

## Liver and biliary

# Comparison of three adrenoreceptor blocking agents in patients with cirrhosis and portal hypertension

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**SUMMARY** The effects of different types of adrenoreceptor blocking agents on portal venous pressure were studied in patients with cirrhosis and portal hypertension. Oral atenolol (selective  $\beta_1$  blocker), propranolol (non-selective  $\beta_1$  and  $\beta_2$  blocker), and prazosin ( $\alpha$  blocker) were compared in three groups of eight patients. Haemodynamic measurements were made before and after two or three and eight weeks of therapy. The dose of beta blockers was sufficient to reduce the exercise heart rate by more than 25%. Propranolol and prazosin produced a sustained reduction in the mean portohepatic venous pressure gradient of the order of 25% and 18% respectively. The cardiac index was significantly reduced by propranolol but not altered by prazosin. Atenolol produced an early reduction in portohepatic venous pressure which, although not sustained, showed a good correlation with reduction in cardiac index. No such relationship was found with propranolol. All three drugs were well tolerated by these patients with advanced cirrhosis. Therefore propranolol and prazosin have proved to be effective agents for the reduction of portal venous pressure.

Lebrec and colleagues have suggested that propranolol can be used in patients with cirrhosis to lower portal venous pressure and thereby reduce the incidence of further variceal haemorrhage.<sup>1,2</sup> Portal venous pressure is determined by the product of the outflow resistance and the portal venous blood flow. Outflow resistance is increased in cirrhosis because of the mechanical compression of portal venous radicles and thereafter somewhat reduced by the development of portal-systemic collateral venous flow. Animal studies have shown that the portal vein contains  $\alpha$  adrenoreceptors only and no  $\beta$  receptors and its tone is partly maintained by adrenoreceptor stimulation.<sup>3</sup> Normally the portal vein shows a linear pressure-blood flow relationship with no evidence of autoregulation, such as is seen in the heart or kidney, whereby blood flow is maintained over a range of pressure changes.<sup>3</sup> Propranolol is thought to act by a  $\beta_1$  blocking effect reducing cardiac output, hence reducing splanchnic blood

flow, leading in turn to a reduced portal venous flow and portal venous pressure.<sup>1</sup> Propranolol, however, is a non-selective  $\beta$  blocker which is metabolised by the liver and is highly protein bound in the circulation. Theoretically, therefore, it is not an ideal drug to use in patients with advanced cirrhosis in whom blood levels may be unpredictably high and clearance delayed.<sup>4</sup>

The present study had two aims. The first was to investigate the immediate and medium term effects of different adrenoreceptor blocking agents on portal venous pressure. Equivalent doses of propranolol, a non-selective  $\beta_1$  and  $\beta_2$  blocker, and atenolol, a selective  $\beta_1$  blocker were compared. Atenolol is ideal for use in patients with liver disease as it is excreted by the kidney and has only limited protein binding. Prazosin, an  $\alpha$  blocker, was studied because its systemic arterio- and venodilating effects might influence splanchnic blood flow and, in addition, it might have a direct action producing dilatation of the portal venous system perhaps opening up more portal systemic collateral veins. The second aim was to assess any complications of adrenoreceptor blockade in patients with advanced

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Received for publication 4 March 1983

cirrhosis. A marked reduction in cardiac output might lead to hepatic or renal failure in such patients.

## Methods

### PATIENTS

Twenty four patients with cirrhosis, portal hypertension, and oesophageal varices took part in the study. Cirrhosis was histologically proven in all cases; 21 had alcoholic cirrhosis and three cryptogenic cirrhosis. There were only two women. All were studied as outpatients and only one of the alcoholics was known to be drinking during the study period. Sixteen of the patients had previously bled from oesophageal varices, all at least three months before the study period, 17 were on treatment for ascites (usually spironolactone), and seven had been treated for hepatic encephalopathy. Consent to take part in the study was obtained from patients individually and the study was approved by the Eastern District Ethics Committee of the Greater Glasgow Health Board.

The study period lasted eight weeks and patients were randomly assigned to receive either propranolol, atenolol, or prazosin. Eight patients were given oral propranolol 20 mg stat followed by 40 mg twice daily for four days, thereafter changing to a once daily regime of 80 mg per day increasing by 40 mg every three days until adequate beta blockade was achieved as judged by a reduction in the exercise heart rate by >25%. Seven patients required 160 mg propranolol once daily and one 120 mg once daily. Eight patients were given oral atenolol 100 mg once daily which produced >25% reduction in the exercise heart rate in all cases. Eight patients were given gradually increasing doses of oral prazosin so that they were receiving 3 mg twice daily at three weeks and 5 mg twice daily at eight weeks. In one patient the prazosin dose was not increased above 3 mg twice daily after three weeks because of marked, but asymptomatic, postural hypertension. Patients were asked to take tablets at 08.00 hours and in addition at 20.00 hours in the case of prazosin.

Clinical and laboratory assessments were made every two weeks and haemodynamic measurements made before and after two and eight weeks of therapy. In those patients receiving prazosin the second measurements were delayed until three weeks to allow a gradual increase in the dose.

### CLINICAL ASSESSMENT

Resting pulse rate, lying and standing blood pressure, and body weight were measured. A clinical examination for ascites, encephalopathy,

and oedema was made. Any side effects of therapy were recorded.

### LABORATORY MEASUREMENTS

Haemoglobin, serum urea, creatinine, electrolytes, and liver function tests (albumin, bilirubin, alkaline phosphatase, and aspartate transaminase) were recorded every two weeks. Drug levels were monitored in whole blood from two weeks onwards at fortnightly intervals. Samples were taken at 14.00 hours in those receiving propranolol and atenolol and 11.00 hours in those receiving prazosin and stored at  $-20^{\circ}\text{C}$ . Whole blood propranolol was measured by gas liquid chromatography<sup>5</sup> and whole blood atenolol and prazosin by high performance liquid chromatography and fluorescence detection.<sup>6,7</sup>

### HAEMODYNAMIC MEASUREMENTS

The haemodynamic measurements including exercise heart rate, blood pressure, right atrial pressure, cardiac output, and an indirect measure of portal venous pressure was performed after an overnight fast.

Exercise testing was undertaken in those patients receiving propranolol and atenolol as an assessment of the adequacy of beta blockade. A symptom limited test was performed on an upright bicycle ergometer. An initial work load of 50 watts was increased by 50 watts at three minute intervals until leg fatigue occurred. The peak exercise heart rate was recorded by electrocardiograph monitor. All exercise tests were performed at 11.00 hours.

Blood pressure was measured by cuff sphygmomanometer and mean arterial pressure calculated from the diastolic pressure plus one third of the pulse pressure.

The portal venous pressure was determined by passing a Cournand catheter through the femoral vein into the hepatic vein for measurement of wedged and free hepatic venous pressures. The difference between these two pressure measurements is described as the portohepatic venous pressure gradient which is accepted as an excellent indirect measure of the true portal venous pressure, especially in patients with alcoholic liver disease.<sup>8</sup> Measurements were made at 14.00 hours in those receiving propranolol and atenolol, and 11.00 hours in those receiving prazosin.

Cardiac output was determined by the thermodilution method using a Swan-Ganz catheter inserted through the same femoral vein puncture site and passed into the main pulmonary artery.<sup>9</sup> A mean of three measurements was obtained on each occasion and the result expressed as the cardiac index in  $\text{l}/\text{min}/\text{m}^2$ . Right atrial pressure was

recorded in patients receiving prazosin and the systemic vascular resistance calculated as follows:

$$\text{Systemic vascular resistance (dynes.s.cm}^{-5}\text{)} = 80 \frac{(\text{mean arterial pressure} - \text{right atrial pressure})}{\text{cardiac output}}$$

**STATISTICAL ANALYSIS**

Results are expressed as a mean ± SD. In order to avoid making assumptions about the distribution of data, however, the significance of differences (two-tailed test) between paired results were analysed using the Wilcoxon's matched pairs signed rank test and unpaired results using the Mann-Whitney test. Associations were established by calculation of the correlation coefficient.

**Results**

The study randomisation produced three comparable groups of patients with no significant differences observed between mean ages (59, 53, and 55 years respectively) or the baseline haemodynamic measurements of portohepatic venous pressure and cardiac index (Table 1). All the patients had portal hypertension with a portohepatic venous pressure measurement equal to or greater than 10 mmHg (portohepatic venous pressure in eight cardiac patients without liver disease was 3.4±1 mmHg). The baseline cardiac index was raised above the normally accepted range in all three groups.

Exercise heart rates indicate that comparable and adequate beta blockade was achieved with both atenolol and propranolol at two and eight weeks with a reduction in mean exercise heart rates ranging from 29-36% (Table 1).

The haemodynamic responses to atenolol, propranolol, and prazosin are shown in Table 2. Atenolol and propranolol both produced a significant reduction in cardiac index and portohepatic venous pressure but this was better sustained and of a greater magnitude in those patients receiving propranolol. Prazosin produced a

significant reduction in portohepatic venous pressure at eight weeks without significant alteration in cardiac index. No significant change in resting pulse rate, mean arterial pressure, right atrial pressure or systemic vascular resistance was found in those patients receiving prazosin (Table 3).

In patients given atenolol, change in cardiac index correlated with change in portohepatic venous pressure (Fig. 1a; r=0.63, p<0.02). When the data are analysed in terms of percentage change the relationship between cardiac index and portohepatic venous pressure still holds (r=0.73). Change in cardiac index and portohepatic venous pressure, however, were not correlated (Fig. 1b) in patients treated with propranolol (r=0.3, NS), even when the data are analysed in terms of percentage change (r=0.23).

Monitoring of blood concentrations of the three drugs indicated that compliance was complete at the two weekly points of assessment. Blood levels achieved at the time of haemodynamic measurements at two to three weeks and eight weeks are recorded in Table 4.

No complications were observed with atenolol or propranolol during the eight week study period. Two patients felt tired while taking prazosin and six out of the eight had quite marked, but asymptomatic, postural hypotension with a mean 15 mmHg drop in diastolic blood pressure. None of the patients in any of the three groups, however, developed ascites, oedema, weight gain (Table 4), or clinical evidence of hepatic encephalopathy. No significant alteration in the laboratory blood

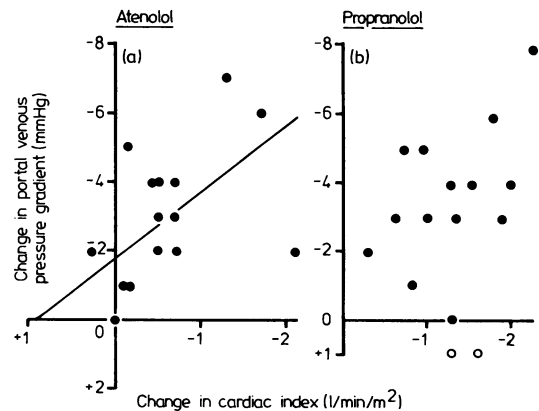


Figure Comparison between change in cardiac index (l/min/m²) and change in portohepatic venous pressure gradient (mmHg) in patients treated with atenolol (1a) and propranolol (1b). Regression line for atenolol: y=1.93x-1.75.

Table 1 Exercise heart rates (beats per minute) in patients treated with atenolol and propranolol

Weeks	Baseline	2	8
Atenolol (n=8)	129±30	84±13	91±10
(% reduction in mean)		(35)	(29)
Propranolol (n=8)	132±20	85±18	88±18
(% reduction in mean)		(36)	(33)

Results expressed as mean ± SD.

Table 2 *Portohepatic venous pressure gradient and cardiac index in patients with cirrhosis and portal hypertension treated with oral atenolol, propranolol, or prazosin*

Weeks	Portohepatic venous pressure gradient (mmHg)			Cardiac index (l/min/m <sup>2</sup> )		
	Baseline	2/3	8	Baseline	2/3	8
Atenolol (n=8) (% reduction in mean)	16.6±3.5	13.6‡±4.6 (18)	14.1±4.2 (15)	4.29±1.4	3.78±0.9 (12)	3.77±1.1 (12)
Propranolol (n=8) (% reduction in mean)	15.4±3.5	12.5*±2.7 (19)	11.6‡±2.1 (25)	4.53±0.9	3.34‡±0.6 (26)	3.14‡±0.5 (31)
Prazosin (n=8) (% reduction in mean)	16.4±5.3	13.6±2.8 (17)	13.5*±4.4 (18)	4.11±0.8	3.98±0.6 (3)	3.85±0.6 (6)

Results expressed as mean ± SD.

Statistical significance of difference from baseline: \*p<0.05; †p=0.02; ‡p=0.01.

measurements was noted during the eight weeks and in particular no rise in serum creatinine was found.

### Discussion

In this study both propranolol, a non-selective  $\beta_1$  and  $\beta_2$  blocker, and prazosin, an  $\alpha$  blocker, produced a sustained reduction in mean portohepatic venous pressure of the order of 25% and 18% respectively in patients with cirrhosis and portal hypertension after an eight week period of therapy. Atenolol, a selective  $\beta_1$  blocker, produced a significant reduction in portohepatic venous pressure at two weeks but this response was not sustained by eight weeks despite adequate beta blockade and full patient compliance with therapy.

Propranolol is thought to affect portohepatic venous pressure by a  $\beta_1$  blocking effect reducing cardiac output, hence reducing splanchnic blood flow, in turn reducing portal venous flow and portal venous pressure.<sup>1-10</sup> The baseline cardiac index was raised and systemic vascular resistance reduced in our patients, as has long been recognised,<sup>11</sup> perhaps making responses to adrenergic blocking drugs less predictable than in a normal population. Propranolol produced a greater reduction in both

cardiac index and portal venous pressure than atenolol in this study, despite equivalent  $\beta_1$  blockade as judged by exercise heart rate measurements. The high blood concentrations of propranolol may partially explain this difference. There was a good correlation between change in both cardiac index and portal venous pressure with atenolol, indicating that the above postulated mechanism of action probably holds true for a selective  $\beta_1$  blocker. No such relationship existed in patients treated with the  $\beta_1$  and  $\beta_2$  blocker propranolol, indicating that it may have a further mode of action in reducing portal venous pressure in addition to  $\beta_1$  blockade. These findings closely mirror similar results from a study of immediate portal venous pressure responses to oral atenolol and propranolol.<sup>12</sup> The  $\beta_2$  blocking effect of propranolol may increase vasomotor tone and therefore possibly lead to a further reduction in splanchnic blood flow and portal venous pressure.<sup>13</sup>

Prazosin produced a sustained reduction in portal venous pressure without alteration in cardiac index. While there was a tendency for a progressive reduction in systemic vascular resistance and mean supine arterial pressure, as might have been expected, the actual changes from baseline were not statistically significant. There was a considerable drop in the diastolic blood pressure on standing and haemodynamic measurements in this position would certainly be of interest in the future. The oral prazosin dose was increased slowly in this study as the drug has substantially first-pass hepatic metabolism and is subsequently also cleared by the liver.<sup>14-15</sup> The mechanism of action of prazosin in lowering portal venous pressure cannot be determined from this study.

The three adrenergic blocking drugs were well tolerated in these patients with advanced cirrhosis. No evidence of renal disturbance or sodium and water retention was noted and no patient developed

Table 3 *Haemodynamic responses to oral prazosin in eight patients with cirrhosis and portal hypertension*

Weeks	Baseline	3	8
Resting supine pulse (beats/min)	78±8	82±11	81±14
Mean arterial pressure (mmHg)	93±19	90±11	86±13
Right atrial pressure (mmHg)	2.4±2	4.6±2	4.6±3
Systemic vascular resistance (dynes/s/cm <sup>-5</sup> )	1016±308	959±115	955±239

Results expressed as mean ± SD.

No statistically significant changes from baseline.

Table 4 Body weight and whole blood drug levels in patients with cirrhosis given atenolol, propranolol, or prazosin

Weeks	Body weight (kg)			Whole blood drug level (ng/ml)	
	0	2/3	8	2/3	8
Atenolol (n=8)	70.2±9	69.5±10	69.4±10	129±48	97±33
Propranolol (n=8)	72.4±14	73.8±12	74.3±13	304±96	285±61
Prazosin (n=8)	69.6±10	69.4±10	69.6±10	12.2±4.8	16.4±3.0

Results expressed as mean ± SD.

clinical evidence of hepatic encephalopathy. Two patients initially felt tired while taking prazosin but this was short lived and improved with continued therapy. The theoretical complication of inducing hepatic encephalopathy because of a reduction in hepatic perfusion has not been reported in either of the longer term controlled studies using propranolol.<sup>2,10</sup> More detailed studies on the use of propranolol in patients with cirrhosis and known encephalopathy have shown no deterioration in trailmaking test times or rise in serum ammonia.<sup>16</sup> There is also a report of propranolol producing a reversible rise in arterial plasma ammonia in patients with compensated cirrhosis,<sup>17</sup> therefore further studies in this area are required.

In conclusion, both propranolol and prazosin would seem to be effective agents for the reduction of portal venous pressure in patients with cirrhosis and portal hypertension without causing significant adverse effects. Propranolol has been shown to reduce the incidence of further variceal haemorrhage in patients with compensated cirrhosis,<sup>2</sup> but whether this will hold true for the patient with decompensated cirrhosis remains to be proven.<sup>18</sup> There is still controversy over whether or not the degree of portal hypertension bears any relationship to the risk of variceal haemorrhage.<sup>19-21</sup> Surgical reduction of portal pressure by portocaval shunting does, however, undoubtedly reduce the incidence of further variceal haemorrhage.<sup>22</sup> It is not yet known whether the apparent success of propranolol in reducing the incidence of variceal haemorrhage is directly related to its pressure reducing properties or to some alternative mechanism such as prevention of stress or exercise related surges in portal venous pressure or a reduction in acid reflux into the oesophagus due to an increase in the lower oesophageal sphincter pressure.<sup>23</sup> Propranolol therapy leads to an increase in both plasma noradrenaline levels and  $\alpha$  adrenoreceptor stimulation.<sup>24</sup> Therefore there may be a reasonable case for studying the effects of a combination of propranolol and prazosin on portal

venous pressure and the incidence of variceal haemorrhage.

This study was generously supported by Stuart Pharmaceuticals. We are grateful to ICI Pharmaceuticals for propranolol assays and to Dr P Rubin of the Department of Materia Medica at Stobhill Hospital, Glasgow, for the atenolol and prazosin assays.

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