mm Hg by means of pharmacological treatment [7, 8] or spontaneously due to an improvement in liver disease [9], variceal bleeding is totally prevented and varices may decrease in size. Besides, if this target is not achieved, a substantial decrease in portal pressure from baseline levels offers an almost total protection from variceal bleed-

ing. This 'substantial' decrease in baseline HVPG needed to achieve protection was found to be of at least 20% [8], a finding confirmed in a number of subsequent studies [10–15]. This reduction in the HVPG of more than 20% and/or a reduction below 12 mm Hg are now accepted as the therapeutic targets in the treatment of portal hypertension. Moreover, the achievement of these targets may be associated with a lower risk of developing ascites, spontaneous bacterial peritonitis, hepatorenal syndrome and death [14], thus demonstrating the reversibility of the portal hypertensive syndrome by means of pharmacological therapy. Additionally, in patients with acute variceal bleeding, an HVPG >20 mm Hg measured within 48 h after admission is the strongest indicator of treatment failure [16–18], suggesting that portal pressure reducing agents may improve the prognosis in this setting. These findings provide the rationale for treatments aimed to reduce portal pressure in patients with portal hypertension.

A basic knowledge of the pathophysiology of portal hypertension is required to understand the pharmacological treatment of portal hypertension. Experimental studies have shown that the initial factor in the pathophysiology of portal hypertension is the increase in vascular resistance to portal blood flow. In cirrhosis this increase in resistance occurs at the hepatic microcirculation (sinusoidal portal hypertension). It is important to emphasize that, in contrast to what was traditionally thought, increased hepatic vascular resistance in cirrhosis is not only a mechanical consequence of the hepatic architectural disorder caused by the liver disease, but there is also a dynamic component, due to the active contraction of portal/septal myofibroblasts, activated hepatic stellate cells and vascular smooth muscle cells in portal venules [19–21]. This increase in the intrahepatic vascular tone is modulated by the increased activity of endogenous vasoconstrictors such as endothelin, α -adrenergic stimulus, leukotrienes, thromboxane A_2 , angiotensin II and others [21–24], and is lessened by nitric oxide (NO), prostacyclin and many vasodilating drugs (organic nitrates, adrenolytic agents, and calcium channel blockers) [25–27]. In cirrhosis, hepatic vascular resistance is increased because of an imbalance between vasodilator and vasoconstrictor stimuli, the former being insufficient to counteract the influence of the latter [19]. Indeed, in cirrhosis these vasoconstrictors are increased, whilst intrahepatic NO production is clearly decreased [19, 28, 29]. This deficient intrahepatic NO production is the result of an endothelial dysfunction in the liver microvasculature [28, 29], and may also favor local thrombosis and fibrogenesis [19].

This provides a rational basis for using NO-based therapies in the treatment of portal hypertension.

A second factor contributing to portal hypertension is an increase in blood flow through the portal venous system due to splanchnic arteriolar vasodilatation. This is caused by an excessive release of endogenous vasodilators (endothelial and neuro-humoral) [30–34]. Splanchnic hyperemia contributes to aggravate the increase in portal pressure and explains why portal hypertension persists despite the establishment of an extensive network of porto-systemic collaterals that may divert over 80% of the portal blood flow. The increased portal venous inflow can be corrected pharmacologically by means of splanchnic vasoconstrictors such as vasopressin and its derivatives, somatostatin and its analogues and nonselective β -adren-ergic blockers, which are the drugs that have been more widely used in the treatment of portal hypertension. Splanchnic vasodilatation is in part due to an increased release of NO, which is amenable to pharmacological manipulation. However, this faces the difficulty of inhibiting NO synthesis only in the splanchnic circulation, which is not feasible at present.

Splanchnic vasodilatation is accompanied by an increased cardiac index and hypervolemia, representing the hyperkinetic circulatory syndrome associated with portal hypertension [35, 36]. An expanded blood volume is necessary to maintain the hyperdynamic circulation, which provides a rationale for the use of a low-sodium diet and spironolactone to attenuate the hyperkinetic syndrome and the portal pressure elevation in patients with cirrhosis [37].

Combined pharmacological therapy attempts to enhance the reduction of portal pressure by associating vasoconstrictive drugs, which act by decreasing portal blood inflow, and vasodilators, which reduce the intrahepatic vascular resistance [38] (fig. 1).

Pharmacological Treatment of Portal Hypertension

The treatment of portal hypertension includes the prevention of variceal hemorrhage in patients who have never bled, the treatment of the acute bleeding episode and the prevention of rebleeding in patients who have survived a bleeding episode from esophageal or gastric varices. An additional scenario may be suggested: the 'pre-primary' prophylaxis, or treatment of compensated patients in order to prevent the development of varices and ascites. Orally active drugs are used for continuous phar-

Fig. 1. Rational basis of the pharmacological therapy of portal hypertension. The initial factor that leads to portal hypertension is an increase in hepatic resistance. The recognition of a functional and, thus, reversible component in the increased hepatic resistance set the rationale for the use of vasodilators in portal hypertension. On the other hand, portal hypertension leads to a cascade of disturbances in the splanchnic and systemic circulation characterized by vasodilation, sodium and water retention and plasma volume expansion, that lead to an increase in portal blood inflow that contributes to maintain and aggravates portal hypertension. This sets the rationale for the use of vasoconstrictors and diuretics in the treatment of portal hypertension.

macological treatment to prevent bleeding, while parenterally administered drugs are used for the treatment of the acute bleeding episode.

Pharmacological Treatment of the Acute Bleeding Episode

Variceal bleeding is a medical emergency that should be managed in an intensive care setting by an experienced medical team, including well-trained nurses, clinical hepatologists, endoscopists and surgeons. The initial therapy is aimed at correcting hypovolemic shock, with judicious volume replacement and transfusion, preventing complications associated with gastrointestinal bleeding, and achieving hemostasis at the bleeding site. The two first goals, which are independent of the cause of the hemorrhage, demand immediate management. Specific therapy to stop bleeding is usually given when the patient has had the initial resuscitation and following diagnostic endoscopy, with the important exception of pharmacological therapy, that can be started earlier in the course of the bleeding episode.

Antibiotics

Infection is a strong prognostic indicator in acute variceal bleeding, both for rebleeding and mortality [39, 40]. Antibiotic prophylaxis has been shown to reduce the risk of rebleeding [41] and mortality in acute variceal bleeding [42]. Antibiotic prophylaxis should be instituted from admission and the presence of infection should be inves-

tigated. Norfloxacin, 400 mg/12 h, is the first-choice antibiotic prophylaxis due to its simpler administration and lower cost [43]. In high-risk patients (hypovolemic shock, ascites, deteriorated liver function) intravenous ceftriaxone has recently been shown to be better than oral norfloxacin in a randomized trial [Fernandez et al., pers. commun.].

Recombinant Activated Factor VIIa

Only recently have clinical studies addressed the role of coagulopathy in the outcome of acute variceal bleeding or possible benefits from its correction. Preliminary data suggest that recombinant activated factor VII (rFVIIa, Novoseven), which corrects prothrombin time in patients with cirrhosis [44], significantly improves the results of conventional therapy in patients with Child-Pugh class B or C cirrhosis, without increasing the incidence of adverse effects [45] (fig. 2).

Drugs to Stop Bleeding

Vasopressin was the first drug used, but was abandoned 25 years ago because of the severity of its cardiovascular adverse events. The association of *vasopressin infusion* (0.4 U/min for 48 h) *plus transdermal nitroglycerin* (20 mg/24 h) results in an enhanced fall in portal pressure and less marked systemic effects, and has been shown to be more effective and safer than vasopressin in randomized controlled trials (RCTs) and meta-analyses [46]. It is still used in countries where neither terlipressin nor somatostatin are available.

Fig. 2. Effects of recombinant factor VIIa on gastrointestinal bleeding in patients with cirrhosis. Treatment failure was defined as a composite end-point composed of the following 3 end-points: failure to control bleeding within 24 h, or failure to prevent rebleeding between 24 h and 5 days, or death within 0–5 days. Overall there was no effect of the drug on treatment failure. However, an exploratory analysis of the subgroup of variceal bleeders with Child-Pugh scores B or C and more severe coagulopathy indicated that significantly fewer rFVIIa-treated patients than placebo-treated patients failed on the composite end-point. Constructed with data from Bosch et al. [45].

Terlipressin is a long-acting triglycyl lysine derivative of vasopressin. On top of its own vasoactive effects, terlipressin is slowly transformed to vasopressin by enzymatic cleavage of the triglycyl residues by tissue peptidases [47]. Clinical studies have consistently shown less frequent and less severe side effects with *terlipressin* than with vasopressin, even when vasopressin (alone or associated with nitroglycerin), and it has been speculated that this reduction may be related to the combination of high tissue concentrations with low circulating levels as a consequence of the slow release of vasopressin [47]. Terlipressin may be initiated as early as variceal bleeding is suspected at a dose of 2 mg/4 h for the first 48 h, and it may be maintained for up to 5 days at a dose of 1 mg/4 h to prevent rebleeding [48]. Compared with placebo or non-active treatment, terlipressin significantly improves the control of bleeding and survival [49]. This is the only treatment that has been shown to improve the prognosis of variceal bleeding in placebo-controlled RCTs and meta-analyses [46, 49]. Terlipressin is as effective as any other effective therapy, including endoscopic injection sclerotherapy, and is safer than vasopressin + nitroglycerin and endoscopic injection sclerotherapy [46, 48, 49]. The overall efficacy of terlipressin in controlling acute variceal bleeding at 48 h is 75–80% across trials [49], and

67% at 5 days [48]. Terlipressin is also useful in hepatorenal syndrome [50]. Thus the use of terlipressin for variceal bleeding may prevent renal failure, which is frequently precipitated by variceal bleeding [51]. F-180, another long-acting $V_{1\alpha}$ -selective vasopressin analogue, has further been shown to prevent the increase in portal pressure caused by blood transfusion [52].

Somatostatin has been used for over two decades [53] in the treatment of acute variceal bleeding, based on its ability to decrease portal pressure and collateral blood flow [54]. The usual scheme for somatostatin administration is an initial bolus of 250 μ g followed by a 250- μ g/h infusion that is maintained until the achievement of a 24-hour bleed-free period. Therapy may be further maintained for up to 5 days to prevent early rebleeding [55]. Very recently, the use of higher doses (500 μ g/h) has been shown to translate into increased clinical efficacy in a subset of patients with more severe hemorrhage, pointed out by the finding of active bleeding at emergency endoscopy [56]. Several RCTs showed that somatostatin compared with placebo or nonactive treatment significantly improves the rate of control of bleeding [46, 57]. However, despite the beneficial effect on control of bleeding, somatostatin did not reduce mortality [46]. Somatostatin has been compared with terlipressin and no differences were found for failure to control bleeding, rebleeding and mortality. Side effects were similar in both treatment groups [46]. Major side effects with somatostatin are negligible.

Octreotide is a somatostatin analogue with a longer half-life. This, however, is not associated with longer hemodynamic effects than somatostatin [58]. The optimal doses are not well determined. It is usually given as an initial bolus of 50 μ g, followed by an infusion of 25 or 50 μ g/h [57]. As with somatostatin, therapy can be maintained for 5 days to prevent early rebleeding. The efficacy of octreotide as a single therapy for variceal bleeding is controversial. No benefit from octreotide was found in the only trial using octreotide or placebo as initial treatment [59], which may be due to rapid development of tachyphylaxis [58]. However, RCTs using octreotide on top of sclerotherapy or ligation have shown a significant benefit in terms of reducing early rebleeding [60]. It has been speculated that this may be related to its sustained ability to prevent a post-prandial increase in portal pressure [57]. Mortality, however, was not affected [46, 60]. These results suggest that octreotide may improve the results of endoscopic therapy but has no or little effect if used alone. When compared with other vasoactive drugs, octreotide was better than vasopressin and equivalent to

terlipressin, again suggesting a clinical value from the use of octreotide [46]. Side effects were less frequent and severe with octreotide than with either vasopressin or terlipressin, but the difference was significant only for vasopressin [46].

Drug Selection

The decision depends on local resources. In general terms, terlipressin should be the first choice if available, since the results of double-blind RCT vs. placebo are more consistent than with other drugs and is the only shown to improve survival [61]. Somatostatin or octreotide are second choice [46, 57]. If these drugs are not available, vasopressin plus nitroglycerin is an acceptable option [46].

Combined Medical Therapy

The current recommended hemostatic treatment for variceal bleeding is to start on a vasoactive drug from admission, and to associate endoscopic therapy at the time of diagnostic endoscopy [62, 63]. Drug therapy may be started during transferal to hospital by medical or paramedical teams [61] and maintained for up to 5 days to prevent early rebleeding [62]. With this approach, initial control of bleeding is about 75%. The rationale for this combined treatment comes from a number of RCTs demonstrating that early administration of a vasoactive drug facilitates endoscopy and improves control of bleeding and 5-day rebleeding [61, 64, 65]. Drug therapy also improves the results of endoscopic treatment if started just after sclerotherapy or band ligation [46, 57, 60]. Moreover, the association of endoscopic therapy may improve the efficacy of vasoactive treatment [66]. However, this combined approach failed to improve 6-week mortality with respect to endoscopic therapy [67] or a vasoactive drug [66] alone. On the other hand, single vasoactive therapy is as effective as endoscopic therapy, but with significantly less side effects [68], which questions the use of endoscopic therapy as single treatment.

Prevention of First Bleeding and of Rebleeding

Continuous treatment to prevent variceal bleeding or rebleeding requires the use of orally active agents that reduce portal pressure. Nonselective β -adrenergic blockers are the most widely used drugs to treat portal hypertension. However, only 30–40% of the patients under long-term therapy reduce their portal pressure by $\geq 20\%$ from baseline or to levels ≤ 12 mm Hg [8]. Lack of achieve-

ment of these hemodynamic targets constitutes the strongest independent predictor of variceal bleeding or rebleeding [8, 10], indicating that the available armamentarium to treat portal hypertension is far from optimal.

Choice of β -Blocker

This should be a nonselective one, acting both on β_1 cardiac receptors and β_2 vascular receptors. There appears to be no difference in the efficacy of propranolol and nadolol, the only nonselective β -adrenergic blockers tested in clinical trials [46]. In the authors' experience, intolerance to one may be overcome by shifting to the other. Nadolol may be more convenient since it is administered once a day, and due to its low-lipid solubility may have lower potential for central side effects [69]. Timolol has also low liposolubility [69], and has the greatest β_2 -adrenoceptor-blocking effect [70].

Dose Adjustment

The dose of β -adrenergic blockers is determined by stepwise increases in dose until reaching the maximum tolerated. This approach is probably more effective than titrating against heart rate to achieve a reduction of about 25% [14].

Contraindications and Intolerance

Up to 15–20% of the cirrhotic patients with varices present contraindications that preclude the use of β -blockers, and an additional 5% develop intolerance to the treatment that results in treatment withdrawal [71].

Combination with Vasodilating Agents

The rationale underlying this approach is that some patients do not respond to propranolol due to an increase in porto-systemic collateral (and, maybe, intrahepatic) resistance [72, 73], hindering the reduction in portal pressure. Indeed, the addition of isosorbide mononitrate (ISMN) has been shown to significantly increase the long-term response to β -adrenergic blockers [74, 75] without adverse effects on renal function [76, 77]. It is not clear, however, that this approach improves the clinical results of β -adrenergic blockers alone.

Prevention of First Bleeding from Esophageal Varices

A total of 12 trials assessing β -adrenergic blockers for the prevention of first bleeding have been conducted. Meta-analysis of these studies shows that continued pro-

pranolol or nadolol therapy markedly reduces the bleeding risk, from 25% with nonactive treatment to 15% with β -adrenergic blockers [46] over a median follow-up of 2 years. Mortality was only slightly reduced from 27 to 23%; this effect barely approached the level of statistical significance. The benefit of therapy has been proved in patients with moderate/large varices (>5 mm), either with or without ascites or with good or poor liver function [46, 78]. A recent trial demonstrated that beta-blockers reduce the rate of progression from small to large varices, and decrease the incidence of variceal bleeding in patients with small varices. Although confirmatory double-blinded trials are required, this suggests that the indication of β -blockers could be extended to patients with small varices [79]. Therapy with β -adrenergic blockers should be maintained indefinitely, since when these are withdrawn the risk of variceal hemorrhage returns to what would be expected in an untreated population [80].

A question still debated is whether the greater portal pressure-reducing effect of the combination of β -blockers + nitrates on portal pressure translates into greater clinical efficacy. An open trial comparing nadolol with nadolol + ISMN demonstrated a significant lower rate of first bleeding in the combination group, that was maintained after 55 months of follow-up, without a survival advantage [81, 82]. However, a large, randomized, double-blind study failed to confirm these results [71]. Current consensus does not recommend combination therapy in primary prophylaxis [62].

About 15–20% of patients are excluded from therapy with β -adrenergic blockers in clinical practice because of relative or absolute contraindications [46, 83]. In this case, treatment with ISMN, despite its mild portal pressure-lowering effect, was ineffective in a double-blind placebo-controlled clinical trial [83]. Variceal band ligation is also effective and may be an alternative to β -blockers for primary prophylaxis, especially in those patients with contraindications or intolerance to β -blockers [84].

Prevention of Recurrent Bleeding from Esophageal Varices

Because of the extremely high risk of rebleeding in untreated patients, all patients surviving a variceal bleeding should receive urgent and active treatments for the prevention of rebleeding [62, 85, 86]. In addition, those with poor liver function or other recurrent complications of portal hypertension should be considered for liver transplantation.

Either pharmacological treatment with β -adrenergic blockers or variceal band ligation are accepted first-line treatments to prevent rebleeding. Pharmacological treatment is based on the use of non-selective β -adrenergic blockers [87]. Meta-analyses consistently found a marked benefit from β -adrenergic blockers, both in terms of rebleeding (from 63% in controls to 42% under β -adrenergic blockers) and mortality (from 27 to 20%) [46]. Again, controversy exists on whether to add nitrates. Two trials are available [88, 89], one of them double-blind and placebo-controlled, but only available in abstract form [88]. These studies failed to consistently show a benefit from combination therapy in terms of rebleeding or survival. β -Adrenergic blockers + nitrates combination therapy has been recommended on the basis of its superiority over sclerotherapy or band ligation [11, 12]. The authors recommend to evaluate, whenever possible, the hemodynamic response to β -adrenergic blockers. If a 20% decrease in HVPG or to ≤ 12 mm Hg is not achieved, ISMN may be added, which enables the target reduction in portal pressure to be achieved in a third of non-responders to β -blockers alone [90].

Since endoscopic therapy is also effective in preventing variceal rebleeding, the question arises on whether pharmacological treatment should be preferred to band ligation. This decision is obvious when there are contraindications to β -adrenergic blockers. In the absence of contraindications, no clear recommendations can be given, since the meta-analysis of the four available trials comparing optimal endoscopic treatment (band ligation) versus optimal pharmacological treatment (the combination of β -blockers + ISMN) [12, 91–93] shows comparable results with the two therapies (fig. 3). Patient preferences and local resources must be taken into account when making the choice [94]. The association of β -blockers and variceal band ligation has been shown to be better than variceal band ligation alone in one study [95]. Ongoing studies will confirm whether this combined approach is really better than variceal band ligation or drug therapy alone.

Prevention of the Formation of Varices ('Pre-Primary' Prevention)

Studies to explore whether long-term therapy with nonselective β -blockers may prevent or delay the development of varices and other complications of portal hypertension, such as ascites, in patients with compensated cirrhosis have been prompted by the results of studies

Fig. 3. Meta-analysis of the available randomized controlled trials that compare optimal pharmacological treatment (β -blockers + nitrates) with optimal endoscopic treatment (endoscopic banding ligation) to prevent rebleeding. There were no differences between the two therapies in terms of variceal rebleeding and survival. In the trial by Romero et al. [92], low-volume sclerotherapy was added to banding ligation.

showing that: (a) development of porto-systemic collaterals is significantly lower in animals with experimental portal hypertension treated chronically with β -blockers than in controls [96]; (b) in patients with cirrhosis, varices decreased in size and may eventually disappear when HVPg is reduced below 12 mm Hg [6, 7], and (c) portal pressure (HVPg) reduction achieved by nonselective β -blockers is significantly greater in patients without varices than in those who already have developed esophageal varices, and most achieve or maintain an HVPg below 12 mm Hg [73]. Despite this solid rationale, a recent large, multicenter, double-blind, randomized trial showed that long-term timolol administration was unable to prevent the development of varices in patients with compensated cirrhosis [97].

New Drugs to Treat Portal Hypertension

Nearly half of the patients treated with the combination of β -adrenergic blockers and nitrates do not achieve the target reduction in portal pressure ($>20\%$ from the baseline or to >12 mm Hg). Therefore, it is clear that there is room for improvement in the currently available armamentarium to treat portal hypertension. Theoretically, the ideal drug to treat patients with cirrhosis and portal hypertension should act by decreasing intrahepatic vascular resistance and portal pressure while maintaining or enhancing hepatic blood flow. To this aim the vasodilator effect of such a drug should be limited to the hepatic circulation to prevent further splanchnic/systemic vasodilation and hypotension. However, such a drug is not currently available. The most recent developments in the search for new drugs for the treatment of portal hypertension are discussed below.

Drugs That Decrease Hepatic Resistance

Prazosin is an α_1 -adrenergic antagonist that markedly reduces HVPg in patients with cirrhosis. This reduction is associated with increased hepatic blood flow, suggesting a reduction in hepatic vascular resistance [98, 99]. However, chronic prazosin administration was associated with a significant reduction in arterial pressure and systemic vascular resistance and activation of endogenous vasoactive systems leading to plasma volume expansion, sodium retention and in some cases, to the accumulation of ascites [99]. These findings discouraged its use in the treatment of portal hypertension. The adverse effects of prazosin on the systemic circulation and renal function are attenuated by the combined administration of prazosin and propranolol. More interesting, the association of propranolol and prazosin was significantly more effective, in terms of reducing HVPg, than the association of propranolol and ISMN [100]. This drug combination has not been assessed in RCTs.

Renin-Angiotensin System Blockers

Activation of the renin-angiotensin system is a frequent finding in patients with cirrhosis, especially in those with more advanced disease. Angiotensin II may act on hepatic circulation, increasing hepatic resistance and contributing to portal hypertension. Blockade of this system has been tested as another approach to treat portal hypertension. In a recent nonrandomized study in patients with portal hypertension, losartan, a nonpeptide

antagonist of angiotensin-receptor type I, caused a dramatic reduction in portal pressure with only slight arterial hypotension and no significant adverse effects [101]. These impressive findings, however, were not confirmed in subsequent RCTs, in which angiotensin II blockade with irbesartan or losartan only had a slight or null effect on portal pressure, while it decreased arterial pressure and GFR [102–106]. These agents, clearly dangerous in advanced cirrhosis, seem to be ineffective in early cirrhosis as well [105].

Endothelin Receptor Blockers

Endothelin also increases hepatic resistance in cirrhosis. However, conflicting results have been obtained with endothelin blockers in experimental models of portal hypertension. Acute administration of the mixed ETA-ETB receptor blocker bosentan decreased portal pressure [107, 108], while chronic administration of RO 48-5695, a second-generation mixed ET-receptor blocker, did not modify portal pressure and even increased liver fibrosis [109]. In contrast, chronic selective blockade of ETA receptor with LU 135252 dramatically decreased collagen accumulation in rats with secondary biliary cirrhosis [110], while acute administration of another ETA blocker (FR 139317) to cirrhotic rats did not lower portal pressure [111]. In humans, preliminary data show that neither ET-A nor ET-B blockers reduce portal pressure, and that ET-A blockers are potentially dangerous since they induce arterial hypotension [112].

Selective Hepatic Delivery of NO

It is increasingly recognized that insufficient availability of NO in the hepatic circulation is implicated in the increase in hepatic vascular tone as well as in fibrogenesis [113] and local thrombotic phenomena that may contribute to the progression of cirrhosis [114]. This suggests that prolonged administration of orally active hepatic NO donors could both modify the dynamic component of increased intrahepatic resistance and ameliorate fibrosis, and delay the progression of cirrhosis. However, in patients with advanced cirrhosis the use of non-liver-selective NO donors, such as ISMN, enhances peripheral vasodilation, further decreasing arterial blood pressure and activating endogenous vasoactive systems. So far, the administration of ISMN has proven clinically ineffective in terms of prevention of variceal bleeding [83, 115–117].

Liver-specific NO donors are being investigated. These agents would be devoid of systemic vasodilator effects, and thus will be close to the attributes of the ideal drug for the treatment of portal hypertension. The drug that

has shown more promising results in experimental studies is NCX-1000, an NO-releasing derivative of ursodeoxycholic acid [118]. NCX-1000 has been shown to reduce hepatic resistance in two different models of cirrhosis [118–120], without affecting systemic hemodynamics. There are no data on the effects of this drug in patients with cirrhosis.

Another potential approach is to enhance NO production in the liver by drugs that enhance endogenous eNOS activity. In that regard, a recent study has shown that simvastatin, a lipid-lowering agent that also increases NO production by upregulating eNOS, acutely decreases hepatic vascular resistance in patients with cirrhosis, without inducing hypotension [121]. A randomized study to evaluate the hemodynamic effects of the continuous administration of this drug in cirrhosis is under way.

Drugs That Decrease Splanchnic Blood Flow

The great amount of information gathered on the mechanism of splanchnic vasodilation and increased portal inflow in cirrhosis [19, 122] has not translated yet in any therapeutic benefit for patients with portal hypertension. ‘Old’ drugs such as β -adrenergic blockers, vasopressin and somatostatin and their respective derivatives remain the only used vasoconstrictors in clinical practice. Vasoconstrictors have other advantages in advanced cirrhosis, since they improve renal function and the hyperdynamic state [50, 123, 124]. These drugs, however, by decreasing portal inflow may impair liver function.

Available data on the effects of systemic NO blockade in patients with cirrhosis are still insufficient. A very recent report showed that systemic administration of the NOS inhibitor N^G-monomethyl-L-arginine (L-NMMA) to patients with cirrhosis and portal hypertension corrected systemic hemodynamics and improved renal function and sodium excretion [125]. However, as observed in the experimental setting [33] and in cirrhotic patients in a previous report with the same drug [126], the increase in hepatic resistance caused by NO inhibition results in no decrease in portal pressure despite the fall in portal blood flow. This is probably due to the fact that intrahepatic NO, although insufficient, still plays a major role in regulating hepatic vascular tone. Furthermore, hepatic NO production, even if reduced, may still be protective and delay the progression of cirrhosis.

Drugs That Decrease Hepatic Resistance and Portal Blood Inflow

Carvedilol: this drug combines a nonselective β -blocker action with an α_1 -adrenoceptor blocking activity and, thus, mimics the effects of the combination therapy of propranolol/nadolol plus prazosin, which causes a very pronounced decrease in portal pressure but is associated with excessive hypotension [100]. In a recent study, the acute administration of carvedilol induced a marked decrease in portal pressure gradient that was significantly greater than that achieved by propranolol, despite causing similar reductions in splanchnic blood flow [127]. This suggests that carvedilol decreases hepatic and/or porto-systemic collateral resistance due to its anti α_1 -ad-

renergic activity. However, studies evaluating its long-term effects showed discrepant results. In one study, a 25-mg/day dose of carvedilol was associated with marked hypotension leading to discontinuation of the treatment in a significant proportion of patients [128]. Subsequent studies showed that lower doses (12.5 mg/day) [129] or careful titration [130] result in good tolerance, maintaining the portal hypotensive effect [129, 130]. Indeed, when compared with propranolol in a randomized trial [130], carvedilol increased significantly the number of patients [54 vs. 23%] achieving a target reduction in HVP (of $\geq 20\%$ from baseline or below 12 mm Hg). This drug should be further evaluated in randomized trials with clinical end-points.

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