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Prevention of first variceal bleeding: new prospects

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PREVENTION OF FIRST VARICEAL BLEEDING: NEW PROSPECTS

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Propranolol lowers portal pressure although the exact mechanism of its action is uncertain. Initial studies of the use of propranolol in cirrhotics were in the prevention of recurrent variceal hemorrhage. However, results are very heterogenous and the use ofpropranolol in this situation remains controversial. Results of trials of primary prophylaxis for variceal bleed are more encouraging and recommendation can be made for the use of propranolol in patients with large varices who have never bled. Practical problems with the use of beta blockers in portal hypertension are a variability of response and the lack of clinical parameters to determine effectiveness.

BACKGROUND AND DEFINITIONS

Pressure in the portal vein is normally between 5-10 mmHg which is only a few mmHg higher than in the inferior vena cava. Vascular resistance to portal flow is thus very low. Portal hypertension is the result of increased flow and increased resistance in the portal system and may be arbitrarily defined as an increase in the resting portal pressure to above 12 mmHg[1]. Pharmacologic therapy is aimed at altering these factors by the use of vasoconstrictors to reduce flow and vasodilators to reduce resistance. Propranolol lowers portal pressure, measured directly[2] or indirectly from the gradient between wedged and free hepatic venous pressures (HVPG-HWVPFHVP) [3]. The exact mechanism of action of propranolol is uncertain but theoretically it may act by lowering cardiac output, by blocking splanchnic arteriolar B2 receptors or by causing reflex stimulation of splanchnic arteriolar alpha-adrenergic receptors, or combination of these, resulting in reduced splanchnic flow[3,4]. The extra-cardiac mechanisms seem important as studies in cirrhotics suggest that selective B-blockers like atenolol[5] and metoprolol[6] have less marked portal hemodynamic effects than propranolol. Azygous blood flow, an indirect measure of collateral blood flow in cirrhotics that includes blood flowing through esophageal varices, is reduced in every patient given propranolol[7]. In 1980, Lebrec et al[8] first proposed the use of oral propranolol as a means of reducing portal hypertension (PHT). Initial trials since then concentrated on the use of propranolol for prevention of rebleeding from varices in cirrhotics with PHT. However, recently attention has been focussed on primary prevention of variceal bleeding. Review of literature on both these aspects and the difficulties with propranolol therapy are presented.

Propranolol for prevention of recurrent variceal bleeding

The pioneering work was reported by Lebrec et at[9] on 74 patients, mostly alcoholic cirrhotics, who were mainly in the Child's category A. Oral propranolol was given twice daily to lower the resting pulse rate by approximately 25%, the mean dose used being 159 ±83 mg. 87% patients in the treatment group were free of rebleeding at 1 year vs 42% in the placebo group with the proportion being 79% vs 32% at two years. There was also a significant difference in survival in patients who had initially bled from varices: 91% (propranolol) vs 53% (placebo). The enthusiasm generated by this study was however dampened by a negative study from Burroughs et al[10]. which showed no statistically significant difference in rebleeding from varices - 46% (propranolol) vs 50% (placebo). However, the difference between the two studies could be explained on the basis of patient selection, as 34% patients in this study had ascites and 38% had encephalopathy and on the smaller sample size (n= 48). Also less than half the patients in this study had cirrhosis due to alcohol. Further studies have reported mixed results.

Villeneuve published his negative study in 1986[11]. 79 patients were randomized into a propranolol and placebo group within 72 hours of bleeding. Out of these, 57 patients had alcoholic cirrhosis. No difference in the rebleeding rate or survival was observed over a two year period. This study was criticized for its early randomization of patients as there was a high incidence of early recurrent hemorrhage and there is evidence that propranolol may not effect portal pressure in the first ten days following variceal bleeding[12]. Nevertheless, even when patients who had rebled within the first ten days were excluded, there was no significant difference in rebleeding at one year. The same was concluded in the study by Queuniet[13] of 99 cirrhotics. 92 of these patients had alcoholic cirrhosis, with about half being in Child's A category and this trial therefore disproved the suggestion from earlier studies that propranolol was only effective in welt compensated cirrhotics. However, some positive studies have also been reported. In the study by Colombo of94 patients[14], there was a significant reduction in rebleeding with propranolol compared to placebo - 47% vs 25%. Survival was not improved, but the number of deaths was small. A more recent study is reported by Garden[15] who found a significant lower incidence of rebleeding in modified Child's C patients receiving propranolol (39%) than those on placebo (90%). The effect on mortality however, was not significant. The picture regarding the use of propranolol in secondary prevention therefore, remains confused. A recent meta-analysis comprising most of the trials of propranolol for prevention of rebleeding from varices shows that the risk of rebleeding is significantly reduced[16], although there was great variability in the magnitude of benefit. Villeneuve11 concludes that propranolol appears to prevent rebleeding in about one-third of patients destined to rebleed, but does not improve survival.

Propranolol for primary prevention of variceal hemorrhag

Approximately one third of cirrhotics with esophageal varices bleed and the average mortality due to the first variceal bleed is around 50%[17]. Thus primary prevention may offer the best opportunity to improve prognosis. Recent studies therefore; seem to have concentrated on this aspect and five of these have been published. Pascalet al reported the first and the largest study in 1987[17]. 230 cirrhotic patients (90% with alcoholism and 46% with Child's grade C classification) with large esophageal varices without previous bleeding were randomly assigned to the propranolol or placebo group, after they had been divided into two groups according to the severity of their liver disease. On a cumulative analysis, significantly higher number of patients were free of bleeding at two years in the propranolol group (74%) compared to the placebo group (39%). Cumulative two year survival was also significantly improved in the propranolol group (72% vs 51%). Patients with Child's category C did better than those with Child's categoryA. The second largest study is the Italian Multicenter Project for propranolol in prevention of variceal bleeding[19]. 174 patients with large varices were randomized to propranolol or placebo (Vit. K). Less than half had alcoholic cirrhosis while 59% were Child's class A. Overall there was no significant difference between the two groups in the number of patients free of bleeding at one year or in survival at one year. However, if patients in Child's class A or those without ascites were analyzed separately, the percentage of patients free of bleeding in the propranolol group was significantly higher. No difference in survival was seen in any of the subgroups. The conclusion of the study was that propranolol could prevent first bleeding in patients with well compensated cirrhosis. Two trials have studied nadolol instead of propranolol for primary prevention of variceal bleeding. Nadolol was chosen since it is non-cardioselective, is not extensively metabolized in the liver, does not interfere with renal bleed flow and has been shown to greatly reduce portal pressure[20]. The larger series was reported by Lebrec[21] of 106 patients, majority of whom had Pugh's grade A or B disease. The difference in the percentage of patients free of bleeding and in survival at one year becomes significant only if "non-complaint" patients were excluded. The smaller of the two trials is by Ideo et al[22]. 79 patients were studied, approximately half with alcoholic cirrhosis and nearly 75% patients had Child's A or B disease. Patients with resistant ascites were excluded. After two years of follow-up, there was a

significant difference in bleeding rates between the treatment and placebo groups, but survival was unchanged. The latest study is reported by Groszman et al[23] of 102 cirrhotics in whom hepatic hemodynamics were measured before and after the administration of propranolol or placebo. Only 6% of patients were in the Child's C category. There was a significant difference in the occurrence of variceal hemorrhage in the two groups (11 placebo, 2 propranolol treated). All patients who bled had a hepatic venous pressure gradient (HVPG) of >12 mmHg and no bleeding occurred in patients whose HVPG decreased to _ 12 mmHg. This agreed with previous studies showing that patients with HVPG of <12 mmHg were at no risk of bleeding[24], therefore, suggesting that this may be the aim of pharmacologic therapy for PHT. Thus these five trials show that treatment with fl-blocker is safe and beneficial in cirrhotic patients with large varices who have not previously bled.

Safety of B-blocker therapy in PHT

No fatal complications are reported due to propranolol treatment in cirrhotic patients[25]. A controlled study of the safety of propranolol in chronic liver disease by Hayes[26] showed that the drug was safe for long term treatment. Hepatic encephalopathy may worsen if this is already present before B-blocker therapy is started[27]. Withdrawal due to patient intolerance is not a great problem, the study by Pascal[18] giving an incidence of 17%.

Practical problems in the use of B-blockers for portal hypertension

There are a number of practical problems related to the use of propranolol therapy in portal hypertension which have to be looked at before solid recommendations about their use can be made.

1. VarIability of response:

It seems clear from various studies that some but not all cirrhotics respond beneficially to propranolol. As discussed, propranolol reduces portal pressure[2,3], probably by a combination of effects[3,4]. However it has been shown that only about 30% of cirrhotics with varices who have not bled previously show a reduction of 20% or more in the basal portal pressure following administration of propranolol[28]. Even studies which found that propranolol always reduces the HVPG[6,8] showed that the extent of response was very variable. The reason for this lack of response or its variability is not clear and does not seem to be predictable on clinical grounds alone. Various explanations have been advanced but none seems to be confirmed from these studies. For example it has been suggested that higher the pretreatment portal pressure the greater the response to propranolol[2], but this was not confirmed in the study by Groszmann[23]. Based on the earlier studies of propranolol in cirrhotics[9,2]. it was suggested that propranolol was more effective in Child's A or B category patients whereas little or less marked reduction in JJVPG was observed in decompensated cirrhotics[7]. However, in 2 studies since then, the severity of liver disease[11,13] did not influence the effect of propranolol. The study by Garden[15] even suggested a reduced incidence of rebleeding in patients in Child's C less treated with propranolol. Similarly Pascal et al[18] demonstrated significant beneficial effects of propranolol on survival in patients in poor condition but not in those in good condition. Nevertheless, patients with more severe disease rebleed more irrespective of treatment (propranolol or placebo). Lebrec et al[3] found that about 75% of cirrhotics who had survived an episode of variceal hemorrhage exhibited a significant lowering in portal pressure.

However, the study by Rector[2] suggested that a history of previous variceal bleed did not predict the response to propranolol. The Italian multicentre study[19] suggested that cirrhotic patients with resistant ascites do not respond to beta blockers and may indeed do badly. The reduced density of B-2 receptors (down- regulation) in these patients has been suggested as the reason why propranolol may not be effective[29]. Continued alcohol abuse may effect the therapeutic response to propranolol[30].

2. Lack of clinical parameters to determine effectiveness:

If variability of response is a problem, things would be easier if there was an easily measurable end-

point to determine whether propranolol was being effective or not so that a decision about long term therapy could be rationally made. However, no such correlate exists. Earlier studies[8,9] took a 25% reduction in heart rate as a measure of the effectiveness of propranolol. This however, does not seem to hold true as in the subsequent negative studies[10,11], patients bled despite a lowering in heart rate by approximately 25%. The study by Rector[2] found no correlation between the fall in pulse rate, systolic blood pressure and portal pressure in response to propranolol. Another study[28] found that the percentage reduction in heart rate correlated only with the plasma propranolol concentration and not with the reduction in hepatic venous pressure gradient Groszmann[23] suggested that heart rate was useful in monitoring patient compliance and the potential toxicity of propranolol therapy but provided no further information. The only reliable indicator of the therapeutic response seems to be a reduction in }WPG of <12 mmHg. Studies[23,24] have clearly shown that patients with HVPG of <12 mmHg were at no risk of bleeding and in addition there seemed to be a higher cumulative rate of survival. However, there were no baseline clinical parameters that would identify the patients who would have a reduction in HVPG to less than 12 mmHg during the course of treatment, except to measure the HVPG at different intervals[23]. As mentioned above, several studies have clearly shown that any cirrhotic patient with varices who has an IIVPG of> 12 mmHg must be at high risk of bleeding. Can such patients be identified on clinical ground alone without resorting to portal hemodynamic studies? It has been shown that variceal size is an independent predictive factor for first bleeding[31] and that the first episode of bleeding usually occurs within the first year of diagnosis of varices. In cirrhotic patients whose variceal size was repeatedly evaluated, variceal bleeding occurred only in those with the largest varices. The bleeding risk is greater than 40% in patients with large varices according to Beppu et al[32]. Cales et al[33] have recently studied the incidence of bleeding in large esophageal varices with reference to application of prophylaxis for first bleeding. 84 cirrhotics were entered into the study, 41 of whom had no varices (grade 0) and 43 had grade one varices. At the end of two years, 31% of those with grade 0 varices at entry and 71% of these with grade one, had developed large varices. The initial Child's score had no predictive value for the occurrence of large esophageal varices. Based on these results they suggest that an upper gastrointestinal endoscopy should be performed every other year in patients with no varices and every year in patients with grade one varices. This schedule could be simplified further if prophylaxis is started from the diagnosis of grade zero varices, considering that 70% of such patients will have grade 2 varices two years later.

CONCLUSION

Results of trials of primary prophylaxis for variceal bleeding with beta blocker treatment are more encouraging than the secondary prevention trials. Primary prophylaxis can be recommended for patients who have large varices at presentation or in whom the variceal size is increasing, except for patients with gross ascites. Further large studies are needed, particularly from our part of the world, before propranolol becomes established therapy for primary prophylaxis for variceal bleeding in patients with cirrhosis.

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