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Clinical trial

B_1 selective adrenoreceptor blockade for the long term management of variceal bleeding. A prospective randomised trial to compare oral metoprolol with injection sclerotherapy in cirrhosis

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SUMMARY Oral metoprolol, in a dose sufficient to reduce resting pulse rate by 25%, was compared with repeated injection sclerotherapy for the long term management of variceal bleeding. The prospective, randomised study was undertaken in 32 patients with biopsy proven cirrhosis and variceal bleeding who were Grade A or B on a modified Child's classification. In the 15 patients receiving metoprolol, portal pressure showed a mean fall of 3·7 mmHg (17·3±1·2 to 13·6±1·2 mmHg, $p<0·01$) after four weeks of continuous therapy, as compared with pretreatment levels. Nine of the 15 patients taking metoprolol had further bleeding (total of 21 episodes) compared with six of 17 in the sclerotherapy group (nine episodes). The risk of bleeding per patient/month of follow up was three times higher in the metoprolol group compared with those treated by sclerotherapy (0·14 and 0·04 respectively, $p<0·025$). Rebleeding in the metoprolol group occurred in six of the patients who had a fall in portal pressure of 10% or more.

Recent reports from Lebrec and colleagues from Paris have suggested that the non-selective B adrenoreceptor blocking agent propranolol, in doses sufficient to reduce resting pulse rate by 25%, not only produce a fall in portal pressure[1] but also significantly reduce the frequency of variceal bleeding in patients with alcoholic cirrhosis.[2] The authors attributed the fall in portal pressure to the reduction in cardiac output produced by the drug.[1] If the fall in cardiac output was the most important factor, it appeared to us that a selective B_1 adrenoreceptor blocker would be equally as effective for the reduction of portal pressure. Furthermore, a selective blocker should be associated with fewer side effects, in particular airways obstruction and peripheral vascular insufficiency which may be precipitated by B_2 adrenoreceptor blockade.

In the present study, the value of the B_1 adrenoreceptor blocker metoprolol for the long term management of variceal bleeding is assessed in relation to its effects on portal pressure and is compared in a prospective randomised trial to injection sclerotherapy.

Since the start of this trial reports by Hillon and colleagues[3] and our own group[4] suggest that the non-selective B receptor blocker propranolol may be more effective in reducing portal pressure than a B_1 selective agent; propranolol having an additional method of action mediated by B_2 receptor blockade on splanchnic vessels.

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Methods

PATIENTS

The investigation was undertaken in patients with biopsy proven cirrhosis and variceal bleeding presenting to the Liver Unit, King's College Hospital. In each of the patients variceal bleeding (requiring two or more units of blood transfusion or a fall in haemoglobin of 3g or greater) was confirmed by endoscopy, and the varices graded 1+, 2+ or 3+ according to size.[5] The severity of the underlying liver disease, at the time of presentation was assessed by using a modified Child's

classification.[6] Because of the potential dangers of B receptor blockade producing hypotension in patients with severe liver disease,[7] those who were Grade C on this classification were excluded from the study. Patients who had known contraindications to B receptor blockade, such as left ventricular failure, airways obstruction or symptomatic peripheral vascular disease, were similarly excluded.

The presenting variceal haemorrhage and any subsequent bleeding (defined by the above criteria) was managed by blood transfusion together with vasopressin and balloon tamponade if bleeding did not stop spontaneously. When the patients had been haemodynamically stable for a period of 24 hours they were allocated, by a system of random numbers to receive either oral metoprolol or to undergo repeated injection sclerotherapy. In those allocated to receive metoprolol, before starting therapy, portal pressure was estimated by the wedged hepatic vein technique, using the free hepatic venous pressure as an internal reference point.[8] The dose of the drug was titrated over a two to three day period from a starting dose of 50 mg bd to produce a reduction in recumbent resting pulse rate of 25%. The portal pressure measurements were repeated after four weeks of continuous therapy. Follow up of the patients was at four monthly intervals and included endoscopy to assess any changes in variceal size that might occur with B receptor blockade.

Patients in the injection sclerotherapy group were injected at intervals of three weeks until the varices were obliterated at, and within, 2 cm of the gastro-oesophageal junction. The flexible oesophageal sheath technique was used[9] and was carried out under sedation alone. After initial obliteration of varices further endoscopy was undertaken at intervals of four months in order to detect any recurrence of varices. When 'new' varices were observed these were injected until clearance of the gastro-oesophageal junction was again achieved.

The results for portal pressure were expressed as means with standard errors. The statistical analysis involved the Wilcoxon's matched pairs signed ranks test to compare changes in portal pressure and the Mann Whitney U test with correction for ties to compare the risk of bleeding in the two groups.

Results

Between 1 April, 1981 and 1 April, 1982 56 patients were admitted to the Liver Unit with cirrhosis and variceal bleeding. Of these, 24 patients were excluded from the study for the following reasons: Child's Grade C liver disease (12 patients); failure to stabilise with conservative management for the minimum period of 24 hours before randomisation (five patients); specific contra-indication to B receptor blockade (four patients); death from hepatocellular failure within the first 24 hours of admission (three patients). The remaining 32 patients were randomised, 17 to receive injection sclerotherapy and 15 oral metoprolol. The present analysis represents the follow up of these patients to January 1, 1983.

Comparison of clinical data at entry into the trial showed no significant differences between the metoprolol and sclerotherapy groups with respect to age, sex ratio, aetiology, and severity of cirrhosis and variceal size (Table 1). A mean fall in resting pulse rate of 30% (range 21–36%) was achieved in those patients treated by metoprolol with an average dosage of 300 mg daily (range 200–400 mg). The mean pretreatment gradient between the free and wedged hepatic venous pressure was 17·3±1·2 mmHg and this fell significantly after four weeks of continuous oral metoprolol to 13·5±1·2 mmHg ($p<0·01$ Fig.1). The fall in the pressure gradient was almost entirely the result of reduction in the wedged hepatic venous pressure, there being no significant change in the free hepatic venous pressure (Table 2). In four patients the fall in the pressure gradient was less than 10% from pretreatment levels. One patient was withdrawn from the study before the second measurement of portal pressure after a large variceal haemorrhage. A third measurement of the pressure gradient was undertaken at 12 to 18 months after entry into the trial in six of the seven patients who remained in the metoprolol group of the study at this time. In four of these six patients the initial fall after four weeks of therapy was maintained or increased, whereas in two patients (one of whom continued to drink heavily) the pressure had returned to pretreatment levels.

Table 1 *A comparison of the clinical data for the two groups at entry into the trial*

	Metoprolol (15)	*Injection sclerotherapy (17)*
Mean age (years)	54·5	53·8
Sex (F:M)	7:8	9:8
Aetiology of cirrhosis		
Alcohol	6	7
Primary biliary	5	6
Cryptogenic	4	2
Chronic active hepatitis	–	2
Modified Child's grading		
A	7	8
B	8	9
Variceal size		
1+	2	1
2+	3	9
3+	10	7

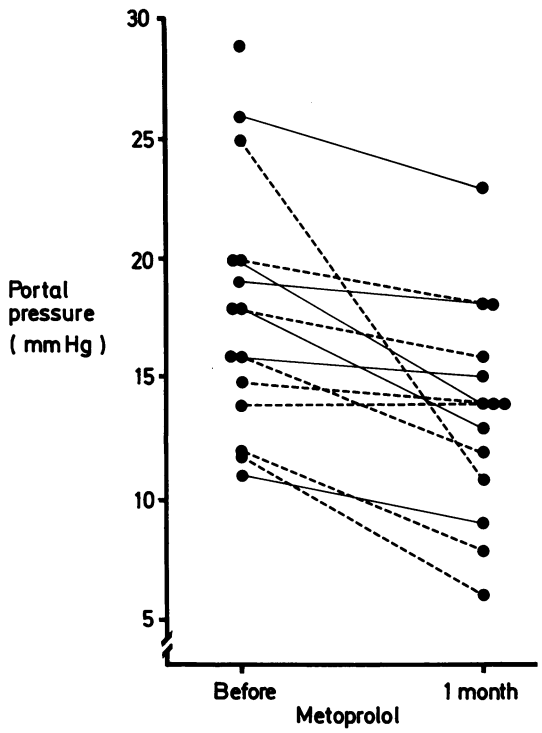

Fig.1 *Portal pressure (WHVP-FHVP) before and after four weeks of continuous therapy with oral metoprolol. One patient was withdrawn from the trial before the four week measurement. The broken lines represent those patients with further episodes of variceal bleeding.*

Further episodes of variceal bleeding occurred in nine of the 15 patients treated with metoprolol, with a total of 21 episodes. In 19 of these 21 episodes the patients had evidence of B receptor blockade at the time of the bleed with a pulse rate of 80/min or less despite volume depletion and frequently marked hypotension. Six of the nine patients who had further bleeding had shown a fall in the pressure gradient of 10% or greater at the time of the four week measurement and included the two patients with the largest fall (56 and 50%) and also two patients in whom the gradient fell to below 10 mmHg (Fig.1). Two patients taking metoprolol developed left ventricular failure during an episode of variceal bleeding. In one of these, the increased peripheral vascular resistance associated with the administration of vasopressin may have contributed to the haemodynamic disturbance. Both cases responded to diuretics and carefully controlled blood transfusions. There was no evidence during the period of the study that B receptor blockade resulted in deterioration of liver function with a similar number of patients in both the metoprolol and sclerotherapy groups (three and two respectively) having progression of the liver disease into the Child's C category. There were no significant changes in variceal size in those patients taking metoprolol.

In the sclerotherapy group six of the 17 patients had further bleeding with a total of nine episodes and the risk of bleeding per patient/month of follow up was over three times less than in those receiving metoprolol (0·04 and 0·14 respectively, $p<0·025$).

Table 2 *The wedged hepatic venous pressure (WHVP), free hepatic venous pressure (FHVP) and the gradient between the two, before and one month after continuous oral administration of metoprolol.*

	Baseline measurements			*One month after continuous oral metoprolol*		
Patient no	*WHVP*	*FHVP*	*Gradient*	*WHVP*	*FHVP*	*Gradient*
1	20	8	12	12	4	8
2	16	4	12	13	7	6
3	(35)	(7)	(28)	—	—	—
4	22	8	14	22	8	14
5	23	8	15	23	9	14
6	38	12	26	30	7	23
7	34	18	16	25	10	15
8	22	4	18	19	6	13
9	28	3	25	16	5	11
10	28	8	20	28	10	18
11	28	9	19	28	10	18
12	16	5	11	13	4	9
13	25	9	16	20	8	12
14	28	8	20	24	8	16
15	26	8	18	24	8	16
Mean±SE	25·3±1·7	8·0±1·2	17·3±1·2	21·2±1·6 p<0·01	7·6±0·6 NS	13·6±1·2 p<0·01

Baseline measurements only in patients 3. p = values for changes from baseline levels. NS = non-significant.

Mean blood transfusion requirements for each episode of bleeding were similar for the two groups (6·6 and 5·6 units metoprolol and sclerotherapy group, respectively). Of the 17 patients treated by injection sclerotherapy, variceal obliteration was achieved in 15 with a mean of 4·5 courses. Eight of the nine bleeding episodes in the sclerotherapy treated patients occurred in the first six months of the study, in each case before variceal obliteration had been achieved. This compared with the metoprolol group in which further episodes of bleeding were observed throughout the 18 months of follow up (Fig. 2). Two patients developed dysphagia after injection sclerotherapy, one of whom required dilation of a lower oesophageal structure on two occasions to relieve the symptoms.

Eight patients in the metoprolol group were withdrawn from the study on account of mutiple bleeds or a single life threatening haemorrhage and subsequently underwent injection sclerotherapy. There were no withdrawals from the sclerotherapy group. Two deaths occurred in both groups during the study, one each as a result of variceal bleeding and hepatocellullar failure (unrelated to bleeding).

Of the 24 patients excluded from this study, 21 were managed by injection sclerotherapy, three patients having died from hepatocellular failure within 24 hours of the initial admission with variceal bleeding. During the period of the trial 12 of the 21 patients had further bleeding with a total of 15 episodes. Two patients died as a result of variceal bleeding, whereas a further six patients, all of whom had Child's Grade C liver disease, died from hepatocellular failure unrelated to bleeding.

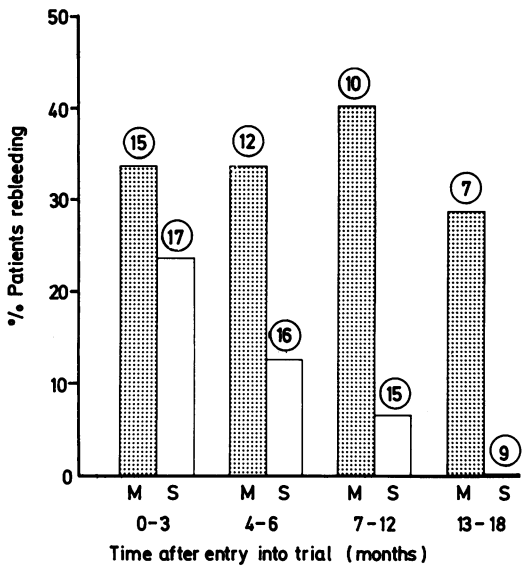

Fig.2 *The percentage of patients in the metoprolol (M) and sclerotherapy (S) groups rebleeding from varices at intervals after entry into the trial. The numbers at the top of each column represent the patients remaining in the trial during each period.*

Discussion

The use of oral metoprolol in this study was associated with a significantly greater risk of recurrent variceal bleeding as compared with those undergoing sclerotherapy, and the risk factor of 0·14 bleeds per patient/month of follow up is similar to that of a comparable control group of the controlled trial of injection sclerotherapy reported from this unit.[10] The results of injection sclerotherapy in the present report are consistent with those in the sclerotherapy group of the previous mentioned trial.[10] The poor results with respect to metoprolol are in marked contrast with those reported by Lebrec and colleagues using the non-selective B receptor blocker propranolol in which only one of 38 patients receiving the drug had further episodes of bleeding compared with 16 out of 36 in a placebo group.[2] As already referred to, however, there is evidence to suggest that the non-selective B receptor blockers are more effective than the selective agents in producing a fall in portal pressure.[3 4] The mean fall in portal pressure observed by Lebrec using propranolol[1] is indeed greater than that seen in this study, but it is to be noted that several patients had large reductions in portal pressure while taking metoprolol and had further episodes of bleeding. This finding must question the importance of changes in portal pressure as a factor in predicting the efficacy of B receptor blockade in the management of variceal bleeding. The lack of a correlation between variceal bleeding and portal pressure is in accord with most previous studies where such a relationship has been sought.[11 12]

Further controversy surrounding the role of B receptor blockade in the long term management of variceal bleeding has arisen from a second controlled trial of propranolol reported from the Royal Free Hospital.[13] In 42 consecutive patients with mixed aetiology cirrhosis and largely Child's Grade A and B severity of liver disease, the authors could find no benefit to those treated by propranolol compared with placebo despite large falls (mean 36%) in portal pressure. Furthermore, in two patients the presence of B receptor blockade during a further episode of variceal bleeding resulted in prolonged hypotension, despite adequate blood volume replacement.

Evidence from the present study with a selective B receptor blocking agent and that from the Royal Free Hospital with propranolol[13] must temper the initial enthusiasm for using these agents for the management of variceal bleeding, both with respect to their efficacy and the risk of associated complications.

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