

Pharmacology of propranolol in patients with cirrhosis and portal hypertension

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SUMMARY Ten patients with cirrhosis and portal hypertension received an initial 20 mg oral test dose of propranolol and subsequently 160 mg of a slow release preparation, orally, each day for seven days. Protein binding, serial plasma propranolol concentrations and effects on heart rate were studied. Protein binding was slightly reduced (mean 85%, range 78.9–88.1%) compared with four normals (mean 87.9%). In patients with severe liver disease (serum albumin <30 g/l) propranolol remained detectable in plasma 24 hours after the single 20 mg dose and high steady state concentrations (mean 266.5 ng/ml, range 84–406) were observed during regular dosing. At steady state there was a significant correlation between log total plasma propranolol concentrations and the percentage fall in heart rate ($r=0.659$, $p<0.05$). We suggest that in patients with severe liver chronic disease (serum albumin <30 g/l), propranolol therapy should be initiated in hospital. The starting dose should be low (20 mg of the conventional formulation tds or 80 mg of the slow release preparation daily) and that regular monitoring of the heart rate should be carried out.

Propranolol has been shown to produce a sustained reduction in portal venous pressure in patients with cirrhosis and portal hypertension.¹ Furthermore, a controlled trial has shown that propranolol is an effective agent in the prevention of recurrent gastrointestinal haemorrhage in such patients.² Although a recent report has failed to confirm this finding,³ other studies of propranolol in the management of recurrent variceal haemorrhage are being undertaken. In addition, many patients with cirrhosis and portal hypertension are receiving propranolol without being included in a clinical trial and they may be started on treatment outside hospital. In patients with chronic liver disease, the bioavailability, half-life and clearance of a drug may be altered. In addition, the unbound fraction may be increased so that its effects may be greater.⁴ The pharmacological response to a drug such as propranolol may therefore be altered considerably in patients with cirrhosis and portal hypertension. The aim of this study was to investigate the

pharmacology of propranolol in a group of patients with cirrhosis and portal hypertension who were likely to be offered this treatment. A slow release preparation of propranolol was chosen because once-daily dosing may increase the chances of compliance during long term therapy. This has potential benefits for patients with alcoholic cirrhosis and portal hypertension, and in those who are taking other medications.

Methods

PATIENTS

Ten patients with cirrhosis and portal hypertension were studied. Patients gave informed consent to the study, which had been approved by the local ethical committee. All had histologically proven cirrhosis and oesophageal varices demonstrated at endoscopy. None of the patients had undergone previous gastrointestinal or portosystemic shunt surgery. Routine physical examination, liver function tests (Table 1) and trail-making test time⁵ were performed before entry into the study. Patients initially received a test dose of 20 mg propranolol orally on the first day of the study after an overnight

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Table 1 Clinical features

Patient no	Diagnosis	Age	Sex	Previous variceal haemorrhage	Ascites	Clinical encephalopathy	Trail making test grade	Liver function tests			Pugh/Childs grade	Other medication
								Albumin (32-50)	Bili (<17)	Ast (5-42)		
1	Chronic active hepatitis	46	F	No	No	No	0	41	18	83	A	Prednisolone azathioprine Cholestyramine
2	Primary biliary cirrhosis	57	F	No	No	No	1	40	33	42	A	
3	Alcohol	46	M	Yes	Yes	No	0	35	28	28	B	Chlormethiazole ranitidine
4	Alcohol	62	M	No	No	No	0	32	26	44	A	Nil
5	Alcohol	59	M	Yes	Yes	Yes	3	32	34	119	C	Spirolactone
6	Primary biliary cirrhosis	78	F	Yes	Yes	Yes	3	29	49	53	C	Spirolactone, lactulose, thyroxine, cimetidine,
7	Haemo- chromatosis	61	F	Yes	Yes	Yes	3	28	63	52	C	metoclopramide Spirolactone
8	Alcohol	61	F	No	Yes	Yes	3	26	160	118	C	Spirolactone frusemide
9	α_1 -antitrypsin deficiency	75	F	No	Yes	Yes	3	24	27	68	C	Aluminium hydroxide, Spirolactone
10	Alcohol	58	M	No	Yes	Yes	2	24	103	70	C	Spirolactone, frusemide

Trail making test grade 0=0-30 secs, 1=30-60 secs, 2=60-90 secs, 3=90-120 secs.

fast. The following day the patients received a dose of slow release propranolol (160 mg Inderal LA), which was then taken each day for seven days.

SAMPLING

Before the test dose, a 10 ml blood sample was taken and serum separated and stored at 4°C for protein binding estimation. Further 10 ml samples were taken into lithium-heparin tubes at 0, 2, and 6 hours on the day of the 20 mg test dose and 0, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 168 hours during the period when propranolol was administered in its sustained release form. Pulse rate and blood pressure were measured after the patient had remained supine for 10 minutes. These measurements were performed at each of the times listed above.

PROPRANOLOL CONCENTRATIONS

Plasma propranolol concentrations were measured by high performance liquid chromatography.⁶ Binding to serum proteins was determined by equilibrium dialysis using 3H-propranolol (Amersham International) at a concentration of 10 ng/ml using an MSE dianorm apparatus. The determinations were performed at a temperature of 25°C after an equilibration time of 16 hours. Propranolol concentrations were measured on both sides of the membrane so as to ensure that no loss of material had occurred due to non-specific binding.

STATISTICS

Regressions of heart rate and change in heart rate on log plasma propranolol concentration were calcu-

lated by the method of least squares. Comparisons between patients with a reduced serum albumin concentration (<30 g/l) and those with a normal serum albumin (>30 g/l) were made by means of a Student's *t* test.

Results

PROTEIN BINDING

Accurate determination of protein binding was possible in nine patients. Protein binding was slightly depressed, averaging 85.0% (range 78.9–88.1%) compared with 87.9% in four normals studied under similar conditions. The extent of binding, however, did not correlate with serum albumin concentrations.

TOTAL PLASMA PROPRANOLOL CONCENTRATIONS

Measurable amounts of propranolol were present in plasma after single oral doses of 20 mg conventional formulation. The concentration at two hours averaged 37±SD 21 ng/ml (range 9–81). In those with good liver function, the concentration had fallen markedly by the time 24 hours had elapsed. In those with severely impaired liver function (serum albumin <30 g/l), propranolol was still present in plasma 24 hours after dosing (Table 2; Fig. 1). During repetitive dosing with the slow release preparation, plasma concentrations rose to reach a 'steady state' by 72 hours. The value for the steady state concentration varied markedly among individuals from 27–406 ng/ml. The highest values were seen in those patients with severe liver disease and serum albumin concentrations below 30 g/l (Table 2;

Table 2 Propranolol pharmacology in 10 cirrhotic patients

Patient no	Serum albumin (g/l)	% bound	Total concentration in plasma (ng/ml) after 20 mg dose average 'steady state'				Heart rate	
			2 h	6 h	24 h	on 160 mg dose	Initial (beats/min)	Reduction after 72 h %
1	41	85.9	9	9	0	37.8	72	22.3
2	40	85.9	39	15	3	26.8	68	14.7
3	35	87.1	17	14	4	93.3	104	26.9
4	32	92.9	50	11	0	38.4	80	7.5
5	32	*	51	21	27	95.0	100	32.0
6	29	87.1	81	58	18	394.0	76	31.6
7	28	82.9	38	43	32	349.0	92	30.4
8	26	84.2	35	27	5	84.3†	100	30.0†
9	24	88.1	34	36	14	406.0	100	36.0
10	24	78.9	14	15	6	99.2	100	44.0
\bar{x} all±SD	31.1±6.1	85.9±3.8	37±21	25±16	11±11	162.4±155	89±14	27.5±10.5
\bar{x} 1–5±SD	36±4.3	87.9±3.4	33±19	15±5	7±11	58.3±33	85±16	20.7±9.7
\bar{x} 6–10±SD	26.2±2.3§	84.2±3.7	40±25	36±16‡	15±11	266.5±161‡	94±10	34.4±5.9‡

* Unsatisfactory due to haemolysis.

† 48 hour value only as patient was withdrawn due to rebleed.

‡ $p < 0.05$. § $p < 0.01$ Student's *t* test of patients 6–10 vs patients 1–5.

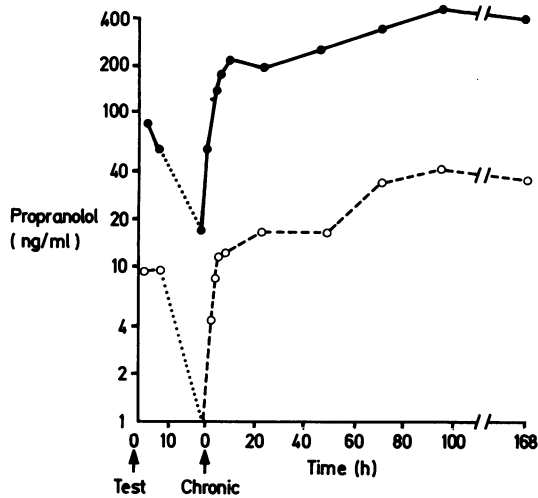


Fig. 1 Plasma propranolol concentrations achieved in two patients after a single 20 mg oral dose and during regular dosing with slow release propranolol 160 mg daily. First patient (no 6) (●—●) had very abnormal liver function and a serum albumin below 30 g/l. Second patient (no 1) (○- -○) had little biochemical evidence of liver dysfunction

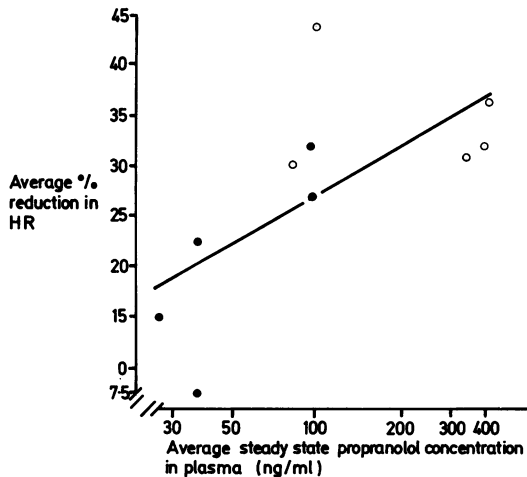


Fig. 2 Relationship between the average steady state propranolol concentration in plasma and the average % reduction in heart rate in 10 patients with hepatic cirrhosis. Five patients (○) had serum albumin concentrations below 30 g/l. The others (●) had serum albumin concentrations in excess of 30 g/l.

Fig. 2). Two of these patients were over 70 years of age. There was a significant correlation between the steady state concentration of propranolol during regular dosing and the 6-hour value after the 20 mg test dose ($r=0.903$, $p<0.01$).

EFFECTS ON HEART RATE

Before propranolol administration, heart rate averaged 89 beats per minute (Table 2). After the administration of propranolol there was a reduction in heart rate to a mean of 64 beats/min, but there was little relationship between the absolute value of heart rate and log total plasma propranolol concentrations. In contrast, there was a significant correlation between the log total plasma propranolol concentration at steady state (beyond 72 hours on slow release propranolol) and the percentage fall in heart rate for each patient ($r=0.659$, $p<0.05$, $n=10$; Fig. 2). Patient no 10 showed a much greater response than the others for a concentration of around 100 ng/ml. Some of this difference could be accounted for on the basis of diminished plasma binding – 21.1% free.

Discussion

Propranolol is a competitive antagonist at beta-adrenoceptors, and its pharmacologic effects are therefore dose-related. Its effects in angina pectoris and cardiac arrhythmias are also dose and concentration related.^{7,8} Being basic and lipid-soluble, however, it is heavily bound to plasma proteins, particularly acid alpha-1-glycoprotein⁹ and albumin.¹⁰ It is the fraction which is free in plasma water that is pharmacologically (and therapeutically) active.

The pharmacokinetics¹¹ of propranolol have been extensively studied in normal volunteers and in patients with a variety of disease states. In normal subjects, propranolol is almost completely absorbed after oral administration, but its bioavailability is low because of extensive presystemic metabolism by the liver.^{12,13} Thus, after 20 mg by mouth, little or none of the drug can be detected in plasma. After reaching the circulation, the drug is removed at a rate which depends upon hepatic blood flow¹⁴ and the half-life is normally three to five hours after a single dose and slightly longer with repeated administration.¹⁵ More recently, the pharmacokinetics of a slow release formulation of propranolol were studied in five normal volunteers.¹⁶ Peak concentrations after eight days therapy reached 50 ng/ml, but values before the next dose fell to a trough of 17.5 ng/ml.

In the present study, the pharmacokinetics of propranolol in patients with cirrhosis and portal

hypertension were grossly abnormal. After a test dose of 20 mg, much higher concentrations than normal were detectable, and in patients with severe liver damage propranolol could be detected 24 hours after the single dose. In addition, very high steady state concentrations were observed in this group after a regular once daily oral dose of 160 mg of the slow release preparation.

These values were associated with a considerable reduction (30% or greater) in heart rate at rest. The effects on heart rate were not only because of the higher total concentrations achieved but also because of an increased free fraction of the drug in plasma water. In a previous study of propranolol pharmacokinetics in patients with liver disease, after the intravenous administration of 40 mg (+)-propranolol, the most prominent abnormalities were found in patients in whom the serum albumin concentration was lower than 30 g/l. The half-life of propranolol was prolonged, distribution volume increased and clearance reduced in these patients. But clearance fell in proportion to that of indocyanine green, suggesting that hepatic blood flow was a limiting factor.¹⁷

In the present study we have confirmed previous observations that the greatest changes and highest total plasma propranolol concentrations occur in patients with serum albumin concentrations below 30 g/l, but our finding of high total plasma propranolol concentrations after oral dosing is new. Two explanations are theoretically possible; firstly, total concentrations may be raised by increased protein binding.¹⁸ This explanation can be discounted, as in the present study the binding of propranolol was slightly lower than normal. The alternative explanation is an increase in bioavailability because of diminished hepatic metabolism of the drug and/or shunting either within the liver or through porto-systemic anastomoses. It is not possible to state which of these latter possibilities is the more important.

Lebrec and colleagues² first reported propranolol to be effective in the prevention of further gastrointestinal bleeding in patients with portal hypertension and well compensated liver disease (approx 85% of patients classified as Pugh/Child's grade A). Subsequently, there has been widespread use of propranolol in patients with portal hypertension, many of whom have decompensated cirrhosis (Pugh/Child's grade B or C).

The present study indicates that patients with severe liver disease (serum albumin <30 g/l, Child's grade C) exhibit very abnormal propranolol pharmacokinetics and excessive effects. Because of this, we suggest that when propranolol therapy is being initiated in such patients it should be under

observation in hospital. In addition to cardiovascular effects, patients should be monitored clinically and by serial number connection test times for development of hepatic encephalopathy.²⁰ The starting dose should be low and can, if necessary, be increased. A dose of 20 mg conventional propranolol and measurement of its effects six hours after dosing gives a good idea of what may occur to heart rate during regular dosing. The results of the present study indicate that 160 mg sustained release propranolol daily may be suitable for patients with well preserved liver function. For the majority of patients with severe liver disease, however, a dose of 80 mg daily would be safer. Excessive beta-blockade and potential difficulties with resuscitation after blood loss may thus be avoided in a group of patients with the highest rate of rebleeding from oesophageal varices.

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