Research from the South

Controlled trial of propranolol to prevent recurrent variceal bleeding in patients with non-cirrhotic portal fibrosis

C F Kiire

Abstract

Fifty patients with non-cirrhotic portal fibrosis who were admitted to hospital because of upper gastrointestinal bleeding were randomly assigned to treatment with either oral propranolol given in doses that reduced the resting pulse rate by 25% (25 patients) or with a placebo (25 patients). One year after the start of the study 20 patients in the propranolol group and five patients in the placebo group were free from recurrent gastrointestinal bleeding ($p<0.0001$).

Giving continuous oral propranolol treatment is therefore effective in preventing recurrent upper gastrointestinal bleeding in patients with non-cirrhotic portal fibrosis.

Introduction

Portal hypertension is a common clinical problem in developing countries. Apart from cirrhosis of the liver, one of the primary causes of portal hypertension in developing countries is portal fibrosis, which is largely due to schistosomiasis of the liver. In Harare, Zimbabwe, bleeding from oesophageal varices accounted for 27% of admissions to hospital in patients who presented with acute upper gastrointestinal bleeding.[1] Similar findings have been reported in many other African countries, especially Egypt and the Sudan, where schistosomiasis is endemic.

For a long time there has been no satisfactory treatment for patients with recurrent variceal bleeding secondary to portal hypertension. Continuous treatment with oral propranolol has been shown to produce a sustained decrease in portal venous pressure in patients with cirrhosis.[2-4] Not all workers have found that the drug can be used to prevent recurrent gastrointestinal bleeding in patients with cirrhosis, however.[4] The difference in results may have been due to including patients with cirrhosis from different causes and with different degrees of liver damage.

The beneficial effect of propranolol has so far been shown only in patients suffering from alcoholism with well compensated liver disease. It is not known whether prophylactic treatment with propranolol reduces the incidence of recurrent variceal bleeding in patients with other types of liver disease.

This study was designed to assess the efficacy of continuous treatment with oral propranolol to prevent recurrent gastrointestinal bleeding in patients with non-cirrhotic portal fibrosis, as the condition is common in Zimbabwe and most of these patients have well compensated liver disease.

Clinical details and results of laboratory tests on two study groups

	Propranolol group	Placebo group
No of patients	25	25
Age (years):		
Mean (SEM)	34 (13)	32 (13)
Range	15-70	17-72
Sex (F:M)	9:16	7:18
Source of bleeding at start of study:		
Ruptured varices	15	17
Acute gastric erosions	10	8
Previous episodes of bleeding:		
None	11	9
Yes	14	16
Causes of portal fibrosis:		
Schistosoma mansoni ova (liver)	8	7
Schistosoma mansoni ova (stool/rectal snip) only	10	12
Idiopathic	7	6
Bilirubin (mean (SEM)) (μmol/l)	25 (22·6)	31 (20)
Albumin (mean (SEM)) (g/l)	36·1 (5.3)	34·2 (7·1)
Alanine aminotransferase (mean (SEM)) (IU)	28·1 (12·5)	26·1 (13·5)

Note: None of the differences between the groups was significant.

Methods

Patients with histologically proved non-cirrhotic portal fibrosis who were admitted to this department because of an episode of upper gastrointestinal bleeding were selected for the study. Additional criteria for inclusion were: (*a*) the source of bleeding as determined by endoscopy was either gastric erosions or oesophageal varices; (*b*) jaundice was absent or mild (serum bilirubin concentration <100 μmol/l); (*c*) ascites was absent or mild and transient. Patients with heart failure, asthma, and other types of liver disease or who had taken β blocker drugs in the past were excluded.

Sixty patients fulfilled the criteria for admission. Four patients died within a few hours of admission before being entered into the study, and six refused to participate. The remaining 50 patients were entered into the study, which was approved by the ethical committee of the hospital. Forty eight hours after bleeding had stopped patients were randomly assigned by sealed envelope to the propranolol group (25 patients) or the placebo group (25 patients). The patients did not know which drug was being prescribed. The two groups did not differ in age, sex, source of bleeding for which the patient was entered into the study, previous episodes of bleeding, causes of portal fibrosis, or results of biochemical tests (table).

Propranolol was given orally twice a day in increasing doses until the resting pulse rate was reduced by 25%. The dosage ranged from 20 to 160 mg twice daily. The other 25 patients received two placebo tablets a day which resembled propranolol.

Department of Medicine, University of Zimbabwe, PO Box A178, Avondale, Harare, Zimbabwe
C F Kiire, MRCP, *consultant gastroenterologist*

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Patients were seen monthly for three months and then at three monthly intervals. At each visit the dosage of propranolol was adjusted if necessary to maintain a reduction in resting pulse rate of about 25% (fig 1).

The end point of the trial was rebleeding from varices or acute gastric erosions, proved by endoscopy and requiring transfusion of at least two units of blood. The percentage of patients in each group who did not rebleed after being entered in the study was calculated according to the Kaplan-Meier method, and these were compared by the log rank test.[5]

Results

The resting pulse rate was significantly reduced in patients in the propranolol group ($p<0·01$). A 25% decrease from baseline rates was maintained throughout the trial (fig 1). Among the 25 patients in the propranolol group five rebled, whereas 20 of 25 patients taking placebo rebled. The percentage of patients who were free of rebleeding at various times is shown in figure 2. The difference between the propranolol group and the placebo group was highly significant ($p<0·0001$).

The percentage of patients who did not rebleed was significantly higher in the propranolol group compared with the placebo group regardless of whether the source of bleeding was ruptured varices or acute erosions. Of the 18 patients who had originally bled from acute gastric erosions, none of the 10 patients given propranolol rebled, whereas six of the eight patients taking placebo rebled ($p<0·001$). Of the 32 patients who had originally bled from varices, five of 15 patients taking propranolol rebled, and 14 of 17 patients taking placebo rebled ($p<0·001$).

The sources of rebleeding were analysed in relation to the original source of bleeding. In the propranolol group three patients rebled from varices and two patients from acute gastric erosions, the original source of bleeding having been ruptured varices in these five patients. In the placebo group, among the six patients whose initial source of bleeding was acute gastric erosions and who rebled, the site of rebleeding was ruptured varices in three and acute gastric erosions in the remaining three. Similarly, among the 14 patients whose original source of bleeding was ruptured varices, the site of rebleeding was acute gastric erosions in three and ruptured varices in 11.

There were six deaths—one in the propranolol group (bleeding varices) and five in the placebo group (four patients from bleeding varices and one patient from liver failure). There was no significant difference between the two groups ($p>0·05$).

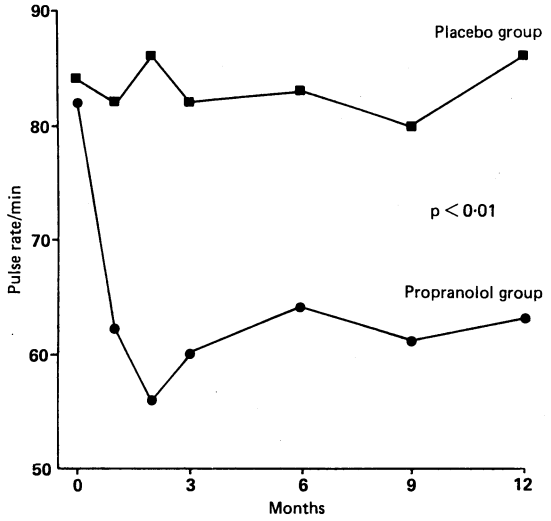

FIG 1—*Pulse rates of patients in the placebo group and propranolol group*

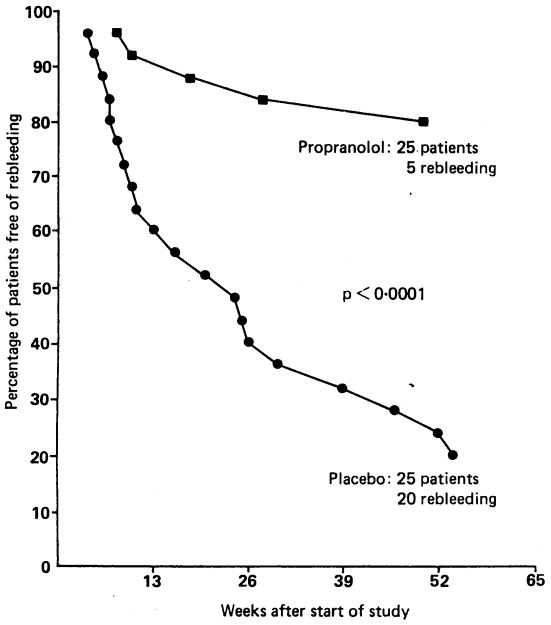

FIG 2—*Percentage of patients with no rebleeding after start of study*

Discussion

For years the only effective way of permanently reducing portal pressure in patients with oesophageal varices was portasystemic shunt surgery. The discovery by Lebrec *et al* in Paris that continuous treatment with oral propranolol not only reduced portal pressure but also reduced the incidence of rebleeding was an advance in the treatment of patients with portal hypertension.[2,3] The French workers, however, emphasised that their impressive results in preventing rebleeding applied only to patients with cirrhosis (due to alcohol in 88% of their patients) who were in good general condition.

In a subsequent study from the Royal Free Hospital Burroughs *et al* also showed that propranolol reduced portal venous pressure.[4] Nevertheless, they failed to show any benefit of propranolol in preventing varices rebleeding in patients with cirrhosis from different causes and varying grades of liver disease. They suggested that the difference in results may have been due to including in their study patients with cirrhosis from other causes and more severe liver disease.

The results of this study show that continuous treatment with oral propranolol in doses which reduce the resting pulse rate by 25% in patients with non-cirrhotic portal fibrosis who presented with upper gastrointestinal bleeding (from varices or acute gastric erosions) decreased the incidence of rebleeding. All our patients were in good general condition and in a state equivalent to Child's grade A. This suggests that propranolol is effective in preventing rebleeding in patients with good liver function regardless of aetiology.

In a study from the liver unit at King's College Hospital, London, treatment with oral metoprolol was associated with a significantly higher risk of recurrent variceal bleeding when compared with sclerotherapy.[6] This supported the earlier observations that non-selective β blockers are more effective than selective β blockers in reducing portal pressure.[7,8] This is because propranolol has an additional method of action mediated by β_2 receptor blockade on splanchnic vessels.

When the results of all the trials, including the one reported here, are considered it is clear that continuous

treatment with oral propranolol is effective in reducing rebleeding in patients with good liver function (equivalent to Child's grade A). In patients with more advanced liver disease, such as those with decompensated cirrhosis, propranolol has not been shown to be effective, and these patients should be treated by other methods such as injection sclerotherapy. The difference in response between patients with compensated and patients with decompensated liver disease can be explained by the higher concentrations of circulating catecholamines in patients with decompensated liver disease. The predominantly vasoconstricting effect in the portal system of these raised catecholamine concentrations would tend to counterbalance any reduction in pressure induced by propranolol.[9]

The results of this study showed no deterioration in liver or renal function. On the contrary, the feeling of wellbeing which is a well recognised side effect of this drug[10] was noted by many of our patients.

Fewer patients taking propranolol died than patients taking placebo, but the difference was not significant, perhaps because of the small number of patients who died and the short follow up period of one year.

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How To Do It

Appoint a colleague

M C Petch

Appointing a colleague is rather like choosing a spouse, except that divorce is not really an option. In both cases you have to live with the consequences of your decision for several decades and you may mistakenly believe that you are in control, whereas in reality there is usually some mother in law like figure manipulating events. Do not be alarmed by this. Arranged marriages can be most successful because neither party has undue expectations of the other. Provided you can live with the other party the marriage can be made to work and your differences will lead to a stronger unit. My experience of seeing the NHS consultant appointments system in action may help show others how to, or not to, choose a colleague.

These comments apply only to senior NHS appointments. Academic posts should be subject to more liberal rules.

NHS consultant committee is made up of:
- Lay chairman appointed by regional health authority
- District representatives:
  (*a*) lay member of the health authority
  (*b*) specialist medical representative
- Medical representatives of:
  (*a*) appropriate college
  (*b*) region concerned (two)
  (*c*) university

Preliminaries

The preliminaries take a long time, often a year or more in the case of a vacancy due to retirement. As soon as a close colleague whispers his or her intention of going start planning. Decide what you want to do because at this stage a short friendly discussion will enable you to take over the desirable parts of your colleague's practice and shed, or at least share, the undesirable parts of yours. Then write down carefully the sessional commitments that must be covered. For a cardiologist this might include two or more clinics, two investigative sessions, three ward rounds, one or two sessions in coronary care, two for administration, one for reading and research, one for teaching, one for travel; already the week is overbooked. It might seem obvious to you that there is a pressing need for a replacement but do not be surprised when this is challenged. Write down why a replacement is essential and take this and your provisional job description to the district medical officer, whose advice should be sought early and in confidence. When your retiring colleague begins to talk about dates the news will already be widespread, and urgent claims for new consultants in other disciplines will be presented from the most surprising quarters. Be prepared.

The details of the job description have to be discussed by the medical advisory committee of the relevant district hospital, often a consultant staff council. Make sure your friends are there; you may find that you don't have many on the day. If the chairman at least understands your case you may get your job description accepted with minor modifications. If the chairman does not then the matter will be deferred for a month, and then another month, and so on. If two districts are concerned your task is at least doubled. Eventually a job description must be agreed even though your secretary can spot the flaws. Keep a careful record of these discussions. Many months may yet elapse before the appointment, and during these months people will forget that they ever took place. They may assert later that they did not have the opportunity for comment. To avoid this it is important to ensure that all potentially interested parties see a copy of the job description.

At this stage you will also become aware that the

Regional Cardiac Unit, Papworth Hospital, Cambridge CB3 8RE
M C Petch, FRCP, *consultant cardiologist*

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