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Concise Review

Drug treatment for portal hypertension

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Abstract

Pharmacological treatment of portal hypertension has played an increasing clinical role in the past 20 years. In the setting of acute variceal bleeding, drug therapy should be considered the initial treatment of choice and can be administered as soon as possible; even during the transfer of the patient to hospital. Several recent trials have reported similar efficacy to emergency sclerotherapy, therefore drug treatment should no longer be considered as a "stop gap" therapy until definitive endoscopic therapy is performed but continued for several days. Antibiotic prophylaxis is an integral part of therapy as it reduces mortality and should be instituted from admission. Non selective b-blockers are the treatment of first choice for secondary and primary prevention. If they are contraindicated or non tolerated banding ligation can be used. There is less evidence for the benefit of ligation for primary prophylaxis. The use of haemodynamic targets for reduction in hepatic venous pressure gradient response need further study, and surrogate markers of pressure response need evaluation.

Key words: Portal pressure, oesophageal varices, gastrointestinal Haemorrhage, vasoactive agents, b-blockers.

Introduction

Cirrhosis of the liver is accompanied by profound disturbances in the splanchnic haemodynamics. These are not limited to resistance within the intrahepatic circulation but involve also the splanchnic and systemic circulatory beds and are characterised by a hyperdynamic circulation, vasodilatation and a reduced pressure to vasoconstrictive substances. These haemodynamic disorders cause the development of portal hypertension in over 90% of patients with cirrhosis.

Portal hypertension is defined by an elevation in portal pressure above the normal values of 1-5 mmHg. When the pressure rises above the threshold of 10 mmHg, portal hypertension is defined as clinically significant due to the potential development of complications. Gastrointestinal haemorrhage is a major complication and cause of death. Prospective studies have shown that up to 90% of patients with cirrhosis will develop oesophageal varices in their lifetime[1] and of these about 30% will have haemorrhage.[2] The mortality for an acute episode of variceal haemorrhage ranges from 5-50%, depending on the severity of liver disease, mainly due to the high rate of failure to control bleeding during the first days after the initial episode.[3] Most of the deaths occur within 7-10 days of bleeding; therefore there is a need for prompt and effective treatment for the control of acute variceal bleeding and prevention of early rebleeding. The risk of rebleeding after an acute bleeding episode is about 70%; hence, all patients who have bled need to have therapy to prevent rebleeding (secondary prophylaxis). Prevention of first bleeding (primary prevention) is the best therapeutic option since 10-15% of unselected patients with cirrhosis die from gastrointestinal bleeding. Screening of cirrhotics for the presence of varices and assessment for prophylactic treatment is essential. Prevention of the development of varices (pre-primary prophylaxis) is currently being assessed in clinical trials.

The rationale for drug therapy is based on haemodynamic factors that influence the pressure gradient (ΔP) in any vascular system. According to Ohm's law the portal pressure gradient (PPG) can be defined as PPG = flow (Q) X resistance to the flow (R). Resistance within both the portal collateral system and most importantly within the hepatic microcirculation accounts for the resistance (R) to flow. Factors that modulate collateral resistance are expressed by Poiseuille's formula $R = 8nl/\pi r^4$ where n is the viscosity of blood, r is the radius and l is the length of the vessel. Under physiologic conditions, n and l are constants. Since resistance changes in proportion to the fourth power of the radius, small changes in vessel size produce large changes in pressure. Regarding the intrahepatic re-

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sistance, it is now known that the fixed 'mechanical' component (a consequence of the hepatic architectural disorder caused by cirrhosis) is accompanied by a 'dynamic' component due to the active contraction of the vascular smooth muscle cells, myofibroblasts and activated stellate cells within or around the hepatic microcirculation.

The occurrence of ruptured varices is not directly correlated with the degree of portal hypertension but clinical studies have shown that a reduction in portal pressure decreases the risk of bleeding and can treat acute bleeding. Hence, in the portal system, drugs could reduce portal pressure and consequently variceal pressure by reducing the portal collateral blood flow (e.g. by means of splanchnic vasoconstrictors), or by decreasing the vascular resistance of the intrahepatic and portal circulation (e.g. by means of vasodilators) – or a combination of the two. Along with the vasoconstricting (vasopressin and its derivatives, SMS and its derivatives, beta-blockers) and vasodilating drugs (nitroderivatives, calcium channel blockers, prazosin, clonidine, antiserotoninergics, and mixed ETA/ET_B receptor antagonists), diuretics, in particular anti-aldosterone drugs have been used for the treatment of portal hypertension; they act by reducing plasma volume. As there is a little selectivity of action on the splanchnic circulation, the determinants of portal pressure are also related to systemic haemodynamics, so that the final effect of a drug on portal pressure results from the interrelationship between systemic and splanchnic haemodynamic effects. The ideal approach to the treatment of portal hypertension and its complications would be to prevent the development of hepatic fibrosis, which plays a role in the development of portal hypertension. However, no clinically effective antifibrotic drug is currently available.

Pharmacologic treatment of acute variceal bleeding

Pharmacologic treatment is aimed at arresting haemorrhage by decreasing pressure and blood flow within the oesophageal varices, thus allowing haemostasis at the bleeding point. Drugs currently used in the treatment of acute variceal bleeding include vasopressin or its analogues, alone or in combination with nitroglycerin and somatostatin or its analogues. These have been compared with emergency sclerotherapy (more recently with band ligation as well) because endoscopic therapy represents the gold standard in the management of acute variceal haemorrhage as it increases hospital survival.[4] Antibiotics are also part of the treatment strategy for acute gastrointestinal bleeding in cirrhotic patients, as they have been shown to decrease mortality in a more substantive fashion than vasoactive drugs and perhaps reduce early rebleeding.

Antibiotic therapy

Bacterial infections have been documented into 35-66% of patients with cirrhosis who have variceal bleeding. In a multivariate analysis in cirrhotic patients admitted for gastrointestinal bleeding who had not received antibiotic therapy in the previous 7 days, Bernard et al identified bacterial infections as a predictive of early rebleeding ($p < 0.02$) with a risk of rebleeding 6-7 times higher in patients with infections than those without. A high Child-Pugh score predicted death ($p < 0.001$).[5] These results were recently confirmed in our institution by Goulis et al; multivariate analysis showed that proven bacterial infection ($p < 0.001$) or as a surrogate antibiotic use ($p < 0.001$) and also active bleeding at endoscopy ($p < 0.001$) and Child-Pugh score ($p < 0.02$) were independent prognostic factors of failure to control bleeding.[6] Likewise, a more recent a prospective study by Vivas et al showed that bacterial infection ($p < 0.001$) and the presence of shock ($p < 0.05$) were independently associated with failure to control bleeding, whereas bacterial infection ($p < 0.01$) together with encephalopathy ($P < 0.05$) and shock ($p < 0.05$) predicted death.[7]

Bernard et al published a meta-analysis on the antibiotic prophylaxis in cirrhotics with gastrointestinal bleeding,[8] and showed that antibiotic prophylaxis significantly increased the mean survival rate (9.1% mean improvement rate, 95% CI 2.9-15.3, $p = 0.004$) and also increased the mean percentage of patients free of infection (32% mean improvement rate, 95%CI 22-42, $p < 0.001$). This evaluation was recently confirmed in a systematic review in which antibiotic prophylaxis decreased mortality (RR 0.73, 95% CI 0.5 to 0.95) and the incidence of bacterial infections (RR 0.40, 95% CI 0.32 to 0.51). None of the antibiotic regimens (quinolones in the majority of the trials) was superior regarding mortality or the incidence of bacterial infections.[9]

Randomized controlled trials for treatment of acute variceal bleeding

Vasopressin

Vasopressin, although now infrequently used in Europe, has been in use for over 30 years. At pharmacological doses, it induces splanchnic arteriolar vasoconstriction and decreases portal tributary inflow with resultant reduction in portal pressure.

In comparison with *non-active treatment or placebo* in 4 randomised control trials (RCTs) comprising 157 patients, there was a clear trend in favour of vasopressin in the control of bleeding but the result was not statistically significant (OR 0.23, 95% CI 0.05-1.02). Moreover, there was no difference in mortality (OR 0.98, 95%CI 0.47-2.1).[10] Vasopressin may actually increase the mortality rate because of the vasoconstrictive effects on other organs.[11]

In addition to doubts regarding its efficacy, vasopressin carries an extensive side effect profile; it may cause severe abdominal colic, cardiac arrhythmia, myocardial ischemia, mesenteric ischemia and cerebrovascu-

lar episodes. The drug needs to be stopped in up to 25% of cases.[3] The systemic vasoconstrictive effects of vasopressin maybe minimized while maximizing the portal hypotensive effect by adding nitrovasodilators. Nitroglycerin is a potent venodilator that reduces the portal vascular resistance and also improves myocardial performance. The recommended dose of vasopressin is 0.4 U/min, as an intravenous infusion; 4-hourly sublingual nitroglycerin should be prescribed simultaneously, maintaining blood pressure at 100 mg Hg or more. Three RCTs (176 patients) compared vasopressin alone with *vasopressin plus nitroglycerin.* Meta-analysis showed that failure to control bleeding was significantly less common with vasopressin plus nitroglycerin (OR 0.39, 95% CI 0.21-0.72) although no survival benefit was demonstrated (OR 0.94, 95% CI 0.49-1.79).[10] Side effects were significantly reduced with the combination treatment, but as the therapy is complicated to use, it has had little impact in clinical practice.

Trials comparing vasopressin with *sclerotherapy*[12-15] have shown no significant differences in the control of bleeding and survival, except in one study[15] where rebleeding was significantly lower in patients treated with sclerotherapy.

Terlipressin

Terlipressin is a synthetic analogue of vasopressin (triglycyl lysine vasopressin), which is converted in vivo into vasopressin by enzymatic cleavage of the triglycyl residues. This results in a low plasma concentration of vasopressin with a concomitant reduction in the side effects and allows terlipressin to be administered every 4 hours. The standard dose is 2 mg every 4 hours for the initial 24 hours; 1 mg 4-hourly for the next 24 hours. Some units prolong its use to 5 days.

It is known that terlipressin produces decreases in portal pressure of 16-35% and in collateral blood flow of 32%. According to a recent double-blind trial with 20 cirrhotics, terlipressin produced significant and prolonged decreases in variceal pressure and in the estimated variceal wall tension greater than the change in wedged HVP. The hypotension and the fall in the cardiac index, known side effects from previous studies, were confirmed.[16] A separate indication that has been suggested for use of terlipressin in cirrhotics is hepatorenal syndrome type 1; several studies have shown improvement in renal function and an increase in survival.[17,18] This beneficial effect of terlipressin has further strengthened its role in the treatment of acutely bleeding varices.

The clinical efficacy of terlipressin *versus placebo* was evaluated in a systematic review of 7RCTs with a total of 443 patients. The results indicated that terlipressin was associated with a statistically significant reduction in failure of initial haemostasis (RR 0.66, 95% CI 0.55-0.93) and in all cause mortality (RR 0.66, 95% CI 0.49-0.88). Similar results were drawn even when only high quality trials (according to the Jadad score) were analysed.[19] In one study, also included in the meta-analysis, terlipressin was administered with glyceryl trinitrate by an intensive care team, within one hour after an emergency call before hospital admission.[20]

Terlipressin was also compared to *vasopressin with or without nitroglycerine* in 5 unblinded studies. A review of these trials showed that failure to control bleeding was less frequent with terlipressin but the result was not statistically significant (OR 0.64, 95% CI 0.36-1.14). There was no difference in mortality between the two treatment arms (OR 1.48, 95% CI 0.85-2.57). The complication rate was significantly lower with terlipressin even when vasopressin was associated with nitroglycerin.[10]

The meta-analysis of 3 RCTs comprising 302 patients comparing terlipressin with *somatostatin* failed to demonstrate a significant difference in failure to control bleeding or in survival.[19] Compared with *octreotide* (in 3 unblinded RCTs including 203 patients), the data suggested that octreotide may be superior to terlipressin with respect to initial haemostasis (RR 1.62, 95% CI 1.05-2.50), but there was no difference in blood transfusion requirements or in mortality.[19]

In addition, terlipressin was found to be as effective as *balloon tamponade* in preventing failure to control bleeding or death but due to different definitions of endpoints and the inherent difficulty to conduct blinded trials using balloon tamponade, it is difficult to interpret the results.[21-23]

Recently, terlipressin was compared to *sclerotherapy* in a multicentre RCT involving 219 patients. The authors concluded that terlipressin and sclerotherapy were equally and highly effective therapies for the initial control of variceal bleeding and prevention of early rebleeding (failure rates 33% *versus* 32% and early rebleeding 43% *versus* 44% in the terlipressin and sclerotherapy groups). They were also similar regarding incidence of complications, transfusion requirements, in-hospital stay and 6-week mortality. Terlipressin was better tolerated than sclerotherapy (side effects 20% *versus* 30%).[24]

Finally the combination of *terlipressin with sclerotherapy* has been reported to be more effective than sclerotherapy alone. Analysis of RCTs with patients treated with sclerotherapy at the initial diagnostic endoscopy (3 RCTs with 271 patients) showed that addition of terlipressin was associated with beneficial effects that were either statistically significant (reduction of failure of initial haemostasis RR 0.75, 95% CI 0.58-0.96) or approached statistical significance (reduction of mortality RR 0.74, 95% CI 0.53-1.04)19 *(Table I).*

Somatostatin

Somatostatin (SMS) is 14-amino acid peptide that has been used in the pharmacological treatment of variceal bleeding. It increases splanchnic vascular resistance mainly by inhibiting the release of vasodilatory peptides such

Table I. RCTs for the combined treatment (Drug + endoscopic therapy) in acute variceal bleeding.

Author-year (ref)	No. pts	Child's C	Rebleeding	Mortality
Terlipressin *vs* placebo after initial variceal sclerotherapy (T/p)				
Levacher 1995	41/43	81%	12/23	12/20
Brunati 1996 A	28/27	36%	5/11	4/4
Patch 1999 A		66/66	62%	37/40
22/28				
Ioannou 2001 (19) total: 135/136		54/74	38/52	
	RR (95% CI):		0.75 (0.58-0.96)	0.74 (0.53-1.04)
Somatostatin + Sclerotherapy *vs* Sclerotherapy alone (SMS + S/S)				
ABOVE 1997 (41)	101/104	26%	35/57*	27/24 (6 wks)
Signorelli 1996 (42)A	33/30 NR	6/11	NR	
Octreotide + Sclerotherapy *vs* Sclerotherapy alone for early rebleeding (OCT + S/S)				
Primignani 1995 (55)	26/32	11/16	8/11	10/7
Octreotide + Sclerotherapy *vs* Sclerotherapy alone or with placebo (OCT + S/S)				
Besson 1995	98/101	37%	11/25	12/12
Brunati 1996		28/27	NR	7/11 4/4
Signorelli 1997	44/42	NR	7/12	NR
Dagher 2000 (10) total:	170/170		25/48	16/16
	POR (95% CI):		0.43 (0.25-0.74) $p = 0.002$	
Freitas 2000 (58)	44/42	14/15	8/16* (in 48 hours)	2/1
Zuberi 2000 (59)	35/35	5.7± 0.8 ± 5.9 ± 0.6	2/8* (in 5 days)	1/1
Octreotide + Variceal ligation *vs* Variceal Ligation alone (OCT + VL/VL)				
Sung 1995 (60)	47/47	20%	4/18	5/11
Early administration of Vapreotide *vs* placebo followed by endoscopic therapy (V/p)				
Cales 2001 (61)	98/98	36/39	65/49* (5 days)	14/21 (42 days)

* statistically significant A: abstract

as glucagon, vasoactive intestinal peptide and substance P. Therefore it reduces splanchnic and azygos blood flow and portal pressure. SMS has also been reported to suppress endothelin-1-induced HSC contraction via SMS receptors type 1.[25] On the other hand, Huang et al recently reported that in the presence of endothelin-1, SMS as well as octreotide, exert a local vasoconstrictive effect on the collateral vessels of portal hypertensive rats.[26] These mechanisms may also play a role in the arrest of haemorrhage by SMS.

In cirrhotics, SMS has variable effects on wedged hepatic venous pressure and is associated with a decrease in hepatic blood flow. However, azygos blood flow decreased in all studies, indicating a decrease in collateral flow.[27,28] SMS induces a dramatic (nearly 50%) but only transient change in portal pressure, azygos flow as well as in variceal pressure when given as a 250 μgr bolus.[29,30] Infusion of 250 μg/hour after bolus achieves a moderate decrease in HVPG (6%) but azygos blood flow returns to values close to baseline.[29] However, SMS infusion of 500 μg/h is associated with more consistent haemodynamic effects (HVPG decreased by 13% and azygos blood flow by 23%).[29] In the setting of acute variceal bleeding, 250 μg/h SMS produced a significant and sustained decrease in HVPG and prevented secondary elevations induced by test meal or blood transfusion. These findings suggest that monitoring HVPG may stratify further bleeding risk and give prognostic information for treatment response.[31]

Three RCTs evaluated the efficacy of SMS *versus placebo* and came to divergent conclusions.[32-34] In the largest trial, 5 days continuous administration of SMS (250μgr/h) was associated with a significant decrease in bleeding control failure (36% versus 59%, p = 0.036) and transfusion requirements.[33] In the other two studies[32,34] the shorter period of administration of SMS (only 30h and 24h respectively) as well as the unusually high placebo response rates observed (83%-the highest in the literature-and 70% respectively) may explain their negative results. These differences in the reported results caused statistically significant heterogeneity in the meta-analysis of the 6 RCTs (401 patients), which compare SMS with placebo or *inactive treatment* (p = 0.004). There was a trend in favour of SMS but the result was not statistically significant (OR 0.6, 95% CI 0.2-1.65). There was no difference in mortality between the two treatment groups (OR 1.20, 95% CI 0.65-1.66).[10] Similarly, no difference between SMS and placebo or no treatment was reported in another meta-analysis.[35]

SMS was compared with *vasopressin with or without nitroglycerin* in 7 RCTs with a total of 301 patients. Two meta-analyses[3,11] showed that SMS is equivalent in efficacy to vasopressin (control of bleed and mortality) but complications were significantly higher with vasopressin (46% *versus* 6.5%).

SMS was also shown to have no statistical difference in either efficacy or mortality when compared with *balloon tamponade* in two trials.[36,37] As expected, the use of balloon was associated with a significant higher complication rate (33% *versus* 9.7%).[36]

Three RCTs with a total of 197 patients, have compared the efficacy of SMS *versus sclerotherapy* in the control of variceal haemorrhage. Meta-analysis showed that there was no statistical difference in failure to control bleeding (OR 1.55, 95% CI 0.76-3.18) or death (OR 1.51, 95% CI 0.8-2.87) although there was a trend in favour of sclerotherapy with all the trials showing sclerotherapy to be slightly more effective. However complications were statistically significantly less frequent in patients treated with SMS (OR 0.41, 95% CI 0.2-0.86).[10] Other meta-analyses confirmed no benefit of SMS compared with sclerotherapy for any of the outcomes. Adverse events were significantly more frequent with sclerotherapy.[38,39] A recently published multicentre, Spanish study[40] comprising 169 patients, showed that continuous SMS infusion for 5 days (250 μg/hr after a 250 μg bolus repeated every 24 hours) after the initial control of bleeding by volume replacement and/or vasoactive drugs was as effective as sclerotherapy in the prevention of early variceal rebleeding (15% *versus* 14%). There was no difference in mortality between the two treatment groups (9% in both groups). The safety of the SMS treatment was also confirmed in this study, as the rate of complications was statistically significantly lower in the SMS group ($p = 0.00019$).

Finally, a large RCT involving 205 patients investigated whether the early administration of *SMS in combination with sclerotherapy* was more effective than sclerotherapy alone.41 Up to 8 bolus injections of 250 μg were given before the emergency endoscopy, followed by 250 μg/h SMS infusion. Treatment failure-defined as the occurrence of at least one of either excess transfusion requirement, haematemesis, haemodynamic instability, rescue therapy or death–was less frequent in the SMS plus sclerotherapy group (35% *versus* 55%, p = 0.004). Deaths during infusion were also less in that group but the result was not statistically significant. There was no difference in the incidence of complications between the two treatment groups. The authors also concluded that the emergency sclerotherapy is much easier in patients receiving SMS than placebo. Active bleeding at endoscopy was observed only in the 27% of patients in the SMS group compared to 42% in the placebo group. Similar results were obtained in a small study with the same design published in abstract form.[42] In this study, control of haemorrhage was achieved in 81% of patients receiving SMS plus sclerotherapy compared with 62% of patients treated with sclerotherapy plus placebo ($p < 0.01$) *(Table I)*. Another, non-randomised study showed that the percentage of active bleeders was further decreased when the dose of SMS was increased to an infusion of 500 μg/h and boluses of 500 μg. Furthermore, in patients undergoing sclerotherapy, the infusion of SMS for only 48 hours was not found as effective as the 5-day administration.[43]

A recent multicentre RCT was conducted to investigate the efficacy of low and high doses of SMS in controlling variceal bleeding. The SMS dose schedules the patients with acute variceal bleed received were (A) one 250 μg bolus + 250 μg/h infusion; (B) three 250 μg boluses + 250 μg/hr infusion; (C) three 250 μg boluses + 500 μg/hr infusion. The results showed that the 500 μg/hr infusion compared with schedules A/B achieved a higher rate of control of bleeding (82% *versus* 60%, $p < 0.05$), less transfusions (3.7 ± 2.7 *versus* 2.5 ± 2.3 UU, $p = 0.07$) and better survival (93% *versus* 70%, $p < 0.05$).[44]

SMS analogues: octreotide and vapreotide

Octreotide is a cyclic synthetic octapeptide analogue of SMS that shares 4 amino acids with the native compound, which are responsible for its biological activity. It has longer half-life and can be administered subcutaneously. Octreotide has only modest effects on the wedged hepatic pressure gradient and variable effects on intravariceal pressure.[45,46] When used as a bolus of 50 μg, it produces a sharp but transient decrease in portal pressure[46] and a transient decrease in azygos blood flow.[47] However these effects appear to be short-lived and a continuous infusion, in a variety of doses (50, 100 or 250 μg/h), neither maintained nor prolonged them.[48-50] Moreover, repeated boluses of octreotide cause a significant tachyphylaxis.[48] Some of the effects of octreotide on variceal bleeding may be mediated by blunting postprandial hyperaemia i.e. blood in the gut and the consequent increase in portal pressure.[51,52] As with SMS, octreotide therapy as a continuous infusion of 50 μg/h can be maintained for 5 days to prevent early rebleeding.

Studies of octreotide have not demonstrated a consistent benefit in efficacy or safety compared with other therapies. The results of a recent meta-analysis favour octreotide in the control of variceal bleeding over all alternative therapies combined (RR 0.63, 95% CI 0.51-0.77), *vasopressin/terlipressin* (RR 0.58, 95% CI 0.42-0.81) or *no additional intervention/placebo* (after initial endoscopic therapy before randomization) (RR 0.94, 95% CI 0.55-1.62).[53] Octreotide treatment for acute variceal bleeding was found to be comparable to *balloon tamponade* in one study.[45] However in contrast, the meta-analysis of octreotide treatment by Gotzsche showed no benefit of the drug over placebo or no treatment, in the use of balloon tamponade or number of patients with rebleeding.[35] No improvement in mortality was seen with octreotide versus any alternative therapy.[35,53]

The effectiveness of octreotide was further questioned in a double blind RCT that was not included in the meta-analyses. In this study, the largest ever carried out to evaluate the efficacy of a vasoactive drug (n = 262 patients), a continuous 5-day infusion of 50 μg/h octreotide, starting as soon as possible after admission was not more effective than placebo, whether or not injection sclerotherapy was needed for active bleeding in drug failure.[54] Finally, two recent studies for the prevention of early rebleeding[55,56] compared octreotide (100 μg 8-hourly subcutaneously) *versus* placebo. Both studies found no difference in early rebleeding or mortality between the two treatment groups *(Table I)*. In particular, in the RCT by D'Amico et al,[56] 262 patients were randomised to octreotide or to placebo and b-blockers and/or sclerotherapy were allowed together with the experimental treatment. Among patients eligible to b-blockers and/or sclerotherapy, while 15-day rebleeding rates were similar in the octreotide and placebo groups, there was a significant reduction of rebleeding episodes ($p = 0.03$), blood transfusions ($p = 0.04$) and days of stay in hospital ($p = 0.0001$) in the octreotide group 6 weeks after randomization.

Octreotide has also been directly compared with *SMS* after initial haemostasis with sclerotherapy. Although both drugs were found equally effective in the control of bleeding, a significant higher transfusion requirement was observed in patients receiving octreotide.[57]

Six RCTs comparing octreotide with *sclerotherapy* were recently reviewed. The trials included 497 patients. No significant difference was identified between the two treatments regarding failure to control bleeding (RD –0.03, 95% CI –0.09 to 0.03) and mortality (RD –0.02, 95% CI –0.1 to 0.06). Adverse events and serious adverse events were more frequent with sclerotherapy (pooled RD 0.06, 95% CI –0.05 to 0.17).[38] These results were confirmed in a recent RCT in 197 patients with recent bleeding58 as well as in two other meta-analyses of octreotide treatment.[10,53]

The comparison and combination of *octreotide with endoscopic treatment* has been the subject of a considerable number of studies. Recently, several clinical trials have used octreotide in combination with sclerotherapy and compared this treatment with placebo or sclerotherapy alone. The pooled data have shown that control of variceal bleeding was significantly better in patients receiving combination therapy (POR 0.43; 95% CI 0.25-0.74).[10] In the randomised study by Freitas et al, octreotide infusion proved a valuable adjuvant treatment to sclerotherapy in active variceal bleeding (control of acute active bleeding $p < 0.001$, haemostasis at 48hours $p < 0.04$).[58] However, another RCT showed no significant difference in the arrest of bleeding in the octreotide+sclerotherapy *versus* octreotide alone groups. Episodes of early rebleeding, blood transfusions and hospital stay were significantly less in the combination group[59] *(Table I)*.

An unblinded study compared *variceal ligation plus octreotide versus* variceal ligation alone; the combination treatment was significantly better in the prevention of rebleeding.[60] In all these studies, mortality was not significantly different between the treatment groups.

Vapreotide is a N synthetic SMS analogue that has longer half-life than the natural hormone (30 mins *versus* 3 mins). Vapreotide has recently been studied and found effective as adjuvant to endoscopic therapy for the control of acute variceal bleeding. Mortality at 42 days was once again not affected.[61] *(Table I)*.

A recently published meta-analysis[62] assessed whether vasoactive drugs (SMS, octreotide, vapreotide) may improve the efficacy of endoscopic treatment. Eight RCTs with 939 patients were summarized and the authors reported that SMS and its derivatives improve the efficacy of endoscopic therapy to achieve initial control of bleeding (RR 1.12, 95% CI 1.02-1.23) and 5-day haemostasis (RR1.28, 95% CI 1.18-1.39) yet failed to improve mortality. This paradox between efficacy in control of bleeding and lack of effect on mortality raises the issue of definitions of control of bleeding in trials – are they clinically relevant?

Long acting octreotide (sandostatin-LAR) failed to decrease portal pressure in cirrhotic patients.[63] Urotensin II, a vasoactive 'somatostatin-like' cyclic peptide has recently be cloned from man and reported to be a potent vasoconstrictor. The pharmacokinetics and pharmacodynamics of urotensin II are presently unknown but it may prove to have a role in the treatment of acute variceal bleeding in the future.[64]

Conclusion

Currently, terlipressin is one of the agents of first choice for the treatment of acute variceal bleeding. Compared with endoscopic therapy (the gold standard therapy for acute variceal haemorrhage) it is equally effective in the initial control of bleeding and the prevention of early rebleeding. Terlipressin reduces mortality and it should be administered as soon as possible before endoscopic investigation and maintained for at least 2 days, preferably 5 days, to prevent early rebleeding. When used as an adjuvant to emergency sclerotherapy, terlipressin improves haemostasis and reduces mortality that approaches statistical significance. Its 'renal protective' role may also favour it as the drug of first choice.

However, SMS in comparative trials with terlipressin has a directly comparable efficacy with fewer side effects. There is insufficient data to support SMS or octreotide monotherapy in the treatment of acute variceal bleeding. Nevertheless, SMS can be safely and effectively used as adjuvant therapy to sclerotherapy during the critical 5-day period following variceal bleeding and it can be administered as early as clinical signs of bleeding are observed. The therapeutic strategy of combined drug and sclerotherapy appears to have a sound basis, so that SMS combined with sclerotherapy is also a reg-

imen of first choice. The evidence currently demonstrating efficacy of octreotide in acute variceal bleeding is less than that for SMS. The optimal dose, route and duration of treatment are not adequately determined.

The currently recommended treatment schedule for acute variceal bleeding is administration of a vasoactive drug at the time of admission followed by with endoscopic treatment at the time of diagnostic endoscopy.[65] According to the latest published meta-analysis, this approach improves initial control of bleeding (RR1.12, 95% CI 1.02-1.23) and 5-day haemostasis (RR 1.28, 95% CI 1.18-1.39) but fails to affect significantly the mortality.[62]

For the treatment of acute bleeding from portal hypertensive gastropathy (incidence ≤ 3% at 3 years), vasoactive drugs have been used with high success rates in uncontrolled trials. Endoscopic or surgical interventions are considered in drug failures.

In contrast to the type of vasoactive drug, there is no doubt that prophylactic antibiotics must be used in all cirrhotics with upper gastrointestinal bleeding independent of the presence of infection. The optimal regime is yet to be decided. The data on antibiotics and infection indicate that all N studies on acute variceal bleeding will need to include data on therapeutic use of antibiotic and diagnosis of infection.

Prevention of recurrent variceal bleeding

Patients surviving the first episode of variceal bleeding are at very high risk of recurrent bleeding (70% or more at 1 year) and death (30%-50%). Therefore, the general consensus is that all patients who survive an episode of variceal bleeding must receive some effective long-term therapy to prevent further variceal bleeding.[66] There is no role for observational policy as active therapy has proved to be superior to none.

Randomized controlled trials for the prevention of variceal rebleeding

Non selective b-blockers versus placebo

Non selective b-blockers (NSBBs), propranolol and nadolol, have been extensively evaluated for the prevention of variceal bleed in RCTs. They decrease the splanchnic blood flow by reduction of cardiac output and reflux splanchnic arterial constriction. They also have a direct effect on portocollateral resistance, decreasing azygos and gastroesophageal collateral blood flow. The effect of propranolol on HVPG is moderate (mean reduction 12-16%)[3,67,68,69] and it is achieved in about one-third to one-half of treated patients.

A recent meta-analysis by Bernard et al summarizes the results of 12 RCTs (769 patients followed up for 21± 5 months) comparing NSBBs *versus* placebo for the secondary prevention of variceal bleeding.[70] Treatment with b-blockers significantly decreased the risk of rebleeding (20% mean improvement rate, $p < 0.001$) and 5 patients are needed to treat to prevent one rebleeding episode. Survival was also significantly improved in patients treated with b-blockers (5.5% mean improvement rate, $p < 0.05$), this being more marked in patients with more advanced liver disease. However, there was significant heterogeneity in this analysis ($p < 0.01$). Fourteen patients are needed to treat to prevent one death. Adverse events, generally mild, occurred in 17% of patients in these RCTs. There was no fatal complication. A previous meta-analysis also reported survival benefit to be almost statistically significant.[3]

NSBBs + *ISMN* versus *NSBBs*

Nitrates have also been shown to reduce portal pressure by selective venodilation in the splanchnic circulation, by promoting reflex splanchnic vasoconstriction as a response to reduced mean arterial and cardiac filling pressures and also by reducing intrahepatic resistance.[71,72] However, it is well known that patients with advanced cirrhosis have marked vasodilatation and the fall in arterial pressure and hepatic blood flow, together with the reduction of preload and cardiac output caused by nitrates, may have deleterious effects, the deterioration of renal function being one of them.[73]

The combination NSBBs and ISMN has been found to be more effective than b-blockers alone in reducing high portal pressure.[73,74] In the clinical setting, in a randomised trial by Gournay et al, the addition of isosorbide mononitrate (ISMN) significantly improved the efficacy of propranolol alone in the prevention of variceal rebleeding but only after stratification according to age (i.e. < 50 *versus* ≥ 50 years old, $p = 0.03$, or by adding an additional year of follow up, $p = 0.05$). However, no significant difference was found in overall rebleeding and survival. Moreover, more patients in the combination group had to discontinue therapy due to side effects.[75] Similarly, no additional benefit from the combination of NSBBs and ISMN was reported in a study published in abstract form. Of note, authors reported higher mortality in the combination group[76] *(Table II)*.

Sclerotherapy versus *drugs*

Twelve RCTs including 971 patients, compared sclerotherapy versus drugs (propranolol or nadolol+ISMN) for the prevention of recurrent bleeding (from any source, e.g. varices, portal hypertensive gastropathy bleeding, or sclerotherapy ulcers). These were systematically reviewed.[10] There was a striking heterogeneity in the evaluation of rebleeding ($p = 0.004$). The POR showed that there was no significant difference between the two treatment modalities (POR 0.88, 95% CI 0.58-1.32). More patients randomised to sclerotherapy survived but the result was not statistically significant (POR 0.95, 95% CI 0.58-1.32). Moreover, the number of patients free of adverse events was significantly higher in the drug group compared to the sclerotherapy group (POR 0.85, 95% CI 0.65-1.11).

Table II. RCTs for the prevention of variceal rebleeding (not included in meta-analyses)

Author-year (ref)	No. pts	Follow up	Rebleeding	Mortality
NSBB/NSBB+ISMN				
Gournay 2000 (75) [PRO]	49/46	2 years	28/18	11/11
Patti 1999 (76)A [NA]	51/53	NR	20/27 7/17*	
VL/NSBB+ISMN				
Minyana 1999 (80) A [NA]	70/69	20/15 months	35/24	27/22
Agrawal 2002 (81)A [PRO]	53/51	18/16 months	10/13	7/7
Lo 2001 (82) A [NA]	60/61	NR	21/30	15/4
Villanueva 2001 (83) [NA]	72/72	21 months	35/24*	30/23
Patch 2002 (84) [PRO]	33/30	168/163 days	17/9*	7/8
VL+nadolol+sucralfate *vs* VL (VL+drugs/VL)				
Lo 2000 (85)	60/62	21 months	14/29*	10/20
TIPS *vs* PRO+ISMN (TIPS / drugs)				
Escorcell 2002 (86)	47/44	2 years	13%/49%*	28%

* statistically significant A: abstract
PRO: propranolol NA: nadolol VL: variceal ligation

Sclerotherapy + drugs versus *sclerotherapy*

There are 12 RCTs that compare sclerotherapy and drugs (propranolol, nadolol and isosorbide-5-mononitrate) *versus* sclerotherapy alone, comprising 853 patients.[10] Theoretically the drug might prevent rebleeding before variceal obliteration. One problem with this group of studies is that in only one study was the effect of b-blockers evaluated after obliteration.[77] In the others, the drug was stopped at eradication. There was statistically significant heterogeneity both in the direction and the size of the effect of treatment but not for survival. POR showed that there was statistically significantly less rebleeding (POR 0.54, 95% CI 0.34-0.86) and fewer deaths (POR 0.65, 95% CI 0.43-0.97) in the combined treatment arm. A recent abstract also favoured the combination of sclerotherapy and propranolol in reducing the incidence of recurrent haemorrhage from gastric sources.[78]

Sclerotherapy and subcutaneous octreotide was also compared with sclerotherapy alone for the prevention of early rebleeding, as already discussed,[55,56] as well as for long term management of patients after variceal haemorrhage.[79] This last study showed significantly better rebleeding (6% and 44% respectively, $p = 0.037$) and mortality rates (0% and 25% respectively, $p < 0.02$) in the combined treatment group. However, the study raised the possibility of a severe selection bias due to the exceedingly high rebleeding rates in the sclerotherapy group. Therefore, the clinical efficacy of subcutaneous octreotide in reducing rebleeding rates remains uncertain.

EVL versus *drugs*

Five RCTs (3 in abstract form) assessed the efficacy of EVL versus NSBBS and ISMN.[80-84] In two there was no significant difference in the variceal rebleeding episodes or in survival.[80,81] In one, the ligation group experienced significantly less variceal episodes (similar upper GI bleeding episodes) but a higher death rate.[82] Finally, Villanueva et al reported favourable results in the drug group regarding rebleeding (the difference was more pronounced among patients whose liver function was well preserved) and complication rates.[83] The study from our unit, soon to be published, has shown drug therapy is equivalent to banding[84] *(Table II)*.

EVL + drugs versus *EVL*

Recently, a triple therapy, (EVL to reduce variceal size, nadolol to lower portal pressure and sucralfate to heal oesophageal ulcers) was compared with EVL alone.[85] This triple therapy proved more effective in terms of prevention of variceal recurrence, variceal and upper GI rebleeding. No significant difference in death rate was identified *(Table II)*.

TIPS versus *drugs ± endoscopic therapy*

When Escorsell et al compared TIPS *versus* drug therapy the 2-year rebleeding rate was significantly less in the TIPS group. However, the drug group experienced less encephalopathy and more frequent improvement of the Child-Pugh score with lower costs.[86] Meta-analysis of RCTs (including 750 patients) comparing TIPS with endoscopic therapy with or without additional drug therapy reached similar conclusions; TIPS reduces the risk of rebleeding but increases the risk of hepatic encephalopathy without effect on survival[87] *(TABLE II)*.

Haemodynamic monitoring of the drug therapy

The pharmacological treatment of portal hypertension is based on the assumption that a sustained reduction in portal

pressure reduces the incidence of variceal haemorrhage. An absolute value of HVPG ≤ 12mmHg or a reduction of ≥ 20% in HVPG from baseline is associated with a very low risk of rebleeding. This approach has been reported to be successful using propranolol for both primary and secondary prophylaxis of variceal haemorrhage.[67,68,88] In particular, achieving a 20% decrease in either variceal pressure or HVPG has been reported highly sensitive and specific for identifying patients not bleeding during follow up.[88] Similarly, the combination of nadolol and ISMN reduced HVPG to these levels in a significantly higher proportion than sclerotherapy treated patients.[89] Other studies however, did not support the above findings. A fall in HVPG of 20% was not a reliable predictor of clinical response since there was no difference in rebleeding rates between responders and non responders (43% *versus* 25%), whereas a threshold value of 12 mmHg was useful but applied in practice to relatively few patients.[90,91]

The use of the above haemodynamic targets could be a useful tool to identify at early stages patients who are "non-responders" to pharmacological therapy. These patients can benefit from treatment adjustments based on monitoring or use of alternative therapies such as variceal ligation, combination drug therapies or TIPS but this has yet to be demonstrated. In our opinion, as the studies of pressure monitoring show the highest rebleeding rates in the group in whom pressure was not measured, a degree of selection took place. In addition, several patients rebleed before re-measurement can take place. It is unclear therefore whether, if universally applied, pressure monitoring would result in less bleeding, and this needs to be tested in a clinical trial.

Conclusion

The first-line treatment for prevention of recurrent variceal haemorrhage is b-blockade (which also prevents from portal hypertensive gastropathy bleeding). B-blockade should be continued indefinitely. Variceal band ligation has replaced sclerotherapy as it is better tolerated with fewer side effects and is more efficacious in the secondary prophylaxis. It should be used if there are contraindications or intolerance to b-blockers. The use of isosorbide mononitrate on its own is contraindicated and its use in combination with b-blockers is not sufficiently studied. Combinations of endoscopic and drug treatments should be further investigated. The management of patients on drug therapy can include monitoring of haemodynamic response, but the evidence for this may not be as strong as initially thought. In addition, in view of lack of non-invasive methods to measure and monitor the portal pressure, it remains clinically difficult to recommend.

Prevention of first variceal bleeding

In patients with cirrhosis the risk of gastrointestinal bleeding is approximately 30% and the initial episode will prove fatal in 30-50%. Consequently, the primary prevention of variceal haemorrhage is an important therapeutic goal.

The optimal prophylactic treatment should be easy to administer, have relatively few side effects, and be reasonably effective. Drug therapy potentially fulfils these criteria best. In addition, drug therapy has the potential to protect against gastric mucosal bleeding, which accounts for a sizeable proportion of first bleeding episode.[92]

Randomized controlled trials for prevention of first variceal bleeding

NSBBs versus *placebo*

The haemodynamic response after administration of b-blockers is better in compensated patients without previous episodes of variceal bleeding. For that reason NSBBs have greater potential in primary rather than secondary prophylaxis.[3]

The pooled data from all 9 prophylactic RCTs of propranolol or nadolol in 996 cirrhotic patients with large varices showed a statistically significant bleeding risk reduction with b-blockers treatment (OR 0.54, 95% CI 0.39-0.74). Mortality rate was reduced with NSBBs but not significantly so (OR 0.75, 95% CI 0.57-1.06).[10] These results are in agreement with previous published meta-analyses.[3,93,94] NSBBs have been shown to be effective independently of cause and severity of cirrhosis, presence of ascites and variceal size in an analysis of individual patient data from 4 of the above trials.[94]

ISMN versus *placebo*

The effectiveness of NSBBs in primary prevention of variceal bleed is currently unequivocal. However, 15-25% of patients have contraindications or develop side effects precluding their use. In a single study, when ISMN was used in these patients, no significant difference in the 1- and 2-year actuarial probability of experiencing first variceal bleed was observed[95] *(Table III)*.

ISMN versus *NSBBs*

ISMN had subsequently been compared to propranolol; no significant differences were noted in bleeding rates or mortality after 29 months of follow up.[96] However, after 7 years, patients receiving ISMN had increased mortality, especially those greater than 51 years of age compared with the propranolol group (72% *versus* 48%).[97] Moreover, ISMN appears to be ineffective compared with nadolol in a very recently published randomised trial with 52 patients with ascites and oesophageal varices; ISMN was well tolerated but failed to prevent variceal bleeding.[98] Therefore, nitrates must not be used as sole agents in cirrhotic patients *(Table III)*.

Table III. RCTs for the prevention of first variceal bleeding (not included in meta-analyses).

Author-year (ref)	No. pts	Follow up	First bleed mortality	
ISMN/placebo				
Garcia-Pagan 2001 (95)	67/66	2 years	15/7	15/9
NSBB/ISMN				
Angelico 1993 (96) [PRO]	61/57	29 months	7/9	9/9
Borroni 2002 (98) [NA]	25/27	21.3 ± 11.6 months	2/10*	8/7
PRO+S/S				
Avgerinos 2000 (103)	44/42 24.6 ± 9.8/26.8 ± 7.7months	10/6 8/6		
PRO+VL/VL				
Agrawal 2002 (106)A	46/46	8/8 months	4/5	NR

* statistically significant A: abstract
PRO: propranolol NA: nadolol S: sclerotherapy VL: variceal ligation

NSBBs and ISMN versus *NSBBs*

The combination of NSBBs and ISMN *versus* NSBBs has been evaluated in 3 RCTs including 552 patients. The combined analysis of the studies showed a non-significant difference in the bleeding rate (10% combination group versus 15% b-blocker group) or mortality (10% both groups).[39] Merkel et al followed up for 7 years the 146 patients of a multicentre RCT[99] that was included in the meta-analysis. The authors reported higher efficacy of the combined treatment in preventing bleeding ($p = 0.02$). The drug combination proved safe with no deleterious effects on ascites occurrence or on survival.[100]

NSBBs versus *sclerotherapy ± NSBBs*

Two studies[101,102] compared NSBBs with endoscopic sclerotherapy for primary prevention of variceal haemorrhage. B-blockers were shown to be superior to sclerotherapy in one (2 of the 42 versus 9 of the 42 patients bled, $p < 0.03$).101 In the other, the combination of b-blocker and sclerotherapy provided no benefit over either therapy alone in the incidence of bleeding and it was associated with higher mortality. The mortality rate without variceal bleeding was 2.75 times higher in the sclerotherapy ± propranolol groups than in the drug or control groups ($p = 0.002$)[102]. Recently, Avgerinos et al evaluated the efficacy of combined sclerotherapy and propranolol *versus* propranolol alone in cirrhotic patients with varices and high (>18 mmHg) intraesophageal variceal pressure. There was no difference in the incidence of first bleed or mortality in the two groups, but a significantly higher complication rate in the combination group ($p = 0.002$)[103] *(Table III)*.

NSBBs versus *EVL*

Four RCTs and a recent meta-analysis[104] have been published on EVL for the primary prophylaxis of oesophageal variceal bleeding. Among 283 subjects in trials comparing ligation with b-blockers therapy, ligation reduced the overall risk from a first variceal bleed from 15.7% to 7.6% [RR 0.48, 95% CI 0.24-0.96 or relative risk reduction of 52% (95% CI 4% to 76%)] but had no effect on all-cause mortality (17% ligation and 19% b-blocker group). No information was given on side effects. The authors concluded that prophylactic ligation should be considered for patients with large oesophageal varices who cannot tolerate b-blockers.

Recently, Aoki et al published a decision analysis of prophylactic treatment for patients with high risk oesophageal varices. The authors used a Markov model to compare variceal ligation, b-blockers and 'watchful waiting' strategies in terms of bleeding-free years. They concluded that variceal ligation is an effective prophylactic therapy in many cases, but nearly a quarter of patients with high risk oesophageal varices and cirrhosis may benefit more from prophylactic treatment with b-blockers.[105]

EVL+NSBB versus *EVL*

When the combination of EVL and propranolol was compared with EVL alone, the actuarial probability of first variceal bleed and death over 18 month period did not decrease but the incidence of variceal recurrence was reduced in the combination group.[106]

Haemodynamic monitoring of the drug therapy

A major issue with clinical relevance with the primary prevention of variceal bleed is the need for haemodynamic monitoring of pharmacotherapy. While several studies have evaluated its clinical effectiveness in secondary prevention, in primary prophylaxis few data are available, and it would be clinically more difficult schedule due to greater numbers (compared with secondary prevention) and the much lower risk of bleeding.

Recently, Merkel et al evaluated the haemodynamic response to NSBBs *versus* NSBBs and nitrates, as defined by HVPG ≤ 12mmHg or by a decrease ≥ 20% of the baseline, in 49 cirrhotic patients. They reported that poor haemodynamic response (41% poor *versus* 7% good responders) was the main factor predicting bleeding (p = 0.0008).[107] Alternatively, De et al have recently proposed that single-sitting haemodynamics assessment of acute response to high dose (80 mg) oral propranolol (HVPG measured before and 90 mins after propranolol) clearly differentiates between responders (reduction in HVPG > 20%) and non-responders.[108] However, although HVPG is easy to measure, it is costly, involves hospital stay and would not be feasible when considering a universal use of b-blockade for all patients with varices. Other, non-invasive methods of haemodynamic monitoring, such as variceal pressure measurement by the endoscopic gauge and Doppler ultrasonography are being studied. Until their accuracy is further assessed, the use of the resting heart rate (25% reduction) and the development of symptoms to titrate the maximum tolerated dose of NSBBs represents the current standard of practice.

Conclusion

Primary prophylaxis depends on the detection of varices. At present there is no standardization of screening practices. In the absence of compelling data suggesting otherwise, every patient with cirrhosis (except those with short life expectancy) should be offered a one-time screening endoscopy to screen for varices given the low risk of endoscopy, the high prevalence of varices and the proven efficacy of primary prophylaxis.

In cirrhotics with large varices, prophylactic b-blocker therapy should be given; it is cheap (the second cheapest generic drug), easy to administer and effective in preventing the first variceal haemorrhage and bleeding from gastric mucosa. We believe that, since most liver diseases are progressive and liver function is an independent predictor of the risk of first bleeding, the presence of varices even small ones, is sufficient indication to prescribe b-blockers provided the patient is tolerant of therapy. This would save the use of repeated endoscopy, usually at 1-2 years to monitor varices. The available evidence does not support the combination of b-blocker and ISMN for primary prophylaxis. ISMN as monotherapy is contraindicated. Sclerotherapy does not offer any additional benefit when combined with b-blockers and it may be harmful in patients with varices who have never bled. Primary prophylaxis with variceal ligation appears to be safe and may be a reasonable alternative for patients with contraindications, intolerant or non-compliant to b-blockers. However it is unlikely to be a routine prophylactic treatment as it is much more expensive and less available than b-blockers and it does not prevent from gastric mucosal bleeding. The future is to improve on current medical therapy and to validate easily measured surrogate markers of portal pressure response.

Prevention of the development of varices

Based on experiments on portal hypertensive rats, it has been shown that propranolol limits the development of collaterals, thus it may prevent from development of varices. The first RCT did not support the above hypothesis and showed that propranolol did not prevent cirrhotics without or with small varices from the development of large oesophageal varices.[109] Moreover, the occurrence of variceal bleeding and the survival rate did not differ significantly in patients with chronic liver disease who received propranolol or placebo.[110] However, one third of patients were lost to follow up. Escorsell et al evaluated the effect of timolol, a NSBB, in cirrhotic patients without varices. The drug proved more effective in reducing the portal pressure in cirrhotics without than with varices,[111] suggesting greater effect of pharmacotherapy when administered in the early stages of portal hypertension, before the formation of varices. Until further encouraging results become available, the usefulness of prevention of formation/growth of varices (pre-primary prophylaxis) in clinical practice is yet unproven.

Drugs for future trials

Endothelin receptor antagonists

Recent evidence indicates that hepatic stellate cells (HSCs), which are resident perisinusoidal mesenchymal cells with a microanatomical position in the sinusoids analogous to vasoregulatory pericytes, may regulate sinusoidal blood flow. This is most evident in the context of liver injury when these cells transform into myofibroblasts (activated stellate cells) but may apply also to the normal liver. Endothelins (ETs) and Nitric Oxide (NO) play important roles in modulating this cell contractility, and their interplay is a determinant factor of local sinusoidal blood flow, especially in injured liver.[112,113]

Endothelin levels are increased in injury and activated HSCs have the ability to respond to ETs via the expression of ETA and ETB receptors. Exposure of stellate cells to ET-1 results in dramatic cellular spreading, proliferation and the acquisition of myofibroblast-like appearance typical of the activated phenotype. Induction of smooth muscle alfa-actin, a marker of activation, is prominent and is dose-dependent after exposure to ETs. Since endothelin is overproduced in liver injury, enhanced stellate cell contractility in this setting may lead to a perisinusoidal constriction and increased intrahepatic resistance. A mixed ET_A/ET_B receptor antagonist (Bosentan) was administered to isolated perfused cirrhotic livers; a high concentration of bosentan reduced portal pressure by 15-20%.[114] Similar compounds are currently undergoing to Phase I clinical

trials, opening N perspectives for the treatment of portal hypertension.

Nitric Oxide

Vasodilatory molecules, NO being one of intense interest, counterbalance the contractile effects of vasoconstrictors in the liver and other organs. NO blockade in normal rat livers has been shown to increase portal pressure and enhance the vasoconstriction induced by norepinephrine.[115]

Vascular beds with defective NO synthesis demonstrate an abnormally increased vascular resistance. A recent experimental study has demonstrated that in the cirrhotic liver, there is a deficit in the production of NO that is associated with an impairment in the intrahepatic vasodilatory response to an endothelial agonist such acetylcholine.[116] Elevation of hepatic NO is another approach that holds promise as a means to compensate the NO deficit and reduce activated HSCs contractility. Orally administered nitrates may serve this purpose but so far because of their effect in the systemic circulation, they have only been shown to be beneficial in combination with beta-blockers. Aiming to increase the intrahepatic production of NO, portal injection of adenovirus coupled with the gene encoding endothelial NO synthase has been reported. This approach enhances the expression of NO synthase in liver cells and although still experimental and far from being clinically applicable, significantly reduced portal pressure for a short period.[117]

Antifibrotic agents

The vasoactive compounds (angiotensin II, endothelins, NO) play a major role in the injured liver not only by regulation of the intrahepatic blood flow but also by direct modulation of extracellular matrix production and fibrogenesis.

The role of angiotensin II (ANG-II) and its antagonism in portal heamodynamics will be discussed later; recent reports though, have suggested a putative role in hepatic fibrogenesis. ANG-II as reported by Bataller et al, elicits a marked dose-dependent cell contraction and proliferation in activated human HSCs. These effects were totally blocked by losartan and reduced by nitric oxide donors or prostaglandin E2. Of note, the effects of ANGII were barely detectable on quiescent cells.[118] However, while systemic infusion of ANGII induced fibrosis in other organs (heart, kidney), no significant fibrotic response was detected in the liver.[119] Nevertheless, when Captopril was administered in bile duct ligated rats, significantly attenuated the progression of hepatic fibrosis.[120] Further research is required in the pathogenetic role of ANG-II in hepatic fibrogenesis and the possible role of ANGII receptor antagonists or angiotensin-converting enzyme inhibitors as antifibrotic agents.

HSCs are also a major target of ETs via type A and type B receptors. Recently, Cho et al showed that selective ET-A receptor blockade dramatically reduced collagen accumulation in rat secondary biliary fibrosis, a model refractory to most potential antifibrotic agents.[121] Dual receptor antagonism also prevents chronic fibrogenesis as reported by Rockey et al.[122] Poo et al studied the ET system in cirrhotic rats and concluded that the ETs do not play a major role in the pathogenesis of portal hypertension but do participate in an autocrine loop that counteracts the development in liver fibrogenesis.[123] Interestingly, modification of the microcirculation may well have a secondary effect on the fibrogenesis and therefore the interaction of vasoactive drugs/receptor antagonists-HSCs-microcirculation-fibrogenesis becomes much more complex.[124]

Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin II (ANG-II) receptor antagonists

ANG-II is considered a potential mediator of intrahepatic portal hypertension, because its plasma levels are elevated in cirrhosis and its administration induces a rise in portal pressure. Enhancement of the adrenergic vasoconstrictor influence on the portal system, direct contractile influence on stellate cells and therefore increase in the hepatic sinusoidal resistance and, finally, sodium and fluid retention induced by stimulation of aldosterone secretion maybe mechanisms that contribute to the portal hypertensive effect of ANG-II. Hence, the use of (ACE) inhibitors and Angiotensin II (ANG-II) receptor antagonists should improve PHT by inhibiting the actions of ANG-II.

Captopril, an ACE inhibitor has been evaluated in patients with cirrhosis; no significant change in HVPG was detected when it was administered either as a single oral dose or for 3 weeks.[125,126] In addition there was a small but significant decrease in MAP, GFR and urinary sodium excretion in cirrhotics with or without ascites.[125-127] When enalapril, probably a more effective than Captopril ACE inhibitor[128] was tested, a significant reduction in HVPG was observed although there was a poor response in patients with severe liver dysfunction.[129,130] Although MAP fell, renal function did not change significantly. In another study, 5 different ACE inhibitors decreased portal flow volume and total portal circulation resistance index presumably decreasing portal pressure.[131]

ANG-II receptor antagonists where first studied in 1981 when intravenous infusion of saralasin reduced significantly WHPV but also MAP.[132] Losartan produced dramatic reduction 46.8% ± 15.5% in HVPG in all patients with severe and moderate portal hypertension (the majority were alcoholic) without a clinically important decrease in arterial blood pressure. Renal function did not deteriorate.[133] Unfortunately, a recent RCT failed to confirm the above exciting data; long term losartan administration did not significantly reduce HVPG and it caused hypotension and reduced GFR in patients with moderate liver failure.[134] Irbesartan, an ANG-II antagonist that does not require hepatic metabolism to an active metabolite, has been reported

to reduce HVPG by 42%.[135] However, in a recent study, Irbesartan only modestly reduced the portal pressure and induced marked arterial hypotension and renal impairment in patients with advanced cirrhosis.[136] The pronounced effects in arterial pressure with marginal reduction in portal pressure were once again emphasized in a pilot study with 25 cirrhotic patients.[137] ANG II receptor antagonists may prove to be useful in early but not in late cirrhosis for their antifibrotic potential. Due to effects on the kidneys they should not be used in cirrhosis.

Alfa-adrenoceptor antagonists

Prazosin, an alfa 1 adrenergic blocker, is another vasodilator that reduces portal pressure in patients with cirrhosis and may have synergism with propranolol. An initial study comparing prazosin with propranolol showed reduction of the HVPG by 18% and 25% respectively.[138] Larger reductions were reported in later studies; acute reduction of HVPG 25.7% and chronic reduction of HVPG 25.7%. However, significant fall in MAP as well as decrease in sodium excretion and therefore ascites was observed.[139] These findings were confirmed in a subsequent study that compared propranolol plus prazosin with propranolol plus isosorbide-5-mononitrate (ISMN).[140] The authors reported that propranolol plus prazosin caused a greater reduction HVPG ($p < 0.01$), but side effects occurred more frequently in this group (46 % versus 25%). These side effects may preclude its use. At present, no clinical trials using prazosin in primary or secondary prophylaxis of variceal haemorrhage are available.

Carvedilol

Carvedilol is a novel vasodilating non-selective beta-blocker with weak intrinsic anti-alpha-1-adrenergic and calcium channel antagonism.[141] It has a rapid onset of action with 2-4 times greater b-blocking action than propranolol.

The haemodynamic effects of acute and chronic therapy of carvedilol in patients with cirrhosis have been assessed in 5 studies.[142-146] In a RCT, carvedilol as a single dose decreased HVPG to > 20% of baseline and to < 12 mmHg (the threshold for oesophageal variceal bleed) in more than 50% of patients. However, carvedilol, compared with propranol, caused a greater decrease in MAP.[143] The same group expressed concern about the reduction in MAP in a recently published abstract with chronic administration of 31 mg/day carvedilol.[144] Four weeks' therapy with 25 mg/day of carvedilol had similar portal hypotensive effects and no significant effects on MAP, hepatic blood flow or renal function but a high dropout rate was observed, mostly due to systemic hypotension.[145] When recently tested in 10 cirrhotics for 4 weeks, low dose (12.5 mg/day) carvedilol led to a significant reduction in portal pressure with minimal effects on systemic haemodynamics.[146]

Carvedilol has unpredictable bioavailability in the population of cirrhotics; therefore it should be used with caution on account of its potential for systemic hypotension. Low starting dose of 3.125 mg twice daily (as in patients with heart failure) is strongly recommended. To date there are no clinical studies looking at the effect of carvedilol in preventing variceal bleeding.

Clonidine

It is a central alfa 2-adrenoreceptor agonist that induces a sustained decrease in sympathetic nervous activity and portal pressure without adverse effects on hepatic blood flow and liver function.[147] Short and long term clonidine administration did not modify renal haemodynamics or induce natriuretic responses in patients with ascites despite the marked fall in arterial pressure and reduction in cardiac output.[148] Clonidine resulted in a greater fall in the portal pressure compared with propranolol in alcoholic cirrhotics.[147] In a more recent study only when combined with propranolol, clonidine resulted in a fall in the portal blood flow.[149] There is no data on the use of clonidine in the prophylaxis of bleeding; however its hypotensive effect may limit its clinical use.

Diuretics

Most patients with portal hypertension have an expanded plasma volume, associated with a peripheral vasodilation. The use of antialdosteronic drugs aims at decreasing portal pressure through a decrease in blood volume. The administration of loop diuretics causes acute depletion of plasma volume, with a reduction of the porto-hepatic gradient, but this depletion is promptly followed by an increase in sodium retention.[150.151] Chronic administration of spironolactone in patients with cirrhosis without ascites leads to a significant reduction of the HVPG.[152,153] Moreover, a recent study demonstrated the efficacy of spironolactone in reducing oesophageal varix pressure, both as a single agent and in combination with propranolol in patients not-responding to beta-blockers.[154] However Sugano et al[155] showed that spironolactone as an adjunct to low dose transdermal nitroglycerin did not demonstrate therapeutic portal pressure reduction in cirrhotics. The use of antialdosteronic agents, which are already widely used in cirrhotic patients for the treatment of ascites, could be useful adjunctive therapy in the treatment of portal hypertension.

5-hydroxytryptamine (5-HT) receptor antagonists

A serotonin mechanism has been reported to contribute to the hyperdynamic circulation of portal hypertension. Several studies in portal hypertensive rats demonstrated that serotonin antagonists decrease portal pressure, mainly

due to a decrease in portal vein inflow. These findings led to human studies; these showed significant reduction in HVPG (from 23% to 14.6%) as well as in MAP after single[156] or chronic administration of ketanserin.[157] Also, reversible portosystemic encephalopathy was observed in 50% of patients in one study.[158] Combination treatment of 5HT3 antagonists with propranolol has also been studied; it reduced the HVPG in patients who did not initially responded to propranolol.[159] An initial reduction in the portal pressure was not sustained during follow up.[158]

Antibiotics

The strong association between bacterial infections and gastrointestinal bleeding, as discussed earlier, has led to the use of antibiotic prophylaxis in the setting of acute gastrointestinal bleeding. The obvious hypothesis that could explain this connection is that gastrointestinal haemorrhage could predispose bleeding cirrhotic patients to bacteraemia. However, this has been challenged by data that support a different sequence of events; in our unit we have postulated that bacterial infection may be the critical factor that triggers gastrointestinal haemorrhage, particularly variceal bleeding.[160] In patients with varices, the high levels of endotoxin into systemic circulation during episodes of bacterial infection[161,162] result in a further increase in portal pressure through the synthesis of endothelin and contraction of HSCs;[163] induction of cyclo-oxygenase products may also contribute.[164] Furthermore, endotoxin-induced nitric oxide together with prostacyclin induced by both endothelin and endotoxin could inhibit platelet aggregation.[165] The increase in portal and subsequently variceal pressure, coupled with impairment in primary haemostasis could lead to the onset of variceal bleeding. Based on these data, antibiotic treatment in combination with oral NSBBs or other drugs may have a role in the prevention of variceal bleeding and requires serious consideration and testing.

Agents that increase the lower oesophageal pressure

Agents that constrict the physiological lower oesophageal sphincter, e.g. domperidone and metoclopramide have been suggested as therapy in the management of variceal bleeding; they reduce variceal blood flow by constricting the palisade zone, where the collaterals feed the varices. Studies in the past have shown that they decrease azygos blood flow and variceal pressure.[166,167] However, their role in arresting variceal bleeding is uncertain.[168,169]

Haemostatic agents

The therapeutic role of haemostatic agents has not been studied in variceal bleeding. Recently, the availability of recombinant factor VIIa which is known to correct prothrombin time,[170] has led to a large blinded study. The results are awaited with interest.

Mortality from acute variceal bleeding has decreased in the last few decades with the implementation of N therapeutic strategies (pharmacological, endoscopic treatments and antibiotic administration). In hospital mortality is reported to be reduced by 50% over the past 15 years;[171] although deaths in Child-Pugh A patients are rare following gastrointestinal haemorrhage, 25% of Child-Pugh C patients still die from bleeding. Similarly, El-Serag et al demonstrated that mortality has significantly declined at 30 days and 6 years (approximately 30% and 6% respectively) in cohorts 11 years apart. This decline was observed despite the fact that the patients in the late cohort had more severe liver disease.[172] Reduction in bleeding related mortality (from approximately 65% to approximately 40%, $p = 0.024$) has also been observed over a 40-year period in patients with cirrhosis admitted for a first episode of variceal haemorrhage.[173]

Nevertheless, a certain number of patients with portal hypertension still die of gastrointestinal bleeding. More investigations are necessary to evaluate the efficacy of new types of drugs or combinations of drugs in future trials. Although the quality of studies in portal hypertension is the best in Hepatology[174,175] it could be further improved if standardized definitions of critical end points (e.g. bleeding or rebleeding episodes, treatment failure, etc) achieved in recent consensus conferences[65,66] are applied. This will help to reduce the heterogeneity that is present in RCTs in portal hypertension and clarify the best and most applicable treatment options.

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