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Nifedipine increases and glyceryl trinitrate decreases apparent liver blood flow in normal subjects

J. FEELY*
Department of Pharmacology and Therapeutics, University of Dundee, Dundee

The effects of sublingual nifedipine (10 mg) and of glyceryl trinitrate (500 μg), which produce arterial and venous vasodilatation respectively, on indocyanine green estimated apparent liver blood flow (LBF) were studied in six healthy volunteers. Nifedipine significantly increased (33 ± 12%; mean ± s.e. mean) and glyceryl trinitrate significantly reduced (18 ± 3%) LBF. There was a positive relationship ($r = 0.92$, $P < 0.05$) between the reduction in mean arterial pressure produced by nifedipine and the percentage increase in LBF. These results show that single doses of nifedipine and glyceryl trinitrate significantly alter LBF.

Keywords glyceryl trinitrate apparent liver blood flow

Introduction

Drugs that produce vasodilatation of the venous or arterial system are increasingly used in the management of patients with angina pectoris, hypertension and congestive heart failure. In the latter condition it has been shown that concomitantly with a decrease in cardiac output there is a proportionate reduction in apparent liver blood flow (LBF) (Stenson *et al.*, 1971). LBF in congestive heart failure is increased by prazosin but unchanged by hydralazine (Magorien *et al.*, 1981). Recently, glyceryl trinitrate has been given to patients with portal hypertension in conjunction with the vasoconstrictor vasopressin to offset its detrimental systemic effects while preserving the effect on portal pressure and LBF (Groszmann *et al.*, 1982). *In vitro* evidence suggests that calcium antagonists such as nifedipine relax the portal vein (Vanhoutte, 1981). The effect of nifedipine and glyceryl trinitrate on LBF was therefore studied.

Methods

Six (two female) healthy volunteers (aged 20 to 28 years) participated in this study which was approved by the University Ethical Sub-Committee. All subjects were drug free and were studied after an overnight fast and a 60 min rest in the supine position. Blood samples were taken from the antecubital vein over 20 min following a rapid injection of indocyanine green (ICG, 0.5 mg/kg) for measurement of plasma ICG concentration by a spectroscopic method (Caesar *et al.*, 1961). LBF was calculated as previously described (Feely *et al.*, 1982b) from the plasma clearance of ICG and the measured haematocrit. This indirect method is based on the assumption that the drugs under study do not alter the hepatic extraction ratio of ICG and in the case of glyceryl trinitrate there is no evidence that this occurs in cirrhotic patients (Groszmann *et al.*, 1982). Studies were performed in random order and separated by at least 3 days, as control, 5 min following glyceryl trinitrate (500 μg sublingually) and 30 min following nifedipine (10 mg sublingually) at which time these drugs produce their maximum effects (Maclean & Feely, 1983; Kiowski *et al.*, 1983). Blood pressure and pulse rate were measured at 10 min intervals and the mean of the readings taken immediately prior to and 10 and 20 min following ICG were compared to the baseline pre-drug recordings. Statistical analysis was performed using ANOVA, a Students' two tailed *t*-test and correlation by least square regression analysis.

*Present address: Department of Pharmacology, University of Dublin, Trinity College, Dublin 2.

Results

There was no significant change in the volume of distribution of ICG, however, in comparison to control (2.7 ± 0.2 min; mean ± s.e. mean) the elimination half-life of ICG was significantly ($P < 0.05$) reduced to 2.0 ± 0.2 min and increased to 3.4 ± 0.4 min by nifedipine and glyceryl trinitrate respectively. The effect of these drugs on LBF is shown in Figure 1. Compared with control (1041 ± 94 ml/min) nifedipine increased and glyceryl trinitrate decreased LBF significantly ($P < 0.05$) to 1388 ± 178 and 858 ± 91 ml/min respectively. Although resting pulse rate increased from 65 ± 2 to 71 ± 2 (beats/min; $P < 0.05$) following treatment with glyceryl trinitrate there was no significant alteration in blood pressure. In contrast nifedipine reduced mean arterial blood pressure (systolic + 2 (diastolic)/3) from 90 ± 5 to 83 ± 4 mm Hg. In addition, there was a positive correlation ($r = 0.92$; $P < 0.05$) between the fall in arterial pressure and the percentage increases in LBF (Figure 2).

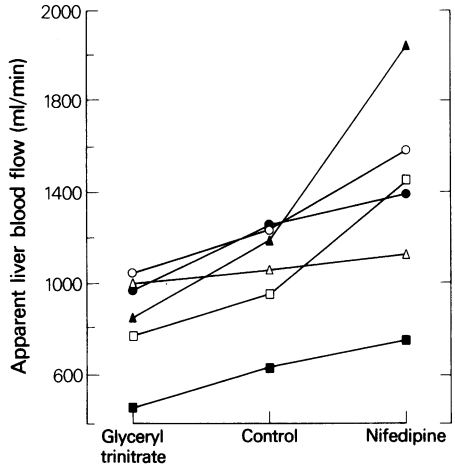

Figure 1 Effect of glyceryl trinitrate (500 μg) and nifedipine (10 mg) on apparent liver blood flow in six subjects.

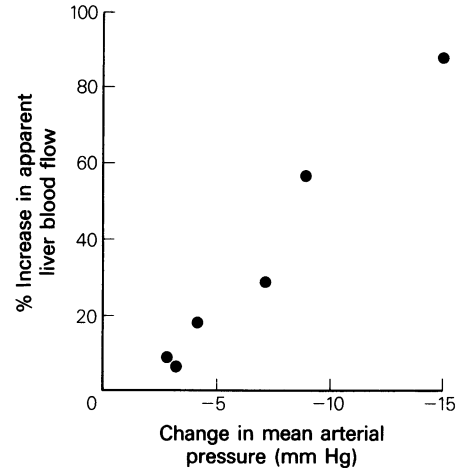

Figure 2 Relationship between changes in mean arterial pressure and in apparent liver blood flow produced by nifedipine.

Discussion

This study demonstrates that vasodilators may alter LBF. It should be noted that these are acute effects and the response to such drugs may be influenced by disease states. For example, blockade of α-receptors with phenoxybenzamine (Daneshmend *et al.*, 1981) or indoramin (Hassan *et al.*, 1983) does not alter LBF in relaxed supine healthy subjects while prazosin increased LBF in patients with congestive heart failure (Magorien *et al.*, 1981). This may not necessarily be due to an increased cardiac output as the effect is not seen with high doses of prazosin or with hydralazine which also increases cardiac output (Magorien *et al.*, 1981). Blockade of the high sympathetic tone in the hepatic and splanchnic vasculature in patients with heart failure may explain the differences in response. Also, in patients with portal hypertension the addition of glyceryl trinitrate to vasopressin while increasing cardiac output is not associated with a rise in LBF but with a further significant reduction in portal pressure (Groszmann *et al.*, 1982). The present study demonstrates that glyceryl trinitrate may reduce LBF in normal subjects presumably by venodilatation of the splanchnic bed reducing flow in the portal system.

The dose of nifedipine that increased LBF has previously been shown in patients with hypertension to increase the cardiac index and forearm blood flow associated with reductions in systemic vascular resistance and mean blood pressure (Kiowski *et al.*, 1983). Because of the relationship (Figure 2) between the magnitude of the effect of nifedipine on arterial blood pressure and on LBF it is probable that arterial vasodilatation produced this effect. Although *in vitro* the portal and mesenteric veins are particularly sensitive to the effects of calcium antagonists (Vanhoutte, 1981) their effect in intact animals is unknown. It should be noted also that the arterial vasodilator minoxidil increases LBF in patients with hypertension (Pratt *et al.*, 1979). Although there is no relationship between blood pressure and LBF in supine normotensive subjects (personal observations in 50 subjects) it is of

interest that nifedipine, while reducing blood pressure, should increase LBF as a decrease in blood pressure *per se* may reduce LBF (Feely *et al.*, 1982b).

Pharmacological agents that alter liver blood flow may significantly affect both drug (George, 1979) and hormonal (Pratt *et al.*, 1979; Feely *et al.*, 1982a) clearance, in addition to their therapeutic potential in patients with portal hypertension. This aspect of vasodilator therapy warrants further investigation.

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References

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**, 43–57.

Daneshmend, T. K., Jackson, L. & Roberts, C. J. C. (1981). Physiological and pharmacological variability in estimated hepatic blood flow in man. *Br. J. clin. Pharmac.*, **11**, 491–496.

Feely, J., Robertson, D., Island, D. P. & Wood, A. J. J. (1982a). Cimetidine alters plasma catecholamine levels and cortisol and aldosterone excretion. *New Engl. J. Med.*, **306**, 1054.

Feely, J., Wade, D., McAllister, C. B., Wilkinson, G. R. & Robertson, D. (1982b). Effect of hypotension on liver blood flow and lidocaine disposition. *New Engl. J. Med.*, **307**, 866–869.

George, C. F. (1979). Drug kinetics and hepatic blood flow. *Clin. Pharmacokin.*, **4**, 433–448.

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

Hassan, S., Abrams, S. M. L. & Turner, P. (1983). The effect of indoramin infusion on apparent liver blood flow in man. *Br. J. clin. Pharmac.*, **15**, 576–577.

Kiowski, W., Bertel, O., Erne, P., Bolli, P., Hulthen, U. L., Tirz, R. & Bühler, F. R. (1983). Hemodynamic and reflex responses to acute and chronic antihypertensive therapy with the calcium entry blocker nifedipine. *Hypertension*, (in press).

Maclean, D. & Feely, J. (1983). Calcium antagonists, nitrates, and new antianginal drugs. *Br. med. J.*, **286**, 1127–1130.

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 hemodyamic effects in relation to dose. *Ann. Intern. Med.*, **95**, 5–13.

Pratt, J. H., Grim, C. E. & Parkinson, C. A. (1979). Minoxidil increases aldosterone metabolic clearance in hypertensive patients. *J. clin. Endocrinol. Metab.*, **49**, 834–837.

Stenson, R. E., Constantine, R. T. & Harrison, D. C. (1971). Interrelationships of hepatic blood flow, cardiac output and blood levels of lidocaine in man. *Circulation*, **45**, 205–211.

Vanhoutte, P. M. (1981). Different effects of calcium entry blockers on vascular smooth muscle. In *New perspectives on calcium antagonists*, ed. Weiss, G. B. pp 109–121. American Physiological Society.

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