Effect of nadolol on liver haemodynamics and function in patients with cirrhosis

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β -adrenoceptor blockers used in the medical management of portal hypertension decrease liver blood flow. The sporadic onset of hepatic encephalopathy during propranolol treatment was ascribed to this decrease. The aim of the present study was to evaluate the effect of chronic treatment with nadolol on liver blood flow and liver function. Nadolol, a non-cardioselective β -adrenoceptor blocker, has been reported to be as powerful as propranolol in decreasing portal pressure. Before and after 1 month of treatment with nadolol at a dose reducing heart rate by 25%, in 15 cirrhotic patients with portal hypertension, the following parameters were determined: hepatic venous pressure gradient, hepatic blood flow, galactose eliminating capacity, aminopyrine metabolic activity, ICG clearance and intrinsic hepatic clearance. Hepatic venous pressure gradient and hepatic blood flow were decreased by nadolol. However liver function was not affected by the drug. We conclude that, despite a lowered hepatic blood flow, liver function is not affected by 1 month of nadolol treatment.

Keywords portal hypertension liver circulation liver cirrhosis liver function nadolol

Introduction

β -adrenoceptor blockers used in the treatment of portal hypertension in patients with cirrhosis decrease hepatic blood flow (Lebrech *et al.*, 1982; Westaby *et al.*, 1984), and the sporadic onset of hepatic encephalopathy (Tarver *et al.*, 1982) or hyperammoniaemia (van Buren *et al.*, 1982) during propranolol treatment was ascribed to this decrease. However the role of the decrease in liver blood flow in provoking unexpected hepatic encephalopathy was not demonstrated. In fact a decrease in liver blood flow did not occur in all patients treated with β -adrenoceptor blockers (Brailon *et al.*, 1985), and a correlation between the decrease in hepatic blood flow and the occurrence of hepatic encephalopathy has not yet been demonstrated. Therefore the relationship between the possible reduction in hepatic blood

flow and liver function, as evaluated by quantitative tests, in cirrhotic patients treated with β -adrenoceptor blockers needs further investigation. Nadolol, a non-cardioselective β -adrenoceptor blocker, has been shown to decrease portal pressure and hepatic blood flow to a similar degree to propranolol (Gatta *et al.*, 1984). In the present study we aimed to evaluate the effect on liver function of a chronic treatment with nadolol.

Methods

Fifteen patients with liver cirrhosis and portal hypertension, aged 31–55 years, were investigated. Diagnosis was based on history, physical examination and common biochemical tests and

was confirmed by liver biopsy. Eight patients had at least one gastro-intestinal bleeding from ruptured oesophageal varices, the other seven patients had large size oesophageal varices (3'–4' degree according to Dagradi's classification (1973)). Two patients had mild degree ascites. Contraindications to β -adrenoceptor-blocking treatment were absent in all patients. Of the fifteen patients, eight were on concomitant treatment with other drugs at least from 1 month before entering the study. Individual pharmacological treatment is reported in Table 1. Of the eleven patients with alcoholic cirrhosis, five were abstinent for at least 3 months before entering the study, while the others continued their alcohol abuse. Main clinical and biochemical data are also given in Table 1. Informed consent after full explanation of the procedure was obtained from all patients. Part of the present research has been previously reported (Gatta *et al.*, 1984).

Hepatic venous pressure gradient, hepatic blood flow and pharmacokinetic parameters of liver function were measured before and 1 month after starting treatment with nadolol at a dose reducing heart rate by approximately 25% (40–160 mg day⁻¹). After an overnight fast, hepatic veins were catheterized from an arm vein using a balloon catheter. Hepatic pressure was first measured in the wedged position, with the balloon inflated with 0.7 ml of diluted Conray, then in the free position, with the balloon deflated. Correct wedging was checked by the absence of reflux after an injection of 2 ml of Conray 60%. Hepatic venous pressure gradient was computed as wedged hepatic venous pressure minus free hepatic venous pressure. Hepatic blood flow was measured using the indocyanine green (ICG) constant infusion technique (Caesar *et al.*, 1961). Briefly, following a bolus of 3.5 mg m⁻² body surface, an ICG solution was infused at a constant rate of 0.25 mg min⁻¹ m⁻² body surface. After a wait of 60 min to obtain a steady state in the dye blood concentration, blood samples were simultaneously drawn from an artery and a hepatic vein. The same procedure was performed 5 and 10 min later to verify maintenance of the steady state. Steady state was considered to have been achieved when the difference between ICG arterial concentrations was less than 5%. The procedure has been extensively described elsewhere (Gatta *et al.*, 1984; Merkel *et al.*, 1985b).

To evaluate liver function quantitatively, galactose eliminating capacity after intravenous load, aminopyrine metabolic activity by the breath test, ICG clearance and ICG intrinsic hepatic clearance were measured.

Galactose eliminating capacity was measured according to Tygstrup's method (1963). Briefly,

0.5 g kg⁻¹ body weight of galactose as a 40% w/v solution (Galatest, Boehringer Biochemia Robin, Milan, Italy) was injected intravenously over 6 min. Blood was sampled from an arm vein every 5 min between 20 and 70 min after the end of infusion. Urine was collected after 3 h. Plasma and urine galactose concentration were determined by an enzymatic assay (Galactose-UV Test, Boehringer Mannheim, Mannheim, West Germany). Plasma concentrations higher than 500 mg l⁻¹ were plotted against time, and regression analysis was performed by the least-squares method. Intercept on the x-axis was extrapolated and provided the time corresponding to zero concentration (T_c = 0). Galactose eliminating capacity was computed as follows:

Galactose eliminating capacity R (A-U)/T_c = 0)

where A = amount injected and U = amount excreted in urine.

Aminopyrine breath test was performed according to Hepner & Vesell (1975). An oral dose of 2 μ Ci of ¹⁴C-dimethyl-aminopyrine (New England Nuclear, Boston, Mass., USA) in aqueous solution (specific activity 110 mCi mmol⁻¹) was given to every patient, and after 2 h breath samples were collected in duplicate asking the patient to blow gently through a glass tube into a liquid scintillation vial containing hyamine hydroxide 1 M in methanol 2 ml, ethanol 2 ml and thymolphthalein 4 drops as pH indicator, until the solution appeared to discolour. This indicated that 2 mmol of CO₂ was trapped. CO₂ specific activity in the expired air was measured in a β -counter (Packard Tri-Carb 460-CD) after addition of 10 ml of scintillation cocktail (Insta-gel, Packard Instrument Company, Warrenton, Ill., USA). Measured counts min⁻¹ were converted to disintegrations min⁻¹ by external standardization. Counting efficiency was between 0.75 and 0.85. Disintegration min⁻¹ measured were between 220 and 850, counting error ranging between 2.94 and 4.72%. As an index of liver metabolic activity for aminopyrine, the amount of radioactive CO₂ expired at 2 h expressed as percentage of the administered amount was computed according to the formula:

Aminopyrine metabolic capacity = disintegrations min⁻¹ – breath $\times 100 \times 9 \times$ b.w./disintegrations min⁻¹ administered

9 mmol kg⁻¹ h⁻¹ being the endogenous CO₂ production of resting man (Winkell *et al.*, 1970) and assuming that CO₂ specific activity does not vary between 90 and 150 min.

ICG clearance was calculated at steady state during ICG infusion as

Table 1 Main clinical and biochemical data in the 15 patients with cirrhosis before and after 1 month of nadolol

Case	Diagnosis	Nadolol dosage (mg day ⁻¹)	Previous G-I bleeding	Concomitant treatment	S-bilirubin (mg dl ⁻¹) before nadolol	S-albumin (g dl ⁻¹) before nadolol	Prothrombin time (%) before nadolol	AST (u l ⁻¹) before nadolol	Ascites before nadolol
1	CC	80	-	Antacids	1.5	3.1	47	148	-
2	AC	80	+	—	0.6	3.9	65	39	-
3	PC	40	-	Frusemide 20 mg	1.5	2.8	47	97	+
4	PC	40	-	—	1.9	3.6	57	27	-
5	AC	80	+	Antacids Spironolactone 100 mg	3.2	3.1	42	53	+
6	AC	80	-	—	3.0	4.5	76	18	-
7	CC	80	-	—	1.8	4.0	62	42	-
8	AC	160	+	Antacids	0.6	3.2	61	34	-
9	AC	80	+	Ranitidine 150 mg	1.2	3.7	39	32	-
10	AC	80	+	—	0.8	3.0	67	72	-
11	AC	80	+	Antacids	0.9	3.8	72	57	-
12	AC	160	+	—	2.3	3.3	39	129	-
13	AC	80	+	Vitamin K ₁ 40 mg	1.5	2.7	31	63	-
14	AC	80	-	—	0.8	4.0	52	31	-
15	AC	40	+	Spironolactone 100 mg	1.8	3.4	61	23	-

CC = Cryptogenic cirrhosis; AC = Alcoholic cirrhosis; PC = Posthepatic cirrhosis

$$\text{ICG clearance} = R/A$$

where R = rate of infusion and A = ICG arterial concentration. ICG intrinsic hepatic clearance was calculated according to the 'parallel tube' model (Winkler *et al.*, 1973) by the formula:

$$\text{ICG intrinsic hepatic clearance} = \text{HPF} \times \ln(1-E)$$

where HPF = hepatic plasma flow measured by ICG constant infusion; E = ICG hepatic extraction rate ((Arterial ICG-Hepatic vein ICG)/Arterial ICG). This model assumed that drug concentration in blood perfusing the liver decreases exponentially passing through liver sinusoids. The model has been validated in experimental conditions (Keiding & Chiarantini, 1978).

Results

In the fifteen patients with liver cirrhosis wedged hepatic venous pressure decreased after 1 month of nadolol treatment (from 3.2 ± 0.2 kPa to 2.7 ± 0.1 kPa; $P < 0.01$); free hepatic venous pressure did not change significantly (baseline 0.8 ± 0.1 kPa; after nadolol 0.8 ± 0.1 kPa). Therefore computed hepatic venous pressure gradient decreased from 2.4 ± 0.1 kPa to 1.9 ± 0.2 kPa ($P < 0.01$). Hepatic blood flow also exhibited a significant decrease (from 1127 ± 111 ml min⁻¹ to 956 ± 119 ml min⁻¹; $P < 0.02$), averaging 12%. ICG hepatic extraction rate exhibited a slight and not significant increase (from 0.50 ± 0.05 to 0.54 ± 0.06). Individual

data are given in Table 2. Table 3 shows that the four liver function parameters determined in this study were not affected by the treatment; galactose eliminating capacity went from 269 ± 19 mg min⁻¹ to 275 ± 16 mg min⁻¹; aminopyrine metabolic activity from $5.19 \pm 0.69\%$ to $4.53 \pm 0.47\%$; ICG clearance from 326 ± 52 ml min⁻¹ to 325 ± 53 ml min⁻¹; ICG intrinsic hepatic clearance from 546 ± 134 ml min⁻¹ to 537 ± 123 ml min⁻¹.

Discussion

We previously reported (Gatta *et al.*, 1984), that nadolol decreased hepatic venous pressure gradient and hepatic blood flow, the percent drop averaging 23% and 12%, respectively. Similar results were obtained with propranolol treatment (Lebrec *et al.*, 1982; Westaby *et al.*, 1984), not surprisingly, since both drugs share the same pharmacological activity and site of action. In the present and in the previous studies we used a dose of nadolol ranging from 40 to 160 mg day⁻¹, as it is commonly administered to patients with arterial hypertension (O'Connor *et al.*, 1982). The between patients differences are likely to depend on baseline adrenergic tone of the patients, and not on liver function, since the drug does not undergo a significant hepatic metabolism. This interpretation is supported by the lack of correlation between dose administered and liver function.

Table 2 Hepatic haemodynamic effects of nadolol in the 15 patients with cirrhosis

Case	HBF (ml min ⁻¹)		E		WHVP (kPa)		FHVP (kPa)		HVPG (kPa)	
	B	N	B	N	B	N	B	N	B	N
1	576	548	0.43	0.42	3.9	2.4	0.9	0.6	3.0	1.8
2	1,069	742	0.43	0.77	3.9	3.3	1.2	1.2	2.7	2.7
3	629	516	0.59	0.58	3.9	3.4	0.8	1.4	3.1	2.0
4	761	380	0.75	0.80	3.9	2.8	0.9	1.6	3.0	1.2
5	1,612	1,034	0.20	0.22	3.6	3.4	1.6	1.6	2.0	1.8
6	532	617	0.67	0.61	3.3	2.5	1.1	0.7	2.2	1.8
7	1,066	679	0.61	0.59	2.0	2.0	0.4	0.6	1.6	1.4
8	1,614	1,418	0.39	0.39	2.8	2.6	1.1	1.1	1.7	1.5
9	1,261	792	0.14	0.27	3.5	2.2	1.2	0.4	2.3	1.8
10	1,050	1,645	0.47	0.16	3.8	2.5	0.8	0.5	3.0	2.0
11	1,825	1,921	0.56	0.80	2.4	2.2	0.4	0.4	2.0	1.8
12	1,736	1,525	0.25	0.46	3.1	2.8	0.4	0.3	2.7	2.5
13	*	735	*	0.55	3.1	3.1	0.3	0.3	2.8	2.8
14	1,374	929	0.91	0.86	2.5	2.0	0.5	0.5	2.0	1.5
15	673	864	0.53	0.64	2.6	2.1	0.5	0.2	2.1	1.9

* = Steady state condition not achieved

HBF = Hepatic blood flow; E = ICG extraction rate; WHVP = Wedged hepatic venous pressure; FHVP = Free hepatic venous pressure; HVPG = Hepatic venous pressure gradient
B, before; N, nadolol.

Table 3 Quantitative liver function parameters in the 15 patients with cirrhosis before (B) and after 1 month of nadolol (N) treatment

Case	GEC (mg min ⁻¹)		ABT (%)		ICG-CL (ml min ⁻¹)		ICG-IHC (ml min ⁻¹)	
	B	N	B	N	B	N	B	N
1	312	367	3.33	4.16	164	161	214	209
2	312	367	6.50	5.38	291	320	381	609
3	199	196	3.90	2.29	202	249	305	373
4	314	318	5.53	5.69	197	179	636	361
5	201	245	2.86	3.32	195	133	218	151
6	217	264	6.90	5.68	231	228	382	352
7	250	268	6.89	8.64	435	271	672	409
8	264	181	1.94	2.45	444	390	563	494
9	323	337			120	139	129	162
10	222	298	4.25	4.24	327	237	427	258
11	382	370	7.92	5.69	649	900	953	1,997
12	215	277	5.11	3.58	251	526	288	584
13	225	210	1.64	3.54	*	286	*	410
14	420	435	10.64	10.75	800	442	2,114	1,011
15	225	213	4.05	3.92	251	418	358	668

* = Steady state condition not achieved

GEC = galactose eliminating capacity; ABT = Aminopyrine breath test

ICG-CL = Indocyanine green plasma clearance; ICG-IHC = Indocyanine green intrinsic hepatic clearance.

Despite the lowered hepatic blood flow, liver function evaluated using quantitative methods was not affected by 1 month of nadolol treatment. One might have expected that the drug would have impaired liver function, as it was demonstrated that drugs decreasing liver blood flow, such as vasopressin and somatostatin (Barbare *et al.*, 1984; Merkel *et al.*, 1985a) also affect liver metabolic activity. Furthermore the occurrence of hyperammoniaemia (van Buren *et al.*, 1982) and hepatic encephalopathy (Tarver *et al.*, 1983) was reported in patients receiving propranolol.

Liver function can be quantitatively estimated by measuring galactose eliminating capacity, which represents liver functional reserve in phosphorylating galactose, or aminopyrine metabolic activity, which evaluates liver microsomal functional reserve, or ICG intrinsic hepatic clearance, which is the maximal ability of the liver to remove ICG in the absence of any blood flow limitation. To estimate this latter parameter two models, namely the 'parallel tube' (Winkler *et al.*, 1973) and the 'well stirred' (Wilkinson & Shand, 1975) were developed. In this study the former was employed; however qualitatively similar results were obtained using the latter model. Both galactose eliminating capacity and aminopyrine metabolic activity and ICG intrinsic hepatic clearance estimate liver function independently of liver perfusion. Nadolol did not affect any of these parameters after 1 month of treatment.

At variance, ICG clearance is a parameter of liver metabolic activity which is dependent both on liver blood flow and on liver function in patients with cirrhosis, because dye extraction in this condition is severely affected (Wilkinson & Shand, 1975; Pessayre *et al.*, 1978a). However nadolol treatment did not decrease ICG clearance. Because liver blood flow and liver metabolic activity are the two physiological determinants of ICG clearance in cirrhosis, it is difficult to explain how ICG clearance can be maintained despite a decrease in liver blood flow. A possible explanation may be provided by the fact that the real determinant of ICG clearance is sinusoidal effective blood flow (Pessayre *et al.*, 1978b), and that ICG constant infusion allows measurement of total liver blood flow, which is comprehensive of functional intrahepatic shunt blood flow. Therefore our results could suggest that the drug reduced total liver blood flow without affecting sinusoidal blood flow, i.e., decreased functional intrahepatic shunt fraction (Pessayre *et al.*, 1978b). Further support for this interpretation is given by the observation that in portal hypertensive rats propranolol did not decrease sinusoidal blood flow, as estimated by the hepatic removal of low-dose radio-gold (Hillon *et al.*, 1982). Besides that a different effect of a drug on effective sinusoidal blood flow and on functionally shunted blood flow has been recently claimed to account for the effect of posterior pituitary extract (Barbare *et al.*, 1984).

Patients with hyperammoniaemia after propranolol were reported by van Buren *et al.* (1982) and patients with hepatic encephalopathy by Tarver *et al.* (1983). These authors suggested that the possible mechanisms leading to these alterations were the decrease of liver blood flow and consequent decrease in liver function. We cannot identify from our data the mechanisms which led to hyperammoniaemia (van Buren *et al.*, 1982) or hepatic encephalopathy (Tarver *et al.*, 1983) in other series of patients receiving propranolol. However it is unlikely that these adverse effects may be due to a decrease in liver function following a decrease in hepatic blood flow, since nadolol, which provoked the same haemodynamic effects, did not cause any decrease in liver metabolic activity. We suggest

that hyperammoniaemia may be the consequence of increased renal generation of ammonia (Doffoel *et al.*, 1984), and hepatic encephalopathy may be due to an effect of the drug on central nervous system, as it was demonstrated that propranolol interferes with brain metabolism of serotonin (Jepsson *et al.*, 1984).

In conclusion, after 1 month of treatment, despite a decrease in liver blood flow induced by the drug, nadolol did not further impair liver metabolic activity in patients with cirrhosis.

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