Nifedipine: Kinetics and hemodynamic effects in patients with liver cirrhosis after intravenous and oral administration

The pharmacokinetics and hemodynamic effects of nifedipine were studied in patients with liver cirrhosis and in age-matched healthy control subjects. In a randomized order each subject received nifedipine by intravenous infusion (4.5 mg in 45 minutes) and as a tablet (20 mg). After intravenous nifedipine patients had a longer elimination $t_{1/2}$ (420 ± 254 vs. 111 ± 22 minutes; P < 0.01), a greater volume of distribution (1.29 ± 0.60 vs. 0.97 ± 0.42 L/kg), and a lower systemic clearance (233 ± 109 vs. 588 ± 140 ml/min; P < 0.001). Plasma protein binding of nifedipine was lower in the patients (P < 0.001). After oral nifedipine systemic availability was much higher in patients (90.5% ± 26.2% vs. 51.1% ± 17.1%; P < 0.01) and maximal in patients with a portacaval shunt. Blood pressure decreased and heart rate increased after intravenous nifedipine and these effects could be fitted to plasma concentrations by a sigmoidal model. Maximal effects on heart rate and diastolic blood pressure were not different in liver cirrhosis. When free drug levels were considered, the concentrations corresponding to half the maximal effect were also not different. Blood pressure changes with oral nifedipine were comparable with those after intravenous infusion. We conclude that in patients with liver cirrhosis the pharmacokinetics of nifedipine are considerably altered; dose reduction is recommended when such patients need oral nifedipine. (CLIN PHARMACOL THER 1986;40:21-8.)

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For several reasons it can be anticipated that the disposition of the calcium channel blocker nifedipine, which is increasingly used in hypertension,[1-3] is altered in patients with liver disease. Because nifedipine is extensively metabolized through oxidative biotransformation,[4-6] changes in enzyme activity could substantially influence its oral systemic availability. The presence of portosystemic shunts in patients with liver cirrhosis could also result in increased systemic availability of the drug. In view of its relatively high clearance,[7-9] the rate of elimination of intravenous nifedipine will be determined, in part, by hepatic blood flow, which can be markedly reduced in liver disease. Finally, the protein binding of the drug, (94% to 96% in healthy subjects[10]) might be different in liver disease and so influence its disposition.

At present, information on the pharmacokinetics and hemodynamic effects of nifedipine in patients with liver disease is lacking. Such data are necessary to rationalize, in terms of dosage adjustments, the use of nifedipine in patients with impaired liver function. This information is clinically important, because there is a relevant coincidence of hypertension with impaired liver function.[11]

In our present study the pharmacokinetics of nifedipine were investigated in relation to its hemodynamic effects in patients with liver cirrhosis after single-dose intravenous and oral administration.

METHODS

Seven patients with liver cirrhosis as diagnosed on the basis of clinical and biochemical data and confirmed by biopsy participated in the study. The protocol was approved by the Ethics Committees of the University Hospitals of Leiden and Rotterdam.

Relevant clinical data and concomitant drugs are listed in Table I. The control group consisted of seven

Table I. Subject and patient characteristics, diagnosis, and concomitant drugs

	Age (yr)	Weight (kg)	Sex	Blood pressure (pretreatment) (mm Hg)	Diagnosis*	Portacaval shunt	Varices
Patients							
H	33	69	M	110/72	1	−	+
B	31	62	F	142/76	1	+	+
S	71	70	F	138/80	2,5	−	+
Z	55	95	M	133/85	1	+	+
V	65	66	F	110/66	3	−	+
L	63	71	F	110/72	1	+	+
M	58	84	F	139/96	2,4	−	+
$\overline{X}$	54	74		126/78			
SD	16	12		15/10			
Subjects							
A	35	84	M	116/78	−	−	−
W	54	73	M	173/108	4	−	−
D	64	80	F	118/72	−	−	−
E	50	85	F	120/77	−	−	−
F	62	75	M	122/81	−	−	−
X	46	74	M	117/78	−	−	−
G	37	85	F	124/85	−	−	−
$\overline{X}$	50	79		127/83			
SD	11	5		20/12			

*1 = Alcoholic liver cirrhosis; 2 = cryptogen liver cirrhosis; 3 = chronic active hepatitis with cirrhosis; 4 = essential hypertension; 5 = diabetes mellitus.

†Iso = Isoniazid; Lac = lactulose; MgAl = magnesium aluminum hydroxide; Nit = nitrazepam; Chlor = chlorpropamide; Dia = diazepam; Ran = ranitidine; At = atenolol; Prop = propranolol; Hct = hydrochlorothiazide.

‡Withdrawn 2 weeks before the study.

age-matched healthy subjects. The presence of relevant diseases in this group was excluded by medical history, physical examination, and routine laboratory investigations including aspartate amino transferase, alanine amino transferase, γ-glutamyl transferase, and bilirubin. A randomized two-way crossover experimental design was used. On one occasion nifedipine was infused intravenously (4.5 mg in 45 minutes) and on the other the drug was taken orally (20 mg sustained-release tablet). At least 1 week separated the two parts of the study.

All experiments started at 9 AM. An indwelling cannula with a heparin lock was inserted into an antecubital vein. The infusion was given through a superficial vein of the opposite arm. After a minimal period of stabilization of 15 minutes, basal measurements of heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were made with the participants in the supine position. Blood samples for determination of nifedipine concentrations were drawn at 0, 10, 20, 30, and 45 minutes and 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 24, and 32 hours after the start of intravenous infusion, and at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 24, and 32 hours after tablet dosing. Hemodynamic variables (HR, SBP, and DBP) were measured at the same times.

Blood samples were drawn in heparinized tubes and adequately protected from light. Plasma was separated immediately by centrifugation and stored at −20° C until analyzed (within 1 month). Plasma nifedipine concentrations were determined by a previously described HPLC procedure.[12] Plasma protein binding was determined by ultracentrifugation and spiking with ³H-nifedipine (specific activity 78.4 mCi/mmol) in samples drawn during the elimination phase of the intravenous experiment.[10,13] Each blood pressure value represents the mean of two measurements. HR was determined by pulse frequency counting.

After intravenous nifedipine, compartmental analysis of data was performed in which the following functions were fitted to plasma concentrations (C) by weighted nonlinear regression analysis[14,15]:

$$C = \frac{A}{\lambda_1 T}(1 - e^{-\lambda_1 t}) + \frac{B}{\lambda_2 T}(1 - e^{-\lambda_2 t}) \qquad \text{if } t \leqslant T$$

$$C = \frac{A}{\lambda_1 T}(1 - e^{-\lambda_1 T}) \cdot e^{-\lambda_1(t - T)} +$$

$$\frac{B}{\lambda_2 T}(1 - e^{-\lambda_2 T}) \cdot e^{-\lambda_2(t - T)} \qquad \text{if } t \geqslant T$$

Encephalopathy	Ascites	Edema	Drugs†
−	−	−	Iso, Lac
±	+	+	Lac, MgAl
−	±	±	Nit, Chlor
−	−	−	Lac, MgAl
−	+	±	Lac, Dia, Ran
+	+	+	Lac, MgAl
−	−	−	At
−	−	−	−
−	−	−	Prop, Hct‡
−	−	−	−
−	−	−	−
−	−	−	−
−	−	−	−

in which A and B are hybrid intercepts, λ_1 and λ_2 hybrid coefficients, and T is infusion time. Measurements were weighted by $1/C$. Coefficients and exponents were used to calculate the following kinetic parameters: $AUC = (A/\lambda_1) + (B/\lambda_2)$; volume of central compartment $(V_c) = Dose/(A + B)$; volume of distribution at steady-state $(V_{ss}) = Dose \cdot [(A/\lambda_1^2 + (B/\lambda_2^2)]/AUC^2$; and total systemic plasma clearance $(CL) = Dose/AUC$.

After oral nifedipine the $t_{1/2}$ of the terminal plasma decay was calculated by linear regression analysis after log transformation (which is in fact the absorption $t_{1/2}$[8]). AUCs were calculated by the trapezoidal rule after extrapolation to infinity with the use of intravenous λ_2 values. Systemic availability (F) was calculated as[14,15]:
$$F = (Dose_{iv}/Dose_{po}) \cdot (AUC_{po}/AUC_{iv}).$$

After intravenous infusion, hemodynamic effects were fitted to plasma concentrations by the following function and unweighted nonlinear regression analysis[16]: $E = E_{max} \cdot C^n/(C^n + EC_{50}^n)$, in which C is the nifedipine plasma concentration (total or free), E_{max} is the maximal effect, n is the slope parameter, and EC_{50} is the concentration corresponding to 50% of the maximal effect.

Statistical methods included ANOVA followed by Newman-Keuls test where appropriate.[17] Data are presented as the $\overline{X} \pm$ SD.

RESULTS

Fig. 1 shows representative plasma concentration-time curves as obtained during and after intravenous nifedipine infusion in a patient with liver cirrhosis and in a control subject. Peak concentrations at the end of infusion were quite comparable. After the end of the infusion the concentrations initially declined rapidly (distribution phase) in both patients and subjects. A further decrease in plasma nifedipine concentration (elimination phase) was considerably slower in the patients with liver cirrhosis than in the control subjects (Fig. 1). Individual pharmacokinetic data are listed in Table II. The mean elimination $t_{1/2}$ was 111 ± 22 minutes in control subjects and 420 ± 254 minutes in patients (P < 0.01). The corresponding V_{ss} (0.97 ± 0.42 and 1.29 ± 0.60 L/kg) did not differ significantly, but CL did (558 ± 140 vs. 233 ± 109 ml/min; P < 0.001). The unbound fraction of nifedipine was almost doubled in patients with liver cirrhosis (8.5% ± 2.5%) as compared with healthy subjects (4.4% ± 0.8%; P < 0.001).

Fig. 2 shows representative plasma concentration-time curves after oral nifedipine. The shape of the plasma concentration-time curves was the same in patients and control subjects, but the concentrations were substantially higher in most patients. Individual kinetic data after nifedipine tablets are listed in Table II. The plasma $t_{1/2}$, which in fact is the absorption $t_{1/2}$,[8] was similar for both groups: 14.8 ± 8.2 hours in patients and 12.1 ± 3.9 hours in subjects. The mean peak concentration (C_{max}) was significantly higher in patients with liver cirrhosis than in control subjects (68.3 ± 35.8 vs. 32.3 ± 10.0 ng/ml; P < 0.02), whereas the mean time to C_{max} (t_{max}) was only slightly longer (4.4 ± 1.0 and 3.3 ± 1.2 hours, respectively).Systemic availability (F) was significantly higher (P < 0.01) in the patients (90.5% ± 26.2%) than in healthy subjects (51.1% ± 17.1%). In the three patients with a surgical portacaval shunt, systemic availability was complete (Table II).

Intravenous nifedipine did not significantly change SBP in either group. DBP decreased in both groups, reaching a plateau 20 to 40 minutes after the start of the infusion and returning to baseline values within 4 or 5 hours after the end of the infusion (Fig. 3). A similar time profile was found for the increase in HR (Fig. 3). Representative plasma concentration-effect curves, sigmoidal in shape, are shown in Fig. 3 for a patient (Z) and a control subject (W). E_{max} did not differ, but potency was apparently greater in the patient (curve more to the left of the concentration scale). However, when free nifedipine plasma concentrations were taken
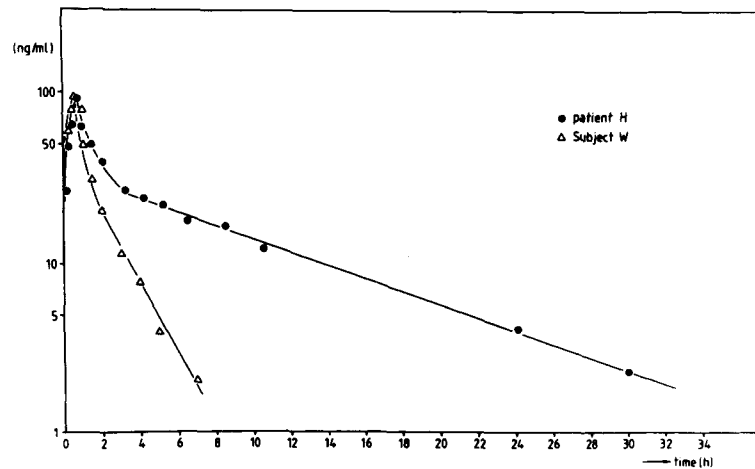
Fig. 1. Representative plasma concentration-time curve after intravenous nifedipine (4.5 mg over 45 minutes) in a patient with liver cirrhosis (H) and in a control subject (W).

Table II. Pharmacokinetics of nifedipine in patients with liver cirrhosis and control subjects

	Intravenous					Oral				
	$t_{1/2\lambda_1}$ (min)	$t_{1/2\lambda_2}$ (min)	V_c (L/kg)	V_{ss} (L/kg)	CL (ml/min)	$t_{1/2a}$ (hr)	C_{max} (ng/ml)	t_{max} (hr)	F (%)	f_u (%)
Patients										
H	24	383	0.48	1.38	202	31.1	63	4.2	99.0	8.1
B	4	394	0.58	0.93	105	ND	141	6.4	105.0	6.0
S	4	963	0.53	2.57	168	13.2	61	3.9	70.9	12.6
Z	6	401	0.55	1.14	282	12.3	58	4.1	119.0	9.1
V	6	318	0.12	1.32	216	12.9	73	3.3	75.5	7.4
L	5	328	0.69	0.91	210	7.3	60	4.7	116.0	10.1
M	11	154	0.13	0.81	448	11.7	22	4.2	48.3	5.5
$\overline{X}$	9	420*	0.44	1.29	233†	14.8	68.3‡	4.4	90.5*	8.5†
SD	7	254	0.22	0.60	109	8.2	35.8	1.0	26.2	2.5
Subjects										
A	20	120	0.29	0.55	353	11.6	47	1.6	42.0	3.1
W	11	125	0.36	1.05	553	13.5	27	1.7	58.0	4.1
D	10	131	0.41	1.80	574	7.1	34	3.6	70.8	5.0
E	4	77	0.24	0.75	687	19.8	30	4.2	58.0	4.3
F	21	116	0.46	1.07	807	9.8	22	3.6	20.1	5.5
X	11	82	0.24	0.58	539	11.6	44	3.2	44.2	4.4
G	8	126	0.19	0.99	605	11.5	22	5.0	64.7	4.1
$\overline{X}$	12	111	0.33	0.97	588	12.1	32.3	3.3	51.1	4.4
SD	6	22	0.09	0.42	140	3.9	10.0	1.2	17.1	0.8

$t_{1/2\lambda_1}$ = distribution $t_{1/2}$; $t_{1/2\lambda_2}$ = elimination $t_{1/2}$; $t_{1/2a}$ = absorption $t_{1/2}$; C_{max} = peak concentration; t_{max} = time to C_{max}; f_u = fraction unbound; ND = not determined.
*$P < 0.01$, †$P < 0.001$, ‡$P < 0.02$ compared with control subjects.

into account, this difference became far smaller (Fig. 3) and disappeared almost completely in most patients.

All concentration-effect data are listed in Table III. The maximal effect on DBP was 17.4% ± 4.8% in the patients and 13.9% + 6.5% in the control group. The respective EC_{50} was considerably different (24.2 ± 8.9 vs. 46.7 ± 20.1 ng/ml; $P < 0.05$), but when free drug levels were corrected for, the EC_{50} became 2.0 ± 1.0 and 1.9 ± 0.6 ng/ml, respectively. The maximal effect on HR was 17.4% ± 4.1% in pa-
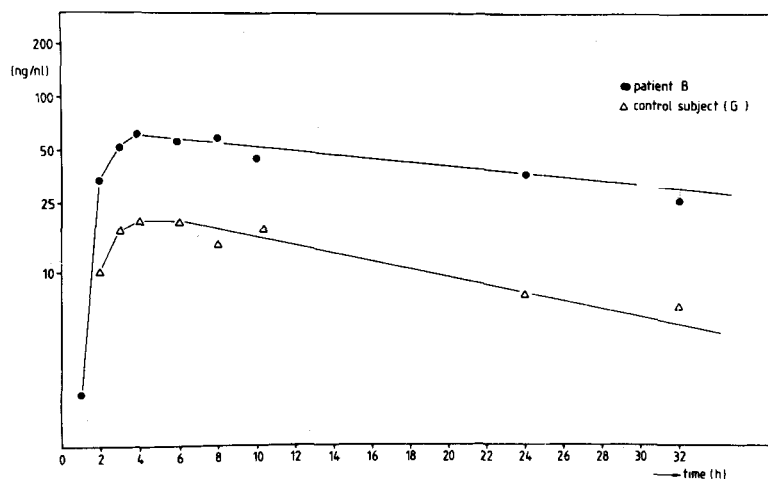
Fig. 2. Representative plasma concentration-time curve after oral nifedipine (20 mg sustained-release tablet) in a patient with liver cirrhosis without a surgical portocaval shunt (B) and a control subject (G).

Table III. Concentration-effect parameters of nifedipine after intravenous infusion

	DBP				HR			
	E_{max} $(-\Delta\%)$	EC_{50} (ng/ml) Total	Unbound	n	E_{max} $(\Delta\%)$	EC_{50} (ng/ml) Total	Unbound	n
Patients								
H	14	33	2.7	5	16	41	3.3	6
B	18	35	2.1	3	14	47	2.8	4
S	18	30	3.8	4	24	36	4.5	3
Z	20	18	1.7	3	20	28	2.5	2
V	26	25	1.8	4	20	41	2.9	10
L	11	14	1.4	2	16	22	2.2	2
M	15	14	0.8	9	12	26	1.4	3
$\bar{X}$	17.4	24.2*	2.0	4.3	17.4	34.3	2.8	4.3
SD	4.8	8.9	1.0	2.3	4.1	9.2	1.0	2.9
Subjects								
A	10	79	2.4	5	6	90	2.8	6
W	18	54	2.2	4	28	35	1.4	4
D	10	24	1.2	6	24	40	2.0	5
E	10	36	1.4	7	23	44	1.9	8
F	27	36	2.0	2	22	62	3.4	7
X	11	66	2.9	2	15	90	4.0	4
G	11	32	1.3	4	28	23	0.9	4
$\bar{X}$	13.9	46.7*	1.9	4.3	20.8	54.9	2.3	5.4
SD	6.5	20.1	0.6	1.9	7.9	26.7	1.1	1.6

n = Exponent for slope.
*$P < 0.05$ compared with control subjects.

tients and 20.8% ± 7.9% in subjects. The respective EC_{50} was 34.3 ± 9.2 and 54.9 ± 26.7 ng/ml for total nifedipine concentrations, but 2.8 ± 1.0 and 2.3 ± 1.1 ng/ml for free drug levels.

Fig. 4 shows the time profile of DBP and HR after tablet dosing. DBP was significantly reduced in both groups, but HR increased significantly only in the patient group (Table IV).
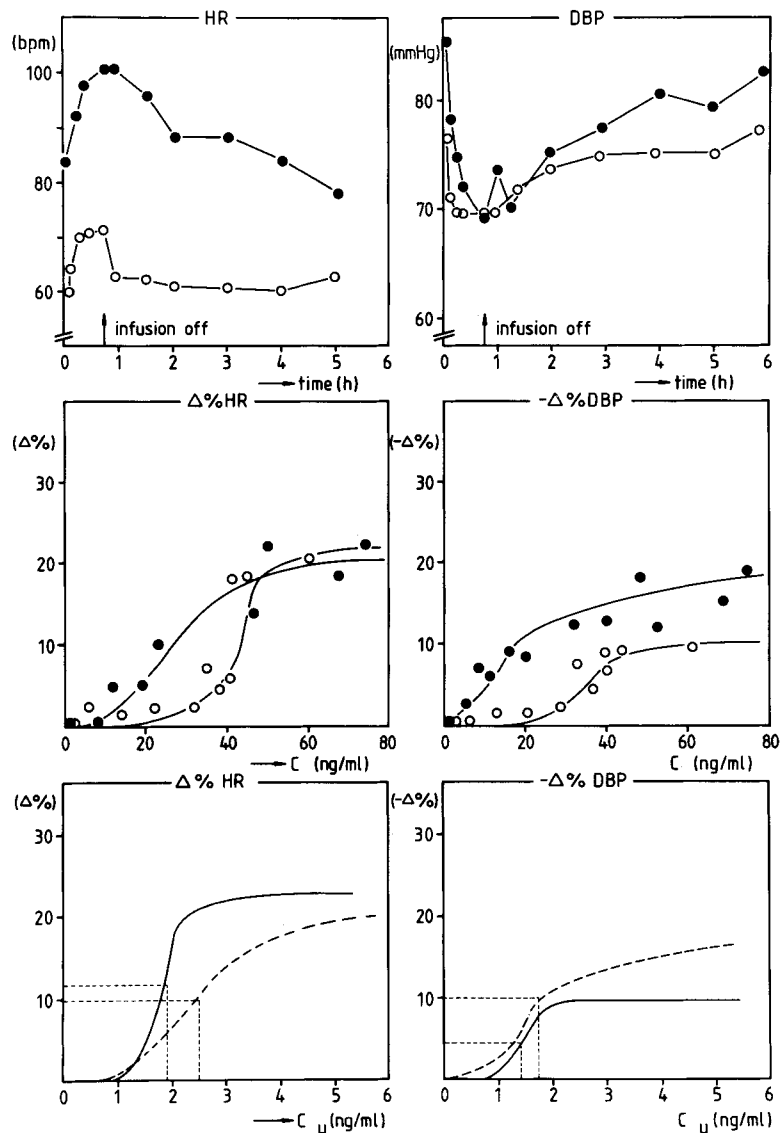
Fig. 3. Top, Representative effects on HR and DBP over time in a control subject (W; ○) and in a patient with liver cirrhosis (Z; ●). Middle, Hemodynamic effects vs. total nifedipine concentration. Bottom, Hemodynamic effects vs. free nifedipine concentration.

DISCUSSION

We have shown that the pharmacokinetics of nifedipine are considerably altered in patients with liver cirrhosis. This was not unexpected because the drug is eliminated rapidly[7,8] and almost completely through oxidative biotransformation,[4-6] which is assumed to take place predominantly in the liver (although metabolism in the gastrointestinal tract has also been suggested[18]). Systemic elimination of nifedipine after intravenous administration is dependent on hepatic blood flow and oxidative drug metabolizing enzyme activity (intrinsic

clearance). Both may be reduced in patients with liver cirrhosis,[19,20] although the reduction in blood flow may partially be compensated for by the hemodynamic effects of the drug. In our patients the CL was substantially reduced and the elimination $t_{1/2}$ was considerably longer. The latter cannot be explained by changes in drug distribution, because the V_{ss} was only slightly larger. Decreased protein binding of nifedipine in cirrhosis is probably not a major factor in its disposition, because it may be assumed that the drug is cleared in a nonrestrictive fashion. Thus it is likely that the re-

Table IV. Mean hemodynamic effects after nifedipine tablets at C_{max}

	HR ($\Delta\%$)	DBP ($-\Delta\%$)
Patients	16.6 ± 2.0*	17.8 ± 5.8
Subjects	10.2 ± 4.3	12.6 ± 3.9

Data are $\overline{X}$ ± SD.
*P < 0.005 compared with control subjects.

duced rate of elimination in patients with cirrhosis is predominantly caused by reduced enzyme activity as a consequence of reduced functioning hepatic cell mass.[20,21]

When taken by mouth, high-clearance drugs are subjected to extensive first-pass elimination. In the case of nifedipine, this amounts to an average degree of 50% in healthy subjects (Table II). Drug metabolizing enzyme activity (intrinsic clearance) primarily determines the systemic availability after oral dosing, but in patients with cirrhosis portalsystemic shunting may also be a very important factor, resulting in higher fractions of drug that reach the general circulation unchanged.[22] Our present results show that the systemic availability of oral nifedipine is considerably higher in cirrhosis and apparently more than complete in the three patients with a surgical portacaval shunt (Table II). This indicates complete bypass of the liver and probably the beginning of drug metabolizing enzyme saturation at the relatively high concentrations reached in these patients.

The fact that the plasma elimination $t_{1/2}$ after intravenous and oral nifedipine differed substantially is explained by the sustained absorption of the drug from the tablets. The oral $t_{1/2}$ reflects the rate of drug release from the tablets (absorption rate) rather than the elimination rate (flip-flop situation[8]). Liver cirrhosis did not significantly affect this, but t_{max} values were slightly longer (Table II).

During and after intravenous nifedipine infusion, DBP was lowered and HR was increased for 4 to 5 hours. As in previous studies with nifedipine, individual hemodynamic effects could be fitted to plasma concentrations by a sigmoidal pharmacodynamic model. Patients with liver cirrhosis seemed to be more sensitive to the effect of nifedipine on DBP and HR, although the maximal effects did not differ. However, this could be explained by differences in free drug levels, because these were significantly higher in patients with cirrhosis.

In our present study and also in previous investigations, after nifedipine tablet dosing to healthy subjects there was hardly any increase in HR, which can most
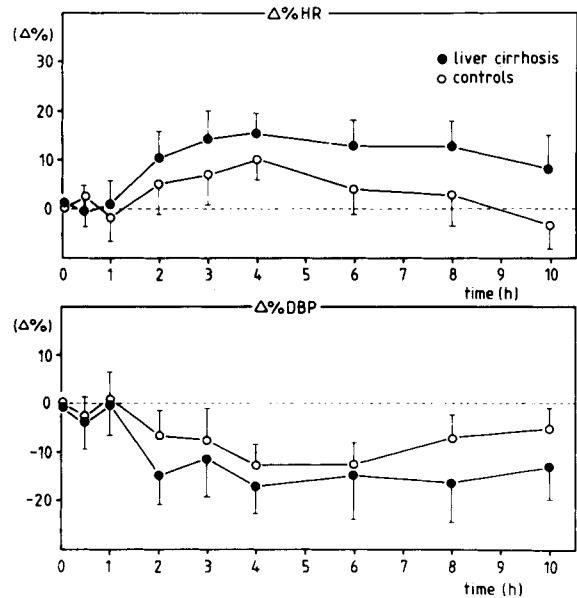

Fig. 4. Mean (± SD) effects on HR and DBP over time after oral nifedipine.

likely be explained by the resetting of the baroreceptor reflex when nifedipine is given at a low input rate.[8,23] In patients with cirrhosis there was some increase in HR during oral dosing, presumably because of the higher rate of change in plasma concentration (higher systemic availability). Probably as a result of the relatively high nifedipine plasma concentrations, one patient developed symptomatic hypotension shortly after tablet dosing. In all other participants nifedipine was well tolerated.

It can be concluded from our present study that although large interpatient variability exists, the pharmacokinetics of nifedipine are considerably altered in patients with liver cirrhosis. These changes may require a dose reduction, in particular in patients with extensive or surgical portacaval shunting. When therapy with nifedipine is indicated for patients with liver cirrhosis, the patient's drug response should be closely followed.

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