THERAPY UPDATE

Drug therapy for portal hypertension

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In patients with cirrhosis, increased intrahepatic vascular resistance and portal blood flow contribute to the development of portal hypertension and its complications.[1] Accordingly, the goal of pharmacological treatment is to reduce portal pressure and thus variceal pressure. This beneficial effect may be obtained by decreasing portal blood flow or intrahepatic vascular resistance, or both. Certain drugs cause splanchnic vasoconstriction and thus reduce portal blood flow and portal pressure and others cause intrahepatic vasodilatation and thus reduce intrahepatic vascular resistance and portal pressure (table 1). The mechanisms of action of certain portal hypotensive drugs have not been clarified.

Table 1 Portal hypotensive drugs

Drugs which reduce portal blood flow
• Agonists of angiotensin receptors
• Agonists of V_{1a} receptors
• Agonists of endothelin receptors
• α_1 Adrenoceptor agonists
• α_2 Adrenoceptor agonists
• β Adrenoceptor antagonists
Non-selective
Cardioselective
• β_2 Adrenoceptor antagonists
• Blockers of ATP sensitive K^+ channels
• Calcium channel activators
• Inhibitors of nitric oxide synthase
Drugs which reduce intrahepatic vascular resistance
• β_2 Adrenoceptor agonists
• ET_A-ET_B receptor antagonists
• Nitrovasodilators
Drugs for which the mechanism of action has not been completely clarified
• α Adrenoceptor antagonists
• Antagonists of AT_1 angiotensin receptors
• Angiotensin converting enzyme inhibitors
• Antiglucagon
• Calcium channel antagonists
• Chinese medecine
• Dimethylxanthine
• Diuretics
• 5-Hydroxytryptamine receptor antagonists
• Growth hormone inhibiting factors
• Natriuretic peptides
• Parathyroid hormones
• Platelet activating factor antagonists

The occurrence of ruptured varices is not directly correlated with the degree of portal hypertension[2] but clinical studies have shown that a reduction in portal pressure decreases the risk of bleeding and can treat acute bleeding. Drug therapy is one way of decreasing portal hypertension. Among approximately 50 substances which reduce portal pressure in patients or animals with portal hypertension, only a few are used to treat or prevent variceal bleeding.[3] The efficacy of certain drugs has been firmly established while the efficacy of others or combinations of drugs is under consideration and thus must only be used in randomised trials. Accordingly, the choice of pharmacological treatment for portal hypertension is simple, and is based on the results of well established studies. Moreover, international experts have met at Baveno workshops to draft consensus statements for the treatment and prevention of gastrointestinal bleeding.[4]

For the treatment of acute gastrointestinal bleeding, vasoactive drugs should be started as soon as possible before endoscopic examination. It would seem that this drug therapy should be maintained for up to five days to prevent early rebleeding. At present, terlipressin administration is effective for acute variceal bleeding and improving survival.[3] Somatostatin or its analogues are also effective. Vasopressin must only be used in combination with nitroglycerin to decrease the risk of side effects. A combination of drugs and endoscopic treatments should be considered. They appear to have some beneficial effects but discrepant results suggest that further trials are needed to confirm their efficacy in acute bleeding.

For the prevention of the first episode of bleeding, patients with portal hypertension should undergo oesophagogastric endoscopy to determine the presence of varices. When large varices are present, non-selective β adrenoceptor antagonists must be prescribed as they reduce the risk of bleeding and mortality rate.[5] The efficacy of these drugs is observed whatever the cause or severity of cirrhosis.[5] The efficacy of other drugs such as nitrates or combinations of drugs has not been clearly established and thus further clinical trials are needed.[3] The results of one study for the prevention of the development of large oesophageal varices with β blockers did not show any beneficial effects compared with placebo.[6] Thus this type of drug cannot be recommended in patients with small or no varices.

For the prevention of recurrent bleeding, β blockade is one of the firstline treatments with band ligation.[7] Other drugs or combinations of drugs cannot be

Key points

- Vasoactive substances may decrease portal hypertension by reducing portal blood flow or intrahepatic vascular resistance.
- Reduction in portal hypertension can treat acute variceal bleeding and decreases the risk of bleeding.
- Pharmacological treatment should be started before endoscopy when variceal bleeding occurs.
- β blockers must be prescribed in patients with large varices.
- β blockers prevent the risk of recurrent gastrointestinal bleeding and improve survival rate.

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recommended but require further investigation.[3] As for the prevention of the first episode of bleeding, β blocker administration should be continued for life, such as occurs in patients treated for arterial hypertension. The combination of β blockers and endoscopic treatments seems to be more effective than one treatment alone but no difference in survival rate has been observed between the two groups.

In conclusion, different drugs are effective in treating portal hypertension and gastrointestinal bleeding. New types of drugs, or combinations of drugs, should be tested. Finally, more clinical and experimental investigations are necessary to determine the efficacy and mechanisms of action of certain substances.

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