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Inhibitory effect of uraemia on the hepatic clearance and metabolism of nicardipine

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1 The principal aim of this study was to investigate the effect of renal impairment on the pharmacokinetics of nicardipine following intravenous and oral dosing.
2 The plasma clearance of nicardipine was significantly lower at 6.5 ml min^{-1} kg^{-1} in patients with impaired renal function, compared with a mean value of 10.4 in patients with normal renal function and with 12.5 ml min^{-1} kg^{-1} in patients on regular haemodialysis treatment.
3 In comparison to the patients with normal renal function, there were significant increases in AUC and C_{max} in the patients with renal impairment. These increases were particularly marked during chronic dosing – AUC was increased by 163%, C_{max} by 127% and apparent oral bioavailability by 90%. There were no such increases in the dialysis group whose values were similar to those for normal renal function.
4 There were no significant differences in volume of distribution or protein binding, nor in the measured indices of hepatic function to account for the reduction in drug clearance in the patients with renal impairment.
5 The results of this study indicate that renal impairment may have a significant and potentially important impact on the disposition of a drug which, under normal circumstances, is highly extracted by the liver. Accumulation of a metabolic 'inhibitor' substance is a possible explanation.

Keywords nicardipine pharmacokinetics renal impairment

Introduction

Nicardipine is a dihydropyridine derivative calcium antagonist drug which is used in the treatment of angina and hypertension. In common with other calcium antagonist drugs, nicardipine undergoes extensive hepatic metabolism (Rush *et al.*, 1986). Several pharmacologically inactive metabolites are produced 60% of which are excreted via bile and 40% excreted via urine, with less than 1% of the parent drug being eliminated unchanged by the kidney. In general, the metabolism of highly extracted drugs is considered only to be significantly affected by disease of the liver, and not by renal impairment, and many investigators have reported that the pharmacokinetics of calcium antagonist drugs such as verapamil (Mooy *et al.*, 1985) or nifedipine (Kleinbloesem *et al.*, 1985) are not affected by renal impairment. However, since cardiovascular disease and renal impairment frequently coincide, it is important to consider and document the clinical pharmacology of calcium antagonist drugs in patients with renal impairment. The present study was designed to investigate aspects of the pharmacokinetics and pharmacodynamics of nicardipine in patients with varying degrees of renal impairment.

Methods

The study followed a single-blind (patient blind), partially randomised design and involved three separate groups of patients whose clinical characteristics are summarised in Table 1.

Group 1: patients with normal renal function and mild to moderate essential hypertension.

Group 2: patients with varying degrees of renal impairment and mild to moderate essential hypertension.

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Group 3: patients with end-stage renal failure on regular haemodialysis treatment (study days were between dialysis days).

All patients gave written, informed consent for their participation in the study which was approved by the hospital Research and Ethics Committee. The three groups were randomly assigned to receive a single intravenous dose and a single oral dose of nicardipine on two separate (acute) study days with an intervening washout period of 7 days. Groups 1 and 2 additionally undertook a third study day (chronic) following 1 week of treatment with nicardipine 45 mg twice daily. On each study day patients reported to the Clinical Pharmacology Research Unit having fasted overnight. For the intravenous dosing, nicardipine was administered as a short intravenous infusion (70 $\mu g\ kg^{-1}$ body weight) over 10 min. Blood samples were collected before the dose and at 2, 5 and 10 min during infusion and 2, 5, 10, 20, 40, 60 min and 2, 3, 4, 5, 6 and 8 h after infusion.

For oral dosing, nicardipine was administered as a biphasic slow release formulation (45 mg) with the morning dose being given at approximately 08.30 h with 150 ml water. Blood samples were collected before the dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8 and 12 h after the dose.

Nicardipine plasma concentrations were determined by a specific chromatography (GC) method following solvent extraction, as described by Wu *et al.* (1984).

Pharmacokinetic analysis

The individual concentration-time profiles were first plotted and visually examined. The plasma nicardipine concentration-time profiles after intravenous infusion were best fitted to a two-compartment model of the form described by Gibaldi & Perrier (1975). Clearance, volume of distribution and terminal elimination half-life were obtained directly from the model.

After oral administration, the concentration-time profiles were biphasic and it was inappropriate to fit the data to a model. Model-independent methods were used to describe the data:

i) peak plasma level (C_{max}) and time to reach the peak (t_{max}) were obtained directly from the profile;
ii) the area under the concentration-time curve (AUC) was calculated by trapezoidal rule from time zero to infinity for single doses and from time zero to 12 h for multiple doses;
iii) clearance/F was obtained by dividing dose/AUC;

Table 1 Clinical characteristics of patients

Group	*CL_{cr} (ml min^{-1})*	*Age (years)*	*Weight (kg)*	*Previous medication*
Normal renal function				
1.1	72	53	57	
1.3	97	61	90	* Bendrofluazide
1.4	89	47	55	
1.5	88	64	85	* Allopurinol
1.6	103	58	80	
1.7	95	41	63	
Mean	91 ± 11	54 ± 9	72 ± 15	
Renal impairment group				
2.1	40	47	75	
2.2	55	57	78	Spironolactone
2.3	43	65	55	Diltiazem, *bendrofluazide
2.4	49	50	65	Nifedipine
2.5	49	62	105	* Bendrofluazide, KCl, aspirin
2.6	22	65	69	* Frusemide
2.7	13	62	77	* Frusemide
Mean	39 ± 16	58 ± 7	75 ± 16	
Dialysis group				
3.1		50	65	Ferrous sulphate
3.2		33	47	Ferrous sulphate
3.3		49	77	
3.4		20	66	
3.5		58	67	* Dipyridamole
3.6		23	47	Ferrous sulphate
3.7		61	75	
3.8		30	73	Floxacililin
Mean		41 ± 16	65 ± 12	

CL_{cr}: Creatinine clearance
* Drugs which are continued throughout the study
Dialysis group (group 3) were continued on vitamin B, ascorbic acid, folic acid, Alu-Cap (aluminium hydroxide) throughout the study.

iv) Bioavailability (F) was obtained form the following equation:

$$F = \frac{AUC_{oral}}{AUC_{iv}} \times \frac{Dose_{iv}}{Dose_{oral}}$$

In addition, the extent of plasma protein binding was investigated by means of standard quilibrium dialysis techniques.

Pharmacodynamic Measurements

Blood pressure and heart rate At times corresponding to the times of plasma drug concentration measurement supine readings were obtained in duplicate by a semi-automated sphygmomanometer (Sentron, Bard Medical).

Apparent liver blood flow An intravenous bolus dose of indocyanine green (ICG) (0.5 mg kg^{-1}) was administered 1 h after nicardipine dosing and liver blood flow calculated from the plasma clearance of ICG. Venous blood samples were withdrawn from the opposite arm through an indwelling catheter at 3 min intervals for 21 min. Plasma ICG concentrations were determined by an h.p.l.c. method described by Rappaport & Thiessen (1982). Clearance and volume of distribution of ICG were determined by fitting the concentration-time profiles to a one-compartment model. Apparent liver blood flow was then calculated from the ICG plasma clearance corrected for haematocrit as described by Caesar *et al.* (1961).

$$\text{Liver blood flow} = \frac{CLp \times 100}{(1 - HCT\%)}$$

Renal function indices Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured 1.5 h after drug dosing from the clearance of [^{51}Cr]-EDTA and [^{125}I]-hippuran respectively. The radiolabelled compounds were administered intravenously and 11 blood samples were then collected over 4 h together with a single cumulative urine collection over the same period. Effective renal plasma flow and glomerular filtration rate were calculated from the ratio of the amount of urinary excretion over 4 h and the area under the plasma concentration-time curve obtained using the trapezoidal rule for [^{125}I]-hippuran and [^{51}Cr]-EDTA respectively (Harries *et al.*, 1972).

Statistical analysis

Logarithmic transformation (to the base e) was required to normalise the distribution of plasma clearance of nicardipine and for liver blood flow data. For comparison between groups, one-way analysis of variance (ANOVA) was used. The relationship between the pharmacokinetic parameters and indices of renal function for the whole group was undertaken by linear regression analysis. Time and treatment effect on blood pressure and heart rate was evaluated by repeated measures analysis of variance using BMDP package. Data throughout are presented as mean ± s.d.

Results

Pharmacokinetics

Intravenous administration (Table 2) The plasma clearance of nicardipine was significantly lower in patients with renal impairment (group 2) compared with those with normal renal function (group 1) : 10.4 *vs* 6.5 ml min^{-1} kg^{-1} ($P < 0.03$), whereas plasma clearance in patients with end stage renal failure on regular dialysis (group 3) (12.5 ml min^{-1} kg^{-1}) did not differ significantly from

Table 2 Summary of pharmacokinetic parameters following intravenous and oral dosing with nicardipine

	Group 1	*Group 2*	*Group 3*
Intravenous			
Clearance (ml min^{-1} kg^{-1})	10.41 ± 3.1	*6.53 ± 2.6	12.54 ± 4.56
V_1 (l kg^{-1})	0.11 ± 0.08	0.096 ± 0.08	0.18 ± 0.15
$t_{½z}$ (h)	1.36 ± 0.54	2.29 ± 1.41	2.38 ± 2.88
Single dose oral:			
AUC (ng ml^{-1} h)	152.7 ± 87.9	*249.3 ± 111.6	183.8 ± 143.5
C_{max} (ng ml^{-1})	30.26 ± 17.00	51.1 ± 28.2	33.4 ± 21.6
t_{max} (h)	4.1 ± 1.7	2.7 ± 1.8	3.1 ± 2.0
CL/F (ml min^{-1} kg^{-1})	105.4 ± 85.1	*50.0 ± 22.3	93.4 ± 47
F(%)	15.2 ± 8.8	17.6 ± 5.2	19.8 ± 12.6
Chronic dosing			
AUC (ng ml^{-1} h)	193.8 ± 147.2	*509 ± 186	–
C_{max} (ng ml^{-1})	38.3 ± 27.6	*87 ± 27.6	–
t_{max} (h)	2.50 ± 1.4	1.99 ± 1.21	–
CL/F	70.2 ± 38.1	20.8 ± 7.6	–
F(%)	17.8 ± 10.6	*33.9 ± 10.7	–

* Significantly different from group 1, $P < 0.05$ (ANOVA).

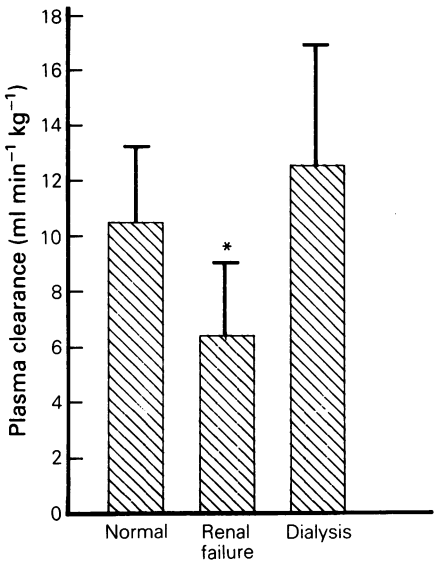

Figure 1 The plasma clearance of nicardipine following intravenous administration. * significantly different from group 1, $P < 0.05$ (ANOVA).

the value in the normal group (Figure 1). The volumes of distribution of the central (V_c) and of the peripheral compartment, although apparently higher in group 3, were not significantly different from group 1 or group 2. There were small but non-significant increases in elimination half-life in groups 2 and 3, compared with group 1.

Single oral doses (Table 2) The AUC(0,∞) after the first dose was significantly higher in patients with renal impairment (group 2) compared with patients with normal renal function (group 1) (153 *vs* 249 ng ml^{-1} h ($P < 0.05$). The AUC in the dialysis group (group 3), 184 ng ml^{-1} h, was not significantly different from group 1. Correspondingly, CL/*F* was decreased from 105 ml min^{-1} kg^{-1} in patients with normal renal function to 50 ml min^{-1} kg^{-1} ($P < 0.05$) in patients with renal impairment but was not significantly different at 93 ml min^{-1} kg^{-1} in the dialysis group. Peak plasma levels were slightly but not significantly higher in patients with renal impairment (group 2) compared with group 1 (30 *vs* 51 ng ml^{-1}). Peak plasma level was 33 ng ml^{-1} in the dialysis group. Bioavailability after single doses of nicardipine was about 15% and there were no significant differences between the three groups.

Chronic oral dosing (Table 2) During continued administration, compared with patients with normal renal function (group 1) the AUC(0, 12 h) was significantly higher in patients with renal impairment (group 2) (509 *vs* 194 ng ml^{-1} h, $P < 0.005$) and CL/*F* was significantly lower (21 *vs* 70 ml min^{-1} kg^{-1}, $P < 0.005$). The mean peak plasma level (C_{max}) of 87 ng ml^{-1} also was significantly higher than the 38 ng ml^{-1} of group 1 ($P < 0.01$). There was a significant difference in apparent bioavailability – 18% in group 1 compared with 34% in group 2 ($P < 0.02$) – and additionally in group 2 the bioavailability had significantly changed between acute and chronic dosing from 18% to 34% ($P < 0.003$). Correspondingly, during the translation from acute to chronic dosing, CL/*F* significantly decreased in group 2 from 50 to 21 ml min^{-1} kg^{-1} (a 58% reduction) ($P < 0.005$) and non-significantly reduced in group 1 from 105 to 70 ml min^{-1} kg^{-1} (a 33% reduction). In group 2, the C_{max} increased from 51 to 87 ng ml^{-1} (by 70%) ($P < 0.006$).

Correlations between pharmacokinetic parameters and renal function indices There were significant inverse correlations between the AUC of nicardipine during chronic treatment and both GFR ($r = -0.73$, $P < 0.005$, $n = 13$) and ERPF ($r = -0.68$, $P < 0.01$, $n = 13$) (Figure 2). In addition, there were significant correlations between AUC and GFR ($r = -0.59$, $P < 0.03$, $n = 13$) and ERPF ($r = -0.55$, $P < 0.05$, $n = 13$) for the magnitude of change in AUC during the translation from acute to chronic dosing.

Pharmacodynamics

Blood pressure and heart rate Blood pressure and heart rate results after acute and chronic dosing are shown in Table 3. In relation to the baseline blood pressure, supine blood pressure was reduced after dosing to a lowest value at about 2 h. In hypertensive patients with

Table 3 Summary of blood pressure and heart rate effects

Group	*Pre-dosing*		*2 h post-dost*	
	BP (mm Hg)	*HR (beats min^{-1})*	*BP (mm Hg)*	*HR (beats min^{-1})*
Group 1				
Acute i.v.	164/100 ± 19/12	72 ± 4	147/90 ± 12/8	69 ± 6
Acute oral	170/100 ± 27/11	71 ± 9	*146/87 ± 6/9	70 ± 9
Chronic oral	162/98 ± 21/12	70 ± 9	*141/88 ± 10/6	68 ± 8
Group 2				
Acute i.v.	173/100 ± 45/14	80 ± 13	158/91 ± 35/16	70 ± 9
Acute oral	174/104 ± 41/20	81 ± 13	153/86 ± 33/13	80 ±16
Chronic oral	169/97 ± 22/9	81 ± 7	*147/84 ± 25/11	80 ± 14
Group 3				
Acute i.v.	147/82 ± 17/11	75 ± 6	144/80 ± 17/13	69 ± 6
Acute oral	152/83 ± 21/14	76 ± 4	147/89 ± 13/11	74 ± 7

* Significantly different from pre-dose value, $P < 0.05$: (ANOVA).

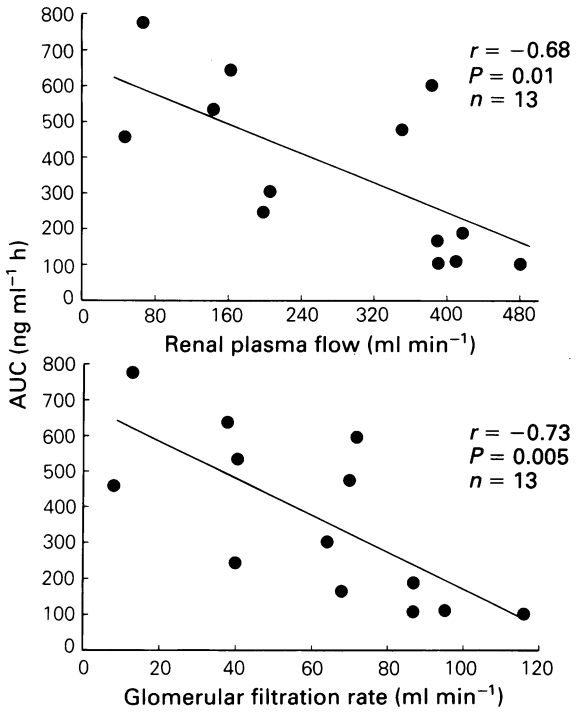

Figure 2 Relationship between AUC following multiple doses of nicardipine and indices of renal function.

normal renal function (group 1) blood pressure was reduced after chronic oral dosing from 162/98 mm Hg to 141/88 mm Hg and in the patients with renal impairment (group 2), from 169/97 mm Hg to 147/84 mm Hg. There was an upward trend in supine heart rate at 2 h after dosing.

Renal and hepatic indices There were no significant differences between the groups in apparent liver blood flow and there were no significant effects attributable to nicardipine. Patients with renal impairment had significantly lower ERPF and GFR compared to patients with normal renal function but there were no significant effects attributable to nicardipine.

Discussion

The present study has shown that the plasma clearance of nicardipine was significantly reduced in patients with renal impairment but restored towards normal in patients with end stage renal failure undergoing haemodialysis. These results are in agreement with a previous study which showed that the AUC after dosing with nicardipine (20 or 30 mg orally) was significantly higher in patients with renal impairment compared with normal subjects (Lee *et al.*, 1986). Similar results have been recently reported for nitrendipine (Ankermann *et al.*, 1989). In these studies the effect of haemodialysis on drug disposition was not studied. There are only a few studies of calcium antagonist pharmacokinetics in patients with end stage renal failure on regular haemodialysis and for nifedipine there were no significant differences (Kleinbloesem *et al.*, 1986; Martre *et al.*, 1985).

The mechanisms underlying the reduction in clearance in renal disease are not well defined but presumably reflect functional rather than structural changes. The overall correlation between the pharmacokinetic parameters, such as AUC, and the level of renal function suggests that the reduction in plasma clearance of nicardipine is related either directly to the deterioration in renal function (which is unlikely) or indirectly to the effects of renal dysfunction on hepatic metabolism. After oral administration nicardipine is subject to extensive hepatic metabolism (Higuchi *et al.*, 1977; Rush *et al.*, 1986) which may be saturable at relatively low concentrations (Graham *et al.*, 1985; Seki & Takenaka, 1977). Thus the clearance of nicardipine ultimately depends on both liver blood flow and hepatocellular function. Since there were no differences between the groups for apparent liver blood flow – albeit by a relatively crude methodology – and since there were positive and significant correlations between the level of renal function and AUC (and changes in AUC) it is possible that the reserve of the capacity limited hepatic enzyme system was reduced or inhibited in patients with renal impairment, so that hepatic metabolism was more easily saturated. Another explanation for the reduction in clearance is accumulation of metabolites (pyridine II) normally excreted by the kidney which in turn saturate or inhibit further metabolism. Although specific data on the metabolites were not available in this study, that the observed changes in clearance occurred after both oral and intravenous single dose administration is more suggestive of inhibition by an endogenous substance.

Calcium antagonist drugs generally undergo extensive hepatic metabolism and there are reports of significant reductions in plasma clearance in liver disease for verapamil, nifedipine, nisoldipine and nimodipine (Gengo *et al.*, 1987; Joeres *et al.*, 1987; Kleinbloesem *et al.*, 1986; Somogyi *et al.*, 1981; Van Harten *et al.*, 1987). The positive findings of these studies of disease state confirmed the general assumption that the metabolism of calcium antagonist drugs is dependent upon hepatic function and that the pharmacokinetics of calcium antagonists are not likely to be significantly affected by renal disease (Bortel *et al.*, 1989; Kleinbloesem *et al.*, 1985; Mooy *et al.*, 1985; Poset *et al.*, 1983). This has largely ignored the potential importance of the influence of renal disease on hepatic metabolic capacity and the possible resultant impact on the metabolism of other dihydropyridine calcium antagonists and has led to a general assumption that renal disease has no effect on the pharmacokinetics of calcium antagonists (Chellingsworth & Kendall, 1987).

Renal disease is frequently associated with alterations in protein binding resulting in increase in free drug concentrations which can more readily be distributed into tissues with a subsequent increase in the volume of distribution. The protein binding of two dihydropyridine derivatives nifedipine and nitrendipine (Ankermann *et al.*, 1989; Kleinbloesem *et al.*, 1985) was found to be reduced in patients with renal impairment resulting in a significant increase in volume of distribution. The protein binding in the present study was about 98% for the three groups and the volume of distribution was not different between groups 1 and 2.

It is perhaps surprising that patients with end stage

renal failure on regular haemodialysis behave similarly to hypertensive patients with normal renal function. It seems that the haemodialysis treatment, which occurred on the days before the pharmacokinetic study days, was able to restore metabolic activity towards normal, possibly, by clearing the blood of an inhibitory substance which interfered with hepatic metabolism.

The extent of the increase in the plasma levels of nicardipine in the patients with renal impairment raises the probability of an enhanced effect. In this respect, exaggerated responses to nifedipine (reduction in diastolic blood pressure) have been reported in renal impairment although these were apparently unrelated to plasma drug levels (Kleinbloesem *et al.*, 1985). It is not possible to draw any definite conclusions about potential effects on blood pressure or heart rate in the present study which was designed primarily to investigate pharmacokinetics.

This study emphasises the importance of studying the pharmacokinetics of drugs which are highly extracted by the liver in patients with renal impairment even if the kidney is not the major site of elimination.

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