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Pharmacokinetics, bioavailability, metabolism and acute and chronic antihypertensive effects of nitrendipine in patients with chronic renal failure and moderate to severe hypertension

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1 The pharmacokinetics, bioavailability, metabolism and antihypertensive effects of nitrendipine have been studied in 12 patients with impaired renal function and moderate to severe hypertension. The drug was administered simultaneously by the i.v. [$^{13}C_4$] and oral (commercial tablet 20 mg) routes.

2 No differences in the pharmacokinetic parameters were observed between the two routes of administration. The systemic clearance after i.v. administration in patients with renal impairment (18.2 ± 6.1 ml min^{-1} kg^{-1}) was similar to that observed in healthy volunteers. Despite complete absorption of drug from the tablet the bioavailability of the parent compound was 21.2 ± 12.5%. Cumulative urinary excretion of nitrendipine metabolites was correlated with the creatinine clearance ($r = 0.946$).

3 Significant reductions in mean arterial blood pressure (mean: 23.6%) at the end of the nitrendipine infusion and after oral administration of 20 mg (mean: 17.5%) were observed. The blood pressure lowering effect of nitrendipine could be correlated within individuals with serum nitrendipine concentrations using a log linear model.

4 Following 4 weeks of therapy an average dose of 77 mg nitrendipine day^{-1} was required to achieve a systolic blood pressure below 160 mm Hg or a diastolic blood pressure below 90 mm Hg. The reduction in blood pressure during multiple dosing was related to the nitrendipine steady-state concentration. There was a significant relationship between the nitrendipine bioavailability and the dose required for sufficient blood pressure control.

5 No accumulation of nitrendipine caused by impaired renal function was observed during multiple dosing. Thus, no reduction of the nitrendipine dose in patients with renal impairment is necessary.

Keywords nitrendipine pharmacokinetics pharmacodynamics renal impairment hypertension

Introduction

Nitrendipine (the racemate of 3-ethyl 5-methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine dicarboxylate) is a dihydropyridine calcium channel blocker which has been introduced recently as an antihypertensive drug. Compared with nifedipine it has a longer terminal elimination half-life (nitrendipine: 8 h; nifedipine: 2 h) (Mikus *et al.*, 1987; Sorkin *et al.*, 1985). The blood pressure lowering effect following oral administration of 20 to 40 mg nitrendipine has been demonstrated to last for up to 22 h in patients with mild to moderate hypertension (Dal Canton *et al.*, 1986; Hansson *et al.*, 1983; Wandel *et al.*, 1987). Thus, it has been claimed that once or twice daily oral administration of 20 to 40 mg nitrendipine suffices to lower blood pressure effectively.

The data available on the pharmacokinetics of nitrendipine in volunteers and in patients with hypertension and normal kidney function as well as impaired

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kidney function are limited and controversial (Goa & Sorkin, 1987). The half-lives reported vary from 2.5 to 22.5 h. Two studies in patients with renal impairment (Aronoff & Sloan, 1985; Bortel *et al.*, 1989) could not demonstrate any differences in the disposition of nitrendipine as compared with subjects with normal renal function. However, a prolongation of elimination half-life to 13.5 h in renal failure as opposed to 4.4 h in control patients and a decreased oral clearance after multiple dosing with 20 mg nitrendipine for 7 days has also been observed (Ankermann *et al.*, 1989). No changes in the binding of nitrendipine to plasma proteins were reported in patients with renal failure (Ankermann *et al.*, 1989; Bortel *et al.*, 1989). Although these studies claimed that a relationship exists between nitrendipine concentrations and the decrease in blood pressure, no attempt was made to evaluate this concentration-effect relationship to determine the concentrations required to elicit a defined reduction in blood pressure. None of these studies administered the drug for longer than 7 days and no concentration-effect data during chronic dosing are available. Therefore, it is not possible to decide if nitrendipine will accumulate in patients with renal failure to an extent exceeding the expected steady-state concentration calculated from single dose studies. In addition no study has been carried out in which the urinary excretion of the metabolites in relation to renal function has been investigated. Furthermore, no data about the dialyzability of nitrendipine have been published. There is also a lack of information concerning the dose of nitrendipine required to lower elevated blood pressure in patients with renal failure and hypertension.

We have therefore studied the pharmacokinetics and acute antihypertensive effects of nitrendipine after single intravenous and oral administration in patients with impaired renal function and hypertension. Possible alterations as compared with healthy volunteers in absorption, absolute bioavailability, urinary excretion of metabolites and protein binding have been assessed. The dialyzability of nitrendipine has been determined in patients with continuous ambulatory peritoneal dialysis (CAPD). In order to keep the blood volume withdrawn as small as possible and to avoid intraindividual variations in nitrendipine disposition, a stable isotope technique has been employed which allows the simultaneous administration of the drug by intra- and extravascular routes. This technique has the advantage that concentrations of the drug after simultaneous i.v. and p.o. administration can be measured in the same sample. In addition to the assessment of the absolute bioavailability, the percent of the dose absorbed can be obtained by measuring the urinary excretion of the metabolites.

After this single dose trial a 4 week treatment period was commenced in order to evaluate the optimal nitrendipine dosage for blood pressure control in these patients. The accumulation of nitrendipine during multiple dosing in relation to the nitrendipine concentrations predicted from the single dose pharmacokinetics was also investigated. The relationship between the blood pressure lowering effect and the serum concentrations of nitrendipine was examined. It was also determined whether this relationship was similar after a single dose and during multiple dosing.

Methods

Subjects

Twelve patients (age: 39–70 years) with moderate to severe hypertension (WHO class I or II) and renal insufficiency attending the outpatient clinic of the Robert-Bosch-Hospital were recruited for this study. All patients had a creatinine clearance below 43 ml min^{-1} and six of these patients with a creatinine clearance below 15 ml min^{-1} were on continuous ambulatory peritoneal dialysis (see Table 1). Eight of the patients had been treated with nifedipine before the study. After the purpose of the study was explained all patients gave written consent to participate in the study which was approved by the local Ethics committee. A complete physical examination and appropriate laboratory tests were performed before the

Table 1 Demographic data of the patients

Patient	*Sex*	*Age (years)*	*Weight (kg)*	*CL_{CR} (ml min^{-1})*	*Renal disease*	*CAPD*	*Medication*	*Nifedipine dose (mg)*	*BP (mm Hg)*
1	female	54	45.5	15	1	yes	1, 2, 5, 7, 9, 10	30	193/95
2	female	55	51.0	4	2	yes	1, 6, 9		176/103
3	male	51	67.0	1	1	yes	2, 7, 10, 11	40	235/117
4	male	70	79.5	2	1	yes	2, 7, 10	20	220/117
5	male	39	62.5	8	3	yes	3, 7, 8	30	161/99
6	male	60	73.4	28	3	no	4, 12		156/105
7	male	61	75.5	15	1	no	1, 3, 4, 5, 7, 10	60	185/95
8	male	59	80.5	32	4	no	3, 4		179/100
9	male	58	70.0	43	4	no	3		176/112
10	male	55	73.0	9	3	yes	3, 7, 10	40	156/100
11	male	57	63.4	9	1	no	1, 2, 3, 4, 6, 7	60	202/106
12	male	52	75.0	11	1	yes	1, 2, 7	60	192/104

renal disease: 1 = diabetic nephropathy; 2 = chronic interstitial nephritis; 3 = glomerulonephritis; 4 = glomerulosclerosis.
medication: 1 = digitalis; 2 = insulin; 3 = β-adrenoceptor antagonist; 4 = diuretic; 5 = nitrate; 6 = L-thyroxine; 7 = nifedipine; 8 = corticosteroid; 9 = aluminium hydroxide; 11 = ofloxazin; 12 = prazosin; medications 3, 7 and 12 were discontinued at least 4 days prior to initiation of the study.
CAPD = continuous ambulatory peritoneal dialysis. BP = blood pressure before nitrendipine treatment.

study. The antihypertensive medication (nifedipine or β-adrenoceptor blocker) was withdrawn at least 4 days before the study commenced and blood pressure was monitored at least 6 times daily during this period until stable values were reached. No antihypertensive drugs were permitted during the study period with the exception of diuretics.

Study protocol

The study started at 07.00 h after an overnight fast. Blood pressure was monitored with an automated Dinamap (Critikon, Germany) over a period of 30 min while the patients were in the supine position. Thereafter, 2 mg [$^{13}C_4$]-nitrendipine (two ampoules containing 1 mg [$^{13}C_4$]-nitrendipine dissolved in polyethyleneglycol/ethanol, diluted with physiological saline to a final volume of 30 ml) was infused over 30 min at a constant rate of 1 ml min^{-1} with a motor driven syringe. The infusion line and syringe were covered to prevent photodecomposition of nitrendipine. Blood pressure was monitored every 15 min. Any effect of the solvent on blood pressure was ruled out by administration of the solvent to healthy volunteers in the same manner showing that over the 30 min infusion period and up to 90 min thereafter blood pressure and cardiac output were stable (Mikus *et al.*, 1991, submitted for publication *Eur. J. clin. Pharmac.*). Either 90 min or 150 min after beginning the infusion, when the blood pressure had returned to pretreatment values, the patients received 20 mg nitrendipine orally (commercial tablet). Two hours later, they had a continental breakfast. The patients remained in the supine position for 4 h after the onset of the study. Blood samples (4 ml) were withdrawn through an indwelling cannula at the following times: 0, 15, 30, 50, 70, 120, 150, 210, 270, 360, 480, 600, 720, 900, 1440, 1500 and 1800 min. Supine blood pressure was measured prior to each blood sampling. Serum was separated and stored in glass tubes at −20° C, which were protected from light with aluminium foil to prevent photodecomposition of nitrendipine. Urine over 24 h and dialysate, if available, over the first 6 h after drug administration were collected in light protected bottles and stored at −20° C until analysis. After the last blood sample had been withdrawn, a 4 week therapy with nitrendipine was started with an initial dosage of 20 to 40 mg daily. Blood pressure was measured by the patients using their own device at least three times a day (morning, afternoon, evening) and recorded in a diary. Every seventh day they attended the outpatient clinic at 08.00 h. The time elapsed since the last dose of nitrendipine was determined. A 4 ml blood sample was withdrawn and supine blood pressure was assessed after a 20 min rest. Blood pressure measurements by the patients were compared with those by the automated device used in the outpatient clinic and they were in good agreement (± 5%). The patients were asked about side effects which they had noted in their diary. The nitrendipine dosage was modified if necessary in order to achieve the targeted systolic blood pressure below 160 mm Hg and diastolic blood pressure below 90 mm Hg. The dosage was administered divided in two or three daily doses.

Drug analysis

Nitrendipine and [$^{13}C]_4$-nitrendipine in serum and dialysate and the four major nitrendipine metabolites in urine were analysed by GC-MS using [$^{2}H]_8$-nitrendipine as internal standard as described (Fischer *et al.*, 1986). This method is specific and has a limit of detection of 0.05 ng ml^{-1}.

Pharmacokinetics

The serum concentration-time data of nitrendipine and [$^{13}C_4$]-nitrendipine were analysed by a modified least squares nonlinear regression computer program (Peck & Barrett, 1979). The pharmacokinetic parameters were calculated using standard procedures (Wagner, 1975). Bioavailability of the nitrendipine tablet was determined by the following equation:

$$F = (AUC_{tab}/AUC_{i.v.})\cdot(dose_{i.v.}/dose_{tab})\cdot 100$$

where AUC_{tab} is the AUC after oral administration of the tablet, $AUC_{i.v.}$ the AUC after i.v. administration, respectively.

The dialyzability (CL_D) of nitrendipine was calculated model-independently by:

$$CL_D = A_D(0,6)/AUC_{iv}(0,6)$$

where $A_D(0,6)$ is the amount of nitrendipine recovered in the dialysate (6 h dialysis period) and $AUC_{iv}(0,6)$ is the area under the serum drug concentration-time curve up to 6 h after intravenous administration of nitrendipine.

Blood pressure measurement

Blood pressure measurements were performed 30 min prior to drug administration and at the times of blood sampling over the first 24 h after the start of the infusion. At each time point at least five measurements were made and the mean values were estimated and used for further calculations. Mean arterial blood pressure was calculated according to the following equation:

$$MAP = (RP_{sys} - RR_{dia})/2.083 + RR_{dia}$$

where MAP = mean arterial blood pressure; RR_{sys} = systolic blood pressure and RR_{dia} = diastolic blood pressure (Wezler & Sinn, 1963).

In order to demonstrate a relationship between serum nitrendipine concentrations and blood pressure lowering a log/linear model was used:

$$E = a\cdot\log(c) + b$$

where E = blood pressure reduction (%); c = serum nitrendipine concentration; a = slope and b = intercept.

The parameters a and b were calculated separately for systolic and diastolic blood pressure reduction in every patient. The results were used to calculate the blood pressure reduction expected during the 4 weeks treatment period at the serum nitrendipine concentrations obtained and compared with the measured blood pres-

sure reduction in order to evaluate the pharmacokinetic/pharmacodynamic model used.

Protein binding

The protein binding of nitrendipine was determined by equilibrium dialysis at 37° C using perspex dialysis cells separated by a Visking cellophane membrane (Serva, Heidelberg, F.R.G.). [^{14}C]-Nitrendipine (100 or 200 ng) was added to aliquots of serum (1 ml) obtained from each patient prior to drug administration and dialysed against 1 ml potassium phosphate buffer (0.05 M, pH 7.4). The specific activity of [^{14}C]-nitrendipine was 25 μCi mg^{-1}. Equilibrium was reached after incubation for 4 h, after which 1 ml of serum and buffer was added to 10 ml Instagel®. The radioactivity was determined by liquid scintillation counting. The fraction unbound (f_u) was calculated by dividing the buffer concentration by the serum concentration.

Statistical analysis

The mean and s.d. were calculated for all pharmacokinetic parameters except for terminal elimination half-life where the harmonic mean was calculated. ANOVA analysis was performed to test for differences between the routes of administration. Linear regression analyses including ANOVA were performed to test the correlations between various parameters.

Results

Pharmacokinetics

To describe the pharmacokinetic data after intravenous and oral administration (Figure 1) an open two compartment model (oral: with lag time) was required. The terminal elimination half-life was 10.4 h after i.v. infusion, almost identical to that observed after the tablet (10.5 h). The area under the serum drug concentration-time curve (AUC) after intravenous administration was 29.6 ± 7.5 ng ml^{-1} h and systemic clearance (CL) was 18.2 ± 6.1 ml min^{-1} kg^{-1}. The bioavailability of the tablet was 21.2 ± 12.5% and showed large interindividual differences (6.2 to 43.3%). The relevant pharmacokinetic data of i.v. and p.o. administration are shown in detail in Tables 2 and 3.

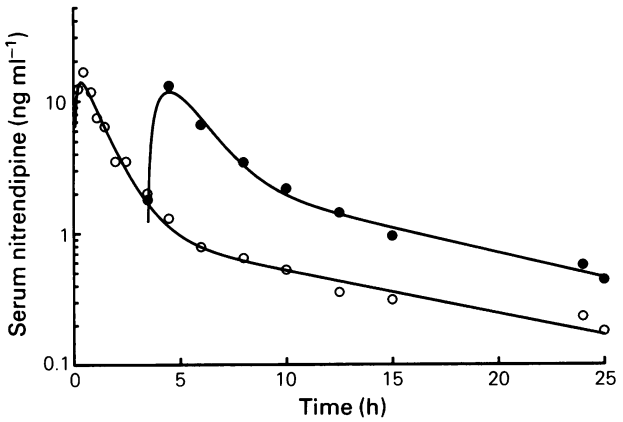

Figure 1 Serum concentration-time curve after 2 mg [$^{13}C_4$]-nitrendipine (○) infusion over 30 min and 20 mg nitrendipine tablet (●) p.o. in a representative patient with renal impairment.

The cumulative urinary excretion of nitrendipine and four of its major metabolites was measured in eight patients with residual urine formation (Table 4). In all patients the amount of unchanged nitrendipine excreted was less than 1% of the dose administered. No significant difference in the proportion of the dose recovered in the urine as metabolites after i.v. and p.o. administration of nitrendipine was observed, indicating that absorption of the nitrendipine from the tablet was complete (102 ± 14%). There was a strong relationship between the percent of dose excreted as metabolites and the creatinine clearance ($r = 0.946$; $P < 0.001$).

The protein binding of nitrendipine was high (> 98%) with the fraction unbound ranging from 0.014 to 0.019 (mean: 0.017 ± 0.002). During the first 6 h after drug administration less than 0.01% of the nitrendipine dose was found in the dialysate. The dialyzability of nitrendipine was therefore extremely low (on average < 10 ml h^{-1}).

Antihypertensive effects

Intravenous infusion of nitrendipine led to a rapid reduction in systolic and diastolic blood pressure. The maximum reduction was reached at the end of the infusion (30 min) and no hysteresis was observed. Mean arterial blood pressure (MAP) was reduced by 29.6 ± 10.4 mm Hg (Table 5). The decrease in MAP after oral administration was less pronounced (23.2 ± 7.4 mm Hg) and the corresponding serum nitrendipine concentrations were lower. The reduction in systolic and diastolic blood pressure was closely correlated with the serum nitrendipine concentration. The log linear model was appropriate to describe the relationship (Table 6). Using the individual parameters the serum nitrendipine concentrations necessary to elicit a 10% reduction of systolic and diastolic blood pressure were determined. A 10% reduction of systolic and diastolic blood pressure was obtained with serum nitrendipine concentrations of 5.1 ± 3.3 ng ml^{-1} and 4.5 ± 2.1 ng ml^{-1}, respectively (Table 6).

Chronic treatment

Patients 1 and 10 were excluded during the early phase of the treatment period because of side effects (subject 1: massive ankle oedema and weight gain; subject 10: muscle spasm 90 min after the nitrendipine tablet). During nitrendipine therapy patient subject 3, who suffered from severe diabetic retinopathy, developed a further deterioration in vision after 15 days and on day 16 of therapy nitrendipine was stopped. During further antihypertensive treatment with nifedipine his vision improved again. Constipation was reported by 6 of the remaining 10 patients, mainly during the first 2 weeks of therapy. One patient reported a headache 1 h after tablet intake, one palpitations and three patients had no side effects. The final daily nitrendipine dose required to achieve a systolic blood pressure below 160 mm Hg and/or a diastolic blood pressure below 90 mm Hg ranged

Table 2 Pharmacokinetic parameters following administration of 2 mg [$^{13}C_4$]-nitrendipine i.v. in 12 patients with chronic renal failure

Patient	C_{max} *(ng ml^{-1})*	t_{max} *(h)*	$t_{½,z}$ *(h)*	*AUC (ng ml^{-1} h)*	*CL (ml min^{-1} kg^{-1})*	V_c *(l kg^{-1})*	V_z *(l kg^{-1})*	V_{ss} *(l kg^{-1})*
1	19.5	0.5	6.2	33.7	21.8	1.7	11.7	6.4
2	28.6	0.5	13.0	34.2	19.1	0.6	24.1	8.9
3	18.0	0.5	11.6	35.7	13.9	1.4	13.9	8.3
4	11.3	0.5	12.2	19.7	21.4	0.6	22.8	13.5
5	10.3	0.5	11.3	15.6	34.1	1.4	33.4	16.8
6	18.9	0.5	16.8	42.5	10.7	2.2	16.4	10.8
7	19.5	0.5	8.2	26.4	16.7	2.0	14.0	8.2
8	19.1	0.5	10.2	32.8	12.6	1.9	11.2	6.0
9	20.0	0.5	11.7	25.8	16.8	2.4	18.6	11.0
10	24.5	0.5	8.5	27.0	20.8	1.3	12.4	5.4
11	16.5	0.5	9.7	35.3	14.1	1.7	12.6	6.3
12	11.1	0.5	14.3	27.0	16.4	1.8	20.3	10.2
Mean	18.1	0.5	10.4*	29.6	18.2	1.6	17.6	9.3
± s.d.	5.4	0.0		7.5	6.1	0.6	6.6	3.4

C_{max} = maximum serum nitrendipine concentration; t_{max} = time to C_{max}; $t_{½,z}$ = terminal elimination half-life; AUC = area under the serum drug concentration-time curve; CL = total systemic clearance; V_c = volume of the central compartment; V_z = area volume of distribution; V_{ss} = volume of distribution at steady-state.
*Harmonic mean.

Table 3 Pharmacokinetic parameters following administration of 20 mg nitrendipine p.o. in 12 patients with chronic renal failure

Patient	C_{max} *(ng ml^{-1})*	t_{max} *(h)*	$t_{½,z}$ *(h)*	*AUC (ng ml^{-1} h)*	F *(%)*
1	10.4	3.5	8.4	58.2	17.3
2	33.1	2.0	13.3	135.2	39.5
3	3.3	2.0	12.0	28.0	7.8
4	4.6	4.5	12.1	41.4	21.0
5	21.9	1.0	10.8	67.5	43.3
6	23.4	2.0	15.2	146.7	34.5
7	11.9	2.5	7.8	49.5	18.8
8	15.6	3.5	10.1	90.8	27.7
9	3.6	3.5	10.8	19.1	7.4
10	5.5	1.0	12.2	16.8	6.2
11	13.0	3.0	7.9	59.2	16.8
12	3.6	3.0	10.4	38.1	14.1
Mean	12.5	2.6	10.5*	65.2	21.2
± s.d.	9.5	1.1		42.2	12.5

C_{max} = maximum serum nitrendipine concentration; t_{max} = time to C_{max}; $t_{½,z}$ = terminal elimination half-life; AUC = area under the serum drug concentration-time curve; F = absolute bioavailability.
*Harmonic mean.

Table 4 Total cumulative urinary excretion of the four major nitrendipine metabolites over 24 h after i.v. and oral administration in patients with renal insufficiency. Patients 1, 5, 7, and 8 were anuric

Patient	CL_{CR} *(ng ml^{-1})*	*Urine volume (ml)*	*% dose excreted as metabolites* *2 mg i.v.*	*20 mg p.o.*	*Ratio p.o./i.v.*
2	4	575	6.4	6.9	1.08
3	1	330	1.4	1.2	0.86
4	2	780	3.5	3.5	1.00
6	28	1630	15.3	18.7	1.22
9	43	2000	28.0	32.0	1.14
10	9	182	1.6	1.3	0.81
11	9	1800	8.6	8.6	1.00
12	11	1610	3.3	3.5	1.06

CL_{Cr} = creatinine clearance.

Table 5 Acute effect of 2 mg [$^{13}C_4$]-nitrendipine i.v. (0.5 h) and 20 mg nitrendipine p.o. on mean arterial blood pressure in 12 patients with chronic renal failure

	2 mg [$^{13}C_4$]-nitrendipine i.v.				*20 mg nitrendipine p.o.*		
Patient	*MAP (mm Hg)*	*Reduction$_{max}$ (mm Hg)*	*t$_{max}$ (h)*	*C at t$_{max}$ (ng ml^{-1})*	*Reduction$_{max}$ (mm Hg)*	*t$_{max}$ (h)*	*C at t$_{max}$ (ng ml^{-1})*
1	140	36.2	0.5	18.3	15.9	3.5	11.7
2	123	24.6	0.5	27.5	18.9	1.0	34.6
3	150	47.4	0.5	18.1	22.4	2.0	4.7
4	144	18.9	0.5	11.1	11.6	2.0	4.6
5	125	22.3	0.5	10.2	26.1	1.0	23.3
6	130	21.4	0.5	17.2	30.7	2.0	24.5
7	138	29.3	0.5	19.5	28.7	1.0	13.0
8	119	14.0	0.5	19.1	15.7	1.0	11.6
9	143	42.5	0.5	20.0	34.7	3.0	4.4
10	123	25.1	0.5	24.5	16.5	0.5	7.5
11	152	40.4	0.5	16.5	29.9	3.0	14.3
12	146	33.3	0.5	11.0	27.9	1.5	4.5
Mean	136	29.6	0.5*	17.8	23.2	1.8	13.2
± s.d.	12	10.4	0.0	5.2	7.4	1.0	9.7

MAP = mean arterial blood pressure (before administration); reduction$_{max}$ = maximal reduction of mean arterial blood pressure; t_{max} = time to reduction$_{max}$; C at t_{max} = serum nitrendipine concentration at t_{max}. *End of the infusion.

Table 6 Correlation between serum nitrendipine concentration and systolic and diastolic blood pressure after simultaneous administration of 2 mg [$^{13}C_4$]-nitrendipine i.v. and 20 mg nitrendipine p.o. in 12 patients with chronic renal failure. The data were analysed by linear regression using a log linear model

	Systolic blood pressure				*Diastolic blood pressure*			
Patient	*a*	*b*	r	*$C_{10\%}$ (ng ml^{-1})*	*a*	*b*	r	*$C_{10\%}$ (ng ml^{-1})*
1	43.1	−32.1	0.944	9.5	26.6	−12.4	0.836	7.0
2	19.7	−11.6	0.921	12.4	23.6	−10.4	0.977	7.3
3	30.7	−6.7	0.929	3.5	25.1	1.9	0.974	2.1
4	12.3	−0.1	0.922	6.6	21.6	−3.4	0.937	4.2
5	11.2	1.3	0.990	6.0	19.2	3.3	0.953	2.2
6	13.5	3.2	0.906	3.2	14.9	−2.8	0.947	7.3
7	18.7	−2.9	0.934	4.9	21.6	−5.2	0.982	5.1
8		fit not possible			17.7	−3.6	0.762	5.9
9	20.2	0.9	0.985	2.8	23.6	−0.1	0.968	2.7
10	9.4	5.8	0.960	2.8	15.0	1.6	0.936	3.6
11	12.1	8.9	0.884	1.5	34.3	−14.6	0.973	5.2
12	16.5	1.5	0.862	3.3	17.7	8.9	0.904	1.2
Mean				5.1				4.5
± s.d.				3.3				2.1

a = slope; b = intercept; r = correlation coefficient; $C_{10\%}$ = serum nitrendipine concentration required to maintain a 10% reduction in blood pressure.

from 20 mg to 120 mg. Figure 2 shows the systolic and diastolic blood pressure and the daily nitrendipine dose in one representative patient during the 4 week treatment period. Systolic blood pressure during the last week of therapy was decreased from on average 188 mm Hg prior to treatment to 160 mm Hg, and diastolic blood pressure was decreased from 106 mm Hg to 85 mm Hg with an average dose of nitrendipine of 77 mg day^{-1} (Table 7). Nitrendipine had a more pronounced effect on the diastolic blood pressure. Regression analysis of the dose required for sufficient blood pressure reduction and the bioavailability revealed a significant correlation of these parameters ($r = -0.781$; $P < 0.008$) (Figure 3). During the treatment period at least 29 blood samples were obtained from the 10 patients and trough serum nitrendipine concentrations (8 to 24 h after dosing depending on the dosage interval) ranged between 1 and 9 ng ml^{-1}. Using the single dose pharmacokinetics of nitrendipine (20 mg p.o.) and the individual dosage of each patient serum trough nitrendipine concentrations could be simulated. The differences between the calculated and the measured serum nitrendipine concentrations were not significantly different from zero (−0.323 ± 2.15 ng ml^{-1}) and ANOVA analysis revealed no influence of the day of the treatment period on this parameter ($P = 0.708$; $n = 29$) (Figure 4).

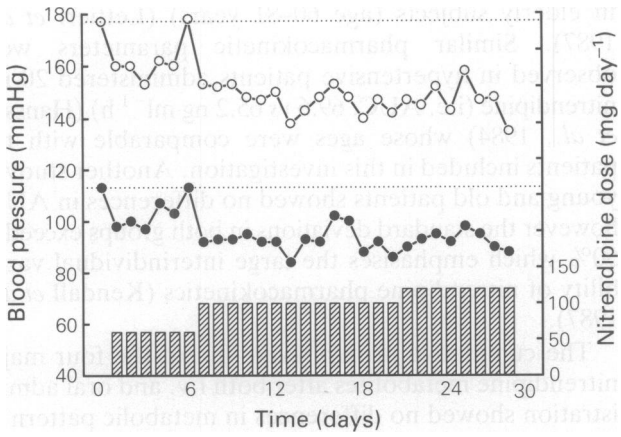

Figure 2 Time course of systolic (○) and diastolic (●) blood pressure during the 4 week treatment period with different daily nitrendipine doses in a representative patient with renal impairment and hypertension. The bars represent the daily nitrendipine dose of this patient.

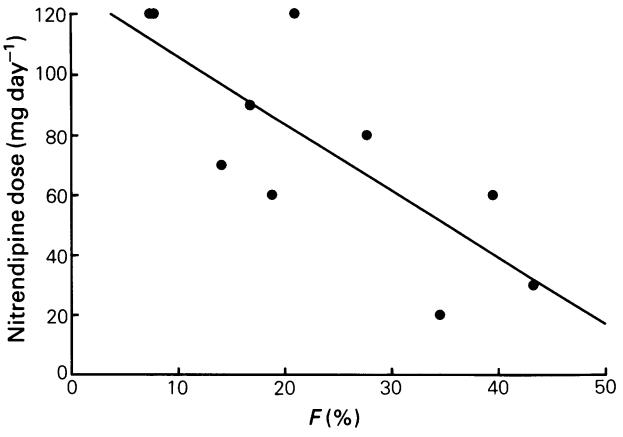

Figure 3 Relationship between nitrendipine dose required for blood pressure control and nitrendipine bioavailability in 10 patients with kidney disease and hypertension. ($r = -0.781$; $P < 0.008$).

Table 7 Systolic (RR_{sys}) and diastolic (RR_{dia}) blood pressure before and during the last week of treatment with nitrendipine in 10 patients with chronic renal failure. The nitrendipine dose required for effective blood pressure reduction is given

	Before treatment		*Last week of treatment*			*Blood pressure reduction*	
Patient	RR_{sys} *(mm Hg)*	RR_{dia} *(mm Hg)*	*Dose (mg)*	RR_{sys} *(mm Hg)*	RR_{dia} *(mm Hg)*	RR_{sys} *(%)*	RR_{dia} *(%)*
2	176	103	60	156	87	11.4	15.5
3	235	117	120	180	90	23.6	23.1
4	220	117	120	178	84	19.1	28.2
5	161	99	30	138	87	14.3	12.1
6	156	105	20	145	96	7.1	8.6
7	185	95	60	160	74	13.5	22.1
8	179	100	80	161	86	10.1	14.0
9	176	112	120	133	88	24.4	21.4
11	202	106	90	175	78	13.4	26.4
12	192	104	70	170	79	11.5	24.0
Mean	188	106	77	160	85	14.8	19.5
± s.d.	25	7	36	17	6	5.7	6.6

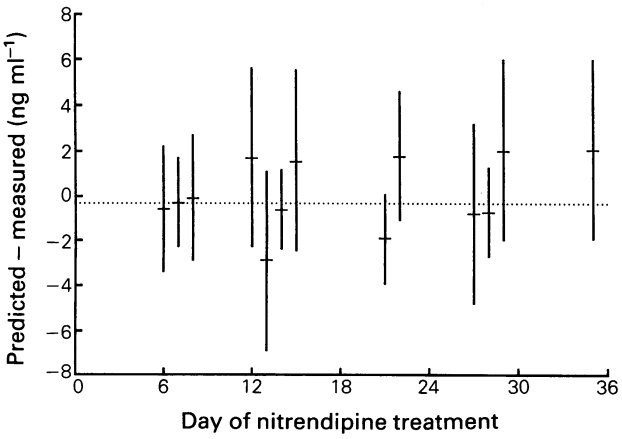

Figure 4 Differences between calculated and measured nitrendipine serum concentrations with 90% confidence limits in relation to the day of nitrendipine treatment in 10 patients with kidney disease and hypertension. The dashed line denotes the average of the 29 data points (mean = -0.323 ng ml^{-1}).

Using the parameters of the log linear concentration effect model (Table 6) and the serum nitrendipine concentrations obtained during the treatment period the expected reductions of systolic and diastolic blood pressure were calculated and compared with the measured blood pressure reductions. Regression analysis showed significant correlations for both systolic and diastolic blood pressure reduction (Figure 5) although large variations were observed.

Discussion

The serum drug concentration-time data following i.v. administration of 2 mg [$^{13}C_4$]-nitrendipine were similar to those obtained in healthy young volunteers (Mikus *et al.*, 1987). The nitrendipine AUC of the patients was in the same range as the AUC of the volunteers (27.7 ± 5.6 ng ml^{-1} h), as was also the case for the systemic clearance

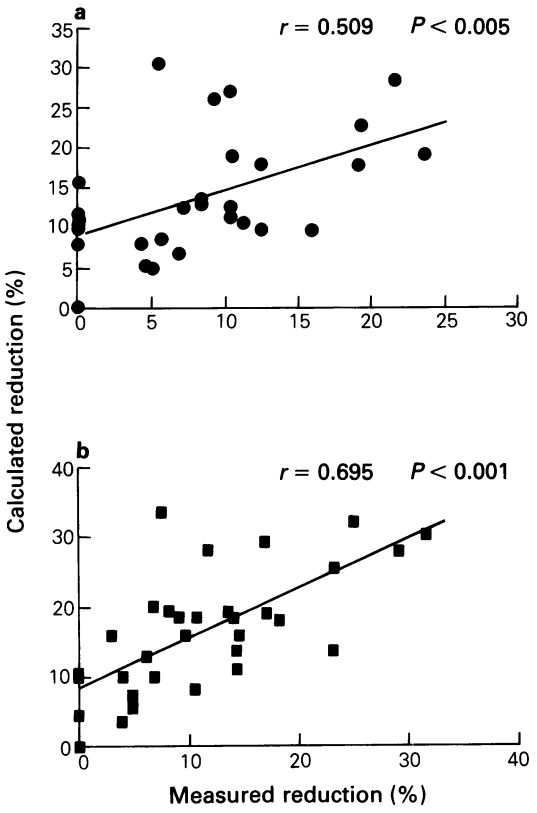

Figure 5 Correlation between measured systolic (a) and diastolic (b) blood pressure reduction during the treatment period and expected blood pressure reduction in 10 patients with kidney disease and hypertension. The expected blood pressure reductions were calculated using the serum nitrendipine concentrations obtained during the treatment period, based on the log linear relationship between serum nitrendipine concentration and blood pressure reduction determined during the acute phase of the study.

(18.7 ± 3.6 ml min^{-1} kg^{-1}). The terminal half-life of 10.4 h observed in this study is somewhat longer than that in volunteers (8.6 h) which can be attributed to the higher volume of distribution in the patients with renal disease (V_{ss}: 9.3 ± 3.4 l kg^{-1} in patients; 5.4 ± 2.4 l kg^{-1} in volunteers) (Mikus *et al.*, 1987). However, the half-life observed is appreciably longer than the half-lives reported previously (Aronoff *et al.*, 1984; Raemsch & Sommer, 1984; Raemsch *et al.*, 1986) owing to the much higher sensitivity of the analytical technique employed for the measurement of nitrendipine.

After oral administration of a 20 mg nitrendipine tablet no differences were observed in the terminal elimination half-life in relation to the i.v. route of administration (10.5 *vs* 10.4 h). The bioavailability showed pronounced interindividual variability (6.2 to 43.3%) which has been observed previously (Eichelbaum *et al.*, 1988; Krol *et al.*, 1987; Mikus *et al.*, 1987; Raemsch & Sommer, 1984; Raemsch *et al.*, 1986). The bioavailability in our patients was somewhat higher than that reported previously in healthy young volunteers (16.0 ± 6.2%) (Mikus & Eichelbaum, 1987), which may be due to less effective first pass metabolism in the older patients (aged 39–70 years). However, the AUC after oral administration of 20 mg nitrendipine observed in this study was lower by a factor of 1.8 than that reported in elderly subjects (age 60–81 years) (Lettieri *et al.*, 1987). Similar pharmacokinetic parameters were observed in hypertensive patients administered 20 mg nitrendipine (i.e. AUC: 69.6 *vs* 65.2 ng ml^{-1} h) (Hansson *et al.*, 1984) whose ages were comparable with the patients included in this investigation. Another study in young and old patients showed no differences in AUC, however the standard deviations in both groups exceeded 50% which emphasises the large interindividual variability of nitrendipine pharmacokinetics (Kendall *et al.*, 1987).

The cumulative urinary excretion of the four major nitrendipine metabolites after both i.v. and oral administration showed no differences in metabolic pattern or the percent of the dose excreted in urine, indicating complete absorption of oral nitrendipine. The correlation between the percent of the dose excreted in urine and the creatinine clearance of the patients indicates a direct relationship between the metabolite excretion and the glomerular filtration rate of the kidney. The protein binding of nitrendipine in patients with kidney disease (f_u 0.017 ± 0.002) is similar to that in healthy volunteers (f_u: 0.020 ± 0.012) (Mikus *et al.*, 1987). This high protein binding and the high volume of distribution, which indicates extensive tissue binding, explains the very low amount of nitrendipine found in dialysate. Hepatic biotransformation is the major route of nitrendipine elimination (Raemsch & Sommer, 1984). Less than 1% of the dose was recovered in the urine as unchanged drug in the patients with residual urine formation. Therefore, no accumulation of nitrendipine is anticipated in patients with impaired renal function compared with patients with normal kidney function.

Nitrendipine caused a significant reduction in systolic and diastolic blood pressure in all patients after i.v. administration of 2 mg and after 20 mg orally. The decrease in MAP after p.o. administration of 20 mg nitrendipine is similar to previously observed reductions (Frohlich, 1985; Ventura *et al.*, 1983). Using a log linear model there was a strong relationship between the serum nitrendipine concentration and the percent reduction in systolic and diastolic blood pressure. From this, the nitrendipine concentration necessary to produce a certain effect was determined. Other investigators have reported a significant relationship between reduction of blood pressure and plasma nitrendipine concentrations in patients with renal failure (Lasseter *et al.*, 1984; Lettieri *et al.*, 1987), but no regression analysis was performed to assess the plasma nitrendipine concentration required to achieve a defined blood pressure lowering effect.

During the 4 week treatment period the patients tolerated nitrendipine well except patients 1, 10 and 4. These patients discontinued therapy with nitrendipine on day 2, 4 and 16 because of major side effects. The 10 patients (including patient 4) required daily doses of nitrendipine from 20 to 120 mg to achieve sufficient blood pressure control (systolic blood pressure < 160 mm Hg; diastolic blood pressure < 90 mm Hg). It is interesting to note that the dose required to achieve the targeted blood pressure correlated strongly with the bioavailability observed in the acute study. Thus, patients who showed only minimal antihypertensive

effects after single oral administration of 20 mg nitrendipine had a low bioavailability and, therefore, required higher doses of nitrendipine to achieve satisfactory blood pressure control. Based on these data the classification of patients into responders and nonresponders (Ventura *et al.*, 1983) is not due to the fact that the drug is ineffective in some patients but rather has a pharmacokinetic basis. The wide variability in daily nitrendipine dose is in agreement with previously reported studies (Burris *et al.*, 1986; Kann, 1987) where up to 80 mg nitrendipine had to be administered to some patients to obtain sufficient blood pressure reduction.

Using the single dose pharmacokinetic parameters and the individual dosage, the calculated serum nitrendipine concentrations were compared with the measured trough serum nitrendipine concentrations. There was no accumulation of nitrendipine over the treatment period to a greater extent than expected from the single dose pharmacokinetics of nitrendipine. These data indicate that during multiple dosing, even at doses up to 120 mg, the first-pass metabolism of nitrendipine was not saturable.

Comparison of the predicted with the measured blood pressure reduction during the treatment period indicated that a prediction of blood pressure reduction on the basis of serum nitrendipine concentrations is reasonable. Diastolic blood pressure reduction could be predicted more reliably than systolic blood pressure reduction. However, the regression functions showed deviations from the line of identity which could be caused by possible changes in protein binding of nitrendipine during multiple dosing. Since nitrendipine is administered as a racemic drug, and the vasodilating potency of the enantiomers differ this deviation may also be associated with changes in the proportion of the enantiomers present in the serum during multiple dosing.

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