The trans-hepatic extraction of nifedipine

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- 1 The trans-hepatic extraction of nifedipine during steady state infusion was studied in six patients undergoing cardiac catheterisation for suspected coronary disease.
- 2 Mean extraction ratio across the liver was 0.64 but hepatic clearance accounted for a mean of only 65% of total body clearance.
- 3 These results are consistent with the liver as the major site of metabolism of nifedipine, but also suggest that significant metabolism occurs outside the liver.

Keywords nifedipine transhepatic extraction calcium channel antagonist

Introduction

The slow-channel calcium blocker nifedipine is a dihydropyridine derivative with a high plasma clearance, negligible renal elimination (Raemisch & Sommer, 1983) and a mean oral bioavailability of 0.43 (Waller *et al.*, 1984). Several studies indicate that nifedipine undergoes extensive and variable first-pass metabolism (Foster *et al.*, 1983; Kleinbloesem *et al.*, 1984; Stern *et al.*, 1984; Waller *et al.*, 1984), via oxidation to a pharmacologically inactive nitropyridine analogue. This reaction probably occurs mainly in the liver (Kroneberg & Krebs, 1980) and may involve cytochrome P450 since this system has been shown to convert felodipine to its pyridine analogue (Baarnhielm *et al.*, 1984). Recent studies, however, have shown that 1,4-dihydropyridines such as nifedipine and felodipine are also co-oxidised by prostaglandin synthetase (Baarnhielm & Hansson, 1986). The present study has assessed the relative contribution of the liver to the plasma clearance and metabolism of nifedipine.

Methods

Six male patients, all of whom were either non-smokers or ex-smokers, aged 44–66 years, and weighing 76–90 kg, were studied while undergoing elective cardiac catheterisation for chest

pain. All gave informed consent to the study which had been approved by the local ethics committee. All other drugs were withdrawn at least 12 h before the study and patients fasted for 12 h before the procedure. Premedication consisted of diamorphine 5 mg i.m., atropine 0.6 mg i.m. and promethazine hydrochloride 10 mg i.m.: this was given after the loading dose of nifedipine. Nifedipine was given intravenously as a solution containing 100 µg ml⁻¹, in an initial loading dose of 3.0 mg over 20 min, followed by a continuous infusion at a constant rate between 0.9 and 1.8 mg h⁻¹ (Table 1). The infusions were commenced at least 1 h prior to cardiac catheterisation using an opaque black syringe and infusion tubing. Right and left heart catheterisation were undertaken under local anaesthesia. An 8F 'Pigtail' catheter was introduced into the descending aorta and blood was taken from this site immediately after left heart catheterisation. A 7F Goodale-Lubin catheter was introduced into the hepatic veins and three simultaneous blood samples were obtained from hepatic veins and descending aorta at 1 min intervals for assay of nifedipine and nitropyridine metabolite concentrations (Figure 1).

Subsequently a single bolus injection of indocyanine green 0.25 mg kg⁻¹ was given via a peripheral cannula and simultaneous aortic and hepatic vein samples were obtained at 3 and 6 min

Figure 1 Diagrammatic representation of study protocol.

Table 1 Plasma concentrations of nifedipine and its nitropyridine metabolite in aorta and hepatic venous blood

	Subjects						
	1	2	3	4	5	6	Mean $\pm$ s.e. mean
Infusion rate ($\mu\text{g min}^{-1}$)	15	15	21	21	30	30	—
Nifedipine concentrations (ng ml^{-1})							
aorta (pre-cath) ^a	14.7	26.0	23.1	22.4	38.4	36.6	26.9 ± 3.7
aorta (post-cath) ^b	10.2	18.7	18.1	17.0	29.8	31.5	$20.9 \pm 3.3^*$
aorta (mean of 3)	13.0	20.1	18.2	20.4	39.4	33.7	$24.1 \pm 4.1^{**}$
hepatic vein (mean of 3)	4.3	8.8	3.7	6.5	18.6	14.0	9.3 ± 2.4
Metabolite concentrations (ng ml^{-1})							
aorta (mean of 3)	2.3	3.5	2.4	2.4	4.5	2.5	$2.9 \pm 0.4^{***}$
hepatic vein (mean of 3)	2.7	5.2	1.6	1.9	4.2	4.1	3.3 ± 0.6
% Nifedipine extraction ^c	66.9	56.2	79.7	68.3	52.8	58.4	63.7 ± 4.0

^a Aorta sample taken prior to cannulation of hepatic veins.

^b Aorta sample taken after cannulation of hepatic veins (approx. 20 min after sample a).

^c $100 \times \frac{\text{mean aorta} - \text{mean hepatic venous}}{\text{mean aorta}}$

* $P < 0.001$ compared to pre-catheter aortic nifedipine concentration.

** $P < 0.001$ compared to mean hepatic vein plasma nifedipine concentration.

*** $P > 0.1$ (NS) compared with mean hepatic vein metabolite concentration.

with further aortic sampling up to 21 min to allow calculation of hepatic plasma flow (Figure 1).

Samples were stored at -20°C , protected from light, until analysis. Plasma samples were assayed for nifedipine and its nitropyridine metabolite by h.p.l.c. (Waller *et al.*, 1984), and for indocyanine green according to the method of Grainger *et al.* (1983). During the initial phase of intravenous nifedipine administration resting heart rate, systolic and diastolic blood pressure were monitored for 30 min using a Datascope Accutor automatic blood pressure recorder and a standard 12 lead ECG.

Data analyses

(a) The hepatic extraction ratio (ER) for nifedipine at steady state and indocyanine green were calculated as:

$$\text{ER} = \frac{\text{Mean aortic concentration} - \text{mean hepatic venous concentration}}{\text{Mean aortic concentration}}$$

(b) Hepatic clearance of indocyanine green was calculated from:

$$\text{Clearance ICG} = \frac{\text{Dose of ICG (mg)}}{\text{AUC (mg l}^{-1} \text{ min)}}$$

The plasma concentration-time curve for indocyanine green was fitted to a two compartment model using non-linear least squares regression analysis (NON-LIN). The AUC was calculated by the trapezoid rule and extrapolated to infinity using the final plasma concentration divided by the slope of the terminal elimination phase.

(c) Hepatic plasma flow (Qp) was derived by:

$$Q_p (\text{ml min}^{-1}) = \frac{\text{Clearance ICG}}{\text{ER (ICG)}}$$

(d) Hepatic clearance of nifedipine (CL(hep)) was calculated from:

$$\text{CL(hep)} (\text{ml min}^{-1}) = Q_p \times \text{ER of nifedipine at steady state}$$

(e) Total body plasma clearance of nifedipine (CL(tot)) was calculated from:

$$\text{CL(tot)} (\text{ml min}^{-1}) = \frac{\text{Infusion rate of nifedipine}}{\text{Mean plasma concentration of nifedipine at steady state}}$$

(f) The percentage hepatic clearance of nifedipine was derived from the ratio of hepatic to total body clearance.

Results are expressed as mean $\pm$ s.e. mean. Statistical assessment was by analysis of variance.

Results

The concentration of nifedipine in the hepatic venous plasma was consistently less than that in the aorta. The mean percentage hepatic extraction of nifedipine was $63.7 \pm 4.0\%$ (Table 1). However, the nitropyridine metabolite which is a major circulating metabolite following oral dosing was not significantly increased in hepatic venous blood. The mean estimated hepatic plasma flow was $978 \pm 88 \text{ ml min}^{-1}$ (Table 2). The mean total body clearance of nifedipine was $956 \pm 75 \text{ ml min}^{-1}$ and mean hepatic clearance of nifedipine $626 \pm 72 \text{ ml min}^{-1}$ (Table 3). Thus, the average hepatic clearance of nifedipine was $65 \pm 4\%$ of total body clearance. Aortic plasma concentrations of nifedipine measured prior to catheterisation were within 10% of post catheterisation values in four of the patients and within 25% in the other two. In all cases the concentration was decreasing with time. A trend to an increase in heart rate and a decrease in both systolic and diastolic blood pressure was seen during the initial loading dose but these

Table 2 Indocyanine green kinetics

ICG	Subjects						Mean $\pm$ s.e. mean
	1	2	3	4	5	6	
Extraction ratio	0.697	0.784	0.909	0.811	0.778	0.671	0.775 ± 0.346
AUC ($\text{mg l}^{-1} \text{ min}$)	21.60	30.73	30.59	18.66	35.96	27.25	27.47 ± 2.61
Dose (mg)	19.38	19	22	17.5	22.5	19	19.89 ± 0.79
Haematocrit	0.440	0.439	0.451	0.377	0.444	0.397	
Clearance ICG (ml min^{-1})	897	618	719	938	626	697	749 ± 56
Hepatic plasma flow (ml min^{-1})	1287	789	791	1157	804	1038	978 ± 88

Table 3 Plasma clearance values for intravenous nifedipine

	Subjects						Mean $\pm$ s.e. mean
	1	2	3	4	5	6	
Total body clearance (ml min ⁻¹)	1154	746	1154	1029	761	890	956 $\pm$ 75
Hepatic clearance (ml min ⁻¹)	861	443	630	790	425	606	626 $\pm$ 72
Hepatic clearance as a percentage of total body clearance	74.6	59.4	54.6	76.7	55.8	68.1	64.9 $\pm$ 3.9

changes were not statistically significant. There were no changes noted on the standard 12 lead ECG during nifedipine infusion.

Discussion

The plasma concentrations of nifedipine were essentially at steady state, although there was a small decrease in concentrations with time. Consequently, the steady state plasma concentration may have been overestimated and therefore total plasma clearance underestimated (Table 1). Despite this, the total body plasma clearance of nifedipine in these patients was higher than found after an intravenous bolus of 3.5 mg in normal volunteers (Waller *et al.*, 1984). The hepatic extraction of nifedipine (64%) at steady state is in agreement with the previously demonstrated oral bioavailability of 0.43 (Waller *et al.*, 1984). This suggests that the liver is the principal site of first pass extraction and metabolism of nifedipine in man.

The values for hepatic plasma flow were about 58% higher than reported previously in healthy volunteers (Grainger *et al.*, 1983), but acute administration of nifedipine increases liver blood flow by a mean of 33% (Feely, 1984). The liver plasma flows measured in the present study are close to the values reported after nifedipine by Feely (1984) when his data are recalculated using 80% hepatic extraction for ICG, as observed in the current study, rather than 100%.

Surprisingly, the hepatic clearance accounted

for only 64.9% of total body clearance, suggesting that significant metabolism occurs outside the liver. One possibility is extra-hepatic metabolism by the cyclooxygenase system (Baarnhielm & Hansson, 1986) but preliminary observations in two volunteers did not demonstrate any change in nifedipine pharmacokinetics after two 100 mg doses of indomethacin (unpublished observations). Concentrations of the nitropyridine metabolite in hepatic venous blood were similar to those in the aorta suggesting that the high concentrations of nitropyridine metabolite found after oral dosing may be due to saturation of subsequent metabolism by the large quantities of drug delivered to the liver in a short time (10–30 mg in 2 h vs 1.6–2.2 mg after i.v. dosing). The present data suggest that low concentrations of nitropyridine metabolite formed in the liver are rapidly hydrolysed to the subsequent carboxylic acid (and hence do not give rise to elevated plasma concentrations of the nitropyridine metabolite). Alternatively, the nitropyridine metabolite detected after oral administration may be formed in the intestinal wall and, due to its higher polarity, may escape hepatic extraction and have a lower volume of distribution such that it produces measurable systemic concentrations. Such a possibility would have important implications in the analysis of the pharmacogenetics of nifedipine (Kleinbloesem *et al.*, 1984).

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