Br. J. clin. Pharmac. (1985), **19**, 393–397

The influence of captopril, the nitrates and propranolol on apparent liver blood flow

A. N. SHEPHERD, P. C. HAYES, MERON JACYNA, LINDSAY MORRISON & I. A. D. BOUCHIER
University Department of Medicine Ninewells Hospital and Medical School Dundee, UK

Indocyanine green estimated apparent liver blood flow was measured in normal volunteers following glyceryl trinitrate, propranolol, isosorbide mononitrate and captopril. Glyceryl trinitrate and propranolol significantly reduced apparent liver blood flow. Isosorbide mononitrate did not alter apparent liver blood flow or produce an additional reduction in apparent liver blood flow when combined with propranolol. Captopril did not alter apparent liver blood flow despite a significant fall in mean arterial pressure and rise in plasma renin activity. Captopril and isosorbide mononitrate if shown to reduce portal pressure, do so without a fall in apparent liver blood flow.

Keywords isosorbide mononitrate indocyanine green captopril liver blood flow

Introduction

Recently there has been increasing interest in the use of pharmacological agents to manipulate liver blood flow (LBF) and to manage portal hypertension (Hayes *et al.*, 1983; Lebrec *et al.*, 1980). Propranolol (Feely *et al.*, 1981), prazosin and hydralazine (Magorien *et al.*, 1981), glyceryl trinitrate and nifedipine (Feely, 1984), have all been evaluated recently for their ability to influence liver blood flow and, in the case of propranolol, portal hypertension.

Propranolol effectively lowers portal pressure but unfortunately has numerous side effects and may complicate resuscitation in patients who bleed from the gastrointestinal tract (Prosner *et al.*, 1982). Glyceryl trinitrate has been used successfully to reduce portal pressure in association with vasopressin (Groszmann *et al.*, 1982) but its use is limited by its short duration of action. Isosorbide dinitrate reduces portal pressure in patients with cirrhosis by 21% (Hallemans *et al.*, 1983) but isosorbide mononitrate which, unlike the dinitrate, does not rely on first pass hepatic biotransformation (Chasseaud, 1983) would seem a more suitable agent particularly in patients with liver disease.

Portal pressure is a function both of liver blood flow and portal vascular resistance. Drugs so far shown to produce a reduction in portal venous pressure also reduce liver blood flow. This reduction in liver blood flow could be deleterious to the diseased liver.

Saralasin, the angiotensin II blocker, produces a significant reduction in wedged hepatic pressure without an apparent reduction in liver blood flow (Arroya *et al.*, 1981). Captopril causes a reduction in angiotensin II by inhibition of the conversion of angiotensin I to angiotensin II (Shepherd *et al.*, 1982). Therefore, like saralasin, captopril may alter portal pressure without the deleterious effect of a reduction in liver blood flow. The effect of captopril and isosorbide mononitrate on liver blood flow was therefore studied and compared with glyceryl trinitrate, propranolol and propranolol with isosorbide mononitrate.

Correspondence: Dr A. N. Shepherd, University Department of Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK

Methods

Captopril group

Eight healthy male volunteers (aged 21–28 years) participated in this study. None of the subjects was on regular medication and had not received any drug therapy for the period up to a week prior to the study period. After an overnight fast and 30 min rest in the supine posture, blood pressure, heart rate, resting plasma renin and aldosterone levels were obtained.

Plasma renin activity and aldosterone were measured using commercially available radioimmunoassay kits (Serono Diagnostic Ltd, London). Following a rapid injection of indocyanine green (ICG 0.5 mg/kg) into the contralateral antecubital vein, blood samples were obtained from the antecubital vein at 2 min intervals for the first 12 min and thereafter at 15 min. Studies in our laboratories have shown ICG clearance can be satisfactorily estimated over a shorter time period than that usually used to estimate clearance. Plasma ICG concentration was measured using a spectroscopic method (Caesar *et al.*, 1961). Apparent liver blood flow was calculated from the plasma clearance of ICG. ICG clearance as a measure of LBF is an indirect method based on the assumption that the drug being investigated does not alter the hepatic extraction ratio of ICG.

Thirty minutes after receiving their injection of ICG all subjects received 25 mg of captopril orally with 20 ml water. One hundred minutes after dosing the resting supine blood pressure, heart rate, plasma renin and aldosterone levels were estimated. Captopril has previously been shown to exhibit its maximal effect at between 90 and 120 min in normal subjects from the first dose (Shepherd *et al.*, 1982). Blood samples were taken as before over 15 min following a rapid injection of ICG (0.5 mg/kg).

Propranolol and nitrate group

Six healthy male volunteers (aged 21–26 years) participated in this study. None of the subjects was on regular medication and none had taken drugs of any kind up to the time of the study period. After an overnight fast blood samples were taken from the antecubital vein at 2 min intervals for 10–12 min following a rapid injection of indocyanine green (ICG 0.5 mg/kg) into the contralateral antecubital vein. Three hours later, 500 μg sublingual glyceryl trinitrate was administered and 5 min later the ICG clearance was remeasured.

Changes in ICG clearance kinetics were measured 2 h following the last dose of administration of propranolol 40 mg three times daily, isosorbide mononitrate 20 mg three times daily alone and propranolol 40 mg three times daily and isosorbide mononitrate 20 mg three times daily combined. Each treatment period was for 24 h. The isosorbide mononitrate alone treatment period was separated by at least 5 days from that of propranolol. Propranolol and isosorbide mononitrate combined treatment followed propranolol alone on consecutive days. Baseline ICG clearance was remeasured the day before the final treatment period as a measure of reproducibility.

Five normal volunteers underwent further study to measure the effects of change in posture on ICG kinetics. The changes were measured in the supine and sitting postures.

Analysis

Half-life ($t_{½}$) was calculated using the formula $0.693/k$ where k equals the slope of the line determined by least square regression analysis of the log concentration time profile; volume of distribution (V) equals the dose/CPO where CPO equals plasma concentration extrapolated to the time of ICG administration; clearance equals $0.693 \times V/t_{½}$. Mean arterial pressure was taken as equivalent to the diastolic pressure plus one-third the difference between systolic and diastolic pressure. Statistical analysis was by two way analysis of variance and the Student's t-test for paired data.

All subjects gave informed witnessed consent to take part and the study received the approval of the Local Research and Ethical Committee.

Results

Captopril group

As predicted the mean arterial pressure fell following oral captopril from 97.6 ± 7.5 to 83.8 ± 49 mm Hg ($P < 0.05$) (mean ± s.d.). No significant changes were seen in heart rate, in particular there was no tachycardia in response to the hypotension produced by captopril.

No significant changes were seen in any of the parameters measured in terms of indocyanine green clearance and liver blood flow. Elimination half-lives, volumes of distribution and clearance did not change despite the fall in mean arterial pressure (Table 1).

Plasma renin activity rose significantly at 100 min following captopril 2.85 ± 1.7 ng ml^{-1} h^{-1} (mean ± s.d.) to 7.78 ± 4.0 ng ml^{-1} h^{-1} ($P <$

Table 1 ICG, blood pressure, heart rate, renin and aldosterone changes prior and following captopril 25 mg (mean ± s.d.).

	Indocyanine green kinetics						
	$t_{1/2}$ *(min)*	V *(l)*	*Clearance (l/min)*	*Mean arterial pressure (mm Hg)*	*Heart rate (beats/min)*	*Renin (ng ml^{-1} h^{-1})*	*Aldosterone (pg/ml)*
Control	3.37 ± 0.51	3.28 ± 1.14	675 ± 215	97.6 ± 7.5	72 ± 5.09	2.85 ±1.7	32.6 ± 3.5
Captopril	3.89 ± 0.94	3.42 ± 0.19	634 ± 257	83.8 ± 4.9*	72.8 ± 5.36	7.78 ± 4.0*	26.87 ± 6.59

*$P < 0.05$

0.05). Plasma aldosterone fell in all subjects from 32.6 ± 3.5 pg/ml to 26.87 ± 6.59 pg/ml, but failed to reach statistical significance.

Nitrate and propranolol group

Significant changes in the clearance of ICG occurred following the administration of glyceryl trinitrate, propranolol and propranolol plus isosorbide mononitrate ($P < 0.01$) but not following isosorbide mononitrate alone. Isosorbide mononitrate when added to propranolol did not produce any additional effect (Table 2) to that of propranolol alone.

Significant prolongation in half-lives was seen following glyceryl trinitrate and propranolol plus isosorbide mononitrate ($P < 0.01$). An increase in V was seen following isosorbide mononitrate and a decrease following propranolol ($P < 0.05$).

Two subjects in the propranolol treated group had to be withdrawn due to side effects of propranolol, one in the isosorbide mononitrate group and one in the propranolol plus isosorbide mononitrate group.

Postural change

No significant changes were seen in the parameters assessed between the sitting and the supine postures (Table 2).

Discussion

This study demonstrates that neither captopril despite effective inhibition of the renin angiotensin system nor isosorbide mononitrate alters the apparent liver blood flow in normal subjects. Both propranolol and glyceryl trinitrate produced a marked reduction in apparent liver blood flow consistent with the findings from other studies in normal subjects (Feely, 1984; Feely *et al.*, 1981).

Maintenance of portal pressure is dependent upon both liver blood flow and portal vascular resistance. Those drugs so far shown to produce a reduction in portal venous pressure have done so by reducing liver blood flow.

Studies into the effects of oral isosorbide dinitrate in patients with portal hypertension

Table 2 Changes (mean ± s.d.), in ICG kinetics following (a) glyceryl trinitrate, propranolol, isosorbide mononitrate, propranolol plus isosorbide mononitrate ($n = 6$) and (b) in the sitting and supine postures ($n = 5$)

(a)	*Control*	*Glyceryl trinitrate*	*Propranolol*	*Isosorbide mononitrate*	*Propranolol and isosorbide mononitrate*
$t_{1/2}$ (min)	3.45 ± 0.34	4.21 ± 0.55*	4.07 ± 0.31	3.69 ± 0.27	4.58 ± 0.01*†
V (l)	4.37 ± 0.61	4.11 ± 0.49	3.72 ± 0.47**	4.50 ± 0.54**	4.10 ± 0.6
Clearance (l/min)	866 ± 97	680 ± 43*	634 ± 69*	45 ± 103	636 ± 114*‡

*$P < 0.01$ compared with control, **P 0.05 compared with control.
†$P < 0.01$ propranolol plus isosorbide mononitrate compared with isosorbide mononitrate alone.
‡$P < 0.05$ propranolol plus isosorbide mononitrate compared with isosorbide mononitrate alone.
Statistical analysis by two way analysis of variance

(b)	*Sitting*	*Supine*
$t_{1/2}$ (min)	3.77 ± 0.71	3.66 ± 0.85
V (l)	3.85 ± 0.50	3.63 ± 0.42
Clearance (l/min)	737 ± 200	711 ± 140

have demonstrated conflicting results with reductions in portal pressure being observed in two studies (Freeman *et al.*, 1983; Hallemans *et al.*, 1983) with no reduction in portal pressure being observed in another (Dawson *et al.*, 1983). Our findings that isosorbide mononitrate does not reduce liver blood flow could be explained by the effect of reciprocity. Reciprocity results from the simultaneous dilatation of both the hepatic artery and portal vein. This produces a reduction in flow through the portal vein and a reciprocal increase in hepatic artery flow. Portal pressure could therefore be reduced without reduction of the liver blood flow (Richardson & Witherington, 1981). The small but significant changes in the *V* following propranolol and isosorbide mononitrate in our study is unexplained but could be due to alterations in the volume of the intravascular compartment.

Captopril has been shown previously to have an effect both on the arterial and venous system (Atkinson & Robertson, 1979; Shepherd *et al.*, 1982) and could reduce portal pressure without a reduction in apparent liver blood flow similar to that seen with the angiotensin II blocker saralasin in cirrhotic patients (Arroyo *et al.*, 1981). A reduction in liver blood flow has been observed in hypertensive subjects (Crossley *et al.*, 1984) and an unaltered liver blood flow in cirrhotic patients (Eriksson *et al.*, 1984) following captopril similar to our observations in normal subjects.

Investigations into the pharmacological effects of drugs and apparent liver blood flow in cirrhotic patients with ascites are often limited by the ability of patients to maintain the supine posture. We observed no changes in any of the parameters of ICG clearance measured in normal subjects when in the supine or sitting posture. It is possible therefore that in patients who are unable to maintain a supine posture for any reason such as ascites or cardiac failure, apparent liver blood flow may be estimated satisfactorily and reproducibly in the sitting position.

In conclusion we have demonstrated a reduction in apparent liver blood flow by both glyceryl trinitrate and propranolol but not isosorbide mononitrate or captopril. If isosorbide mononitrate and captopril are shown to have similar effects to that of saralasin in terms of reducing hepatic wedge pressure without a resultant decrease in liver blood flow in cirrhotic patients they could be potentially useful agents in the management of portal hypertension. The effect of captopril and isorbide mononitrate therapy on portal pressure warrants further investigation.

References

Arroyo, V., Bosch, H., Mauri, M., Ribera, F., Navorro-Lopez, F. & Rodes, J. (1981). Effect of angiotensin II blockade in systemic and hepatic haemodynamics and on the renin—angiotensin—aldosterone system in cirrhosis with ascites. *Eur. J. clin. Invest.*, **11**, 221–229.

Atkinson, A. B. & Robertson, J. I. S. (1979). Captopril in the treatment of clinical hypertension and cardiac failure. *Lancet*, **ii**, 836–839.

Caesar, J., Shaldon, S., Chiandussi, L., Guevara, L. & Sherlock, S. (1961). The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. *Clin. Sci.*, **21**, 43–47.

Chasseaud, L. F. (1983). Pharmacokinetics and bioavailability of different nitrate preparations. *Br. J. clin. Pract.* (Symposium Supplement) **26**, 7–14.

Crossley, I. R., Bihari, D., Gimson, A. E. S., Westaby, D., Richardson, P. J. & Williams, R. (1984). Effects of converting enzyme inhibitor on hepatic blood flow in man. *Am. J. Med.*, **76** (5B), 62–65.

Dawson, J., West, R., Gertsch, P., Mosimann, F. & Elias, E. (1983). Endoscopic variceal pressure measurements: response to isosorbide dinitrate. *Gut*, **24**, A971.

Eriksson, L. S., Kagedal, B. & Wahren, J. (1984). Effects of captopril on hepatic venous pressure and blood flow in patients with liver cirrhosis. *Am. J. Med.*, **76** (5B), 66–70.

Feely, J. (1984). Nifedipine increases and glyceryl trinitrate decreases apparent liver blood flow in normal subjects. *Br. J. clin. Pharmac.*, **17**, 83–85.

Feely, J., Wilkinson, G. P., Wood, A. J. J. (1981). Reduction of liver blood flow and propranolol metabolism by cimetidine. *New Engl. J. Med.*, **304**, 692–695.

Freeman, J. G., Barton, J. R. & Record, C. O. (1983). Effects of vasodilators on portal pressure in patients with portal hypertension. *Gut*, **24**, A971.

Groszmann, R. J., Kravetz, D., Bosch, J., Glukman, M., Bruix, J., Bredfeldt, J., Conn, H. O., Rodes, J. & Storer, E. H. (1982). Nitroglycerin improves the haemodynamic response to vasopressin in portal hypertension. *Hepatology*, **2**, 757–762.

Hallemans, R., Naeije, R., Mols, P., Melot, C. & Reding, P. (1982). Treatment of portal hypertension with isosorbide dinitrate alone and in combination with vasopressin. *Critical Care Medicine*, **11**, 536–540.

Hayes, P. C., Shepherd, A. N. & Bouchier, I. A. D.

(1983). Medical treatment of portal hypertension and oesophageal varices. *Br. med. J.*, **287**, 733–736.

Lebrec, D., Nouel, O., Corbic, M. & J-P. (1980). Propranolol—a medical treatment for portal hypertension. *Lancet*, **ii**, 180–182.

Magorien, R. D., Triffon, D. W., Desch, C. E., Bay, W. H., Unverferth, D. V. & Leier, C. V. (1981). Prazosin and hydralazine in congestive heart failure: regional hemodynamic effects in relation to dose. *Ann. Intern. Med.*, **95**, 5–13.

Prosner, G. L., Huded, F. V. & Fink, S. M. (1982). Propranolol in gastrointestinal bleeding from cirrhosis. *New Engl. J. Med.*, **306**, 1550–1551.

Richardson, P. D. I. & Withrington, P. E. (1981). Liver blood flow. II. Effects of drugs and hormones on liver blood flow. *Gastroenterology*, **81**, 356–375.

Shepherd, A. N., Campbell, B. C. & Reid, J. L. (1982). Effects of captopril, an angiotensin converting enzyme inhibitor, in normotensive sodium replete volunteers. *J. cardiovasc. Pharmac.*, **4**, 381–387.

(Received August 21, 1984, accepted November 4, 1984)