Noninvasive assessment of the haemodynamic effects of nicardipine in normotensive subjects

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1 Calcium antagonists reduce myocardial contractility *in vitro*. Nicardipine is a dihydropyridine derivative with enhanced selectivity for vascular smooth muscle.

2 We have studied the pharmacokinetics and the haemodynamic effects that occur in man following bolus intravenous administration of nicardipine.

3 Ten normotensive male subjects received either nicardipine or placebo i.v., allocated in a randomised double-blind manner, over 60 s

4 Plasma nicardipine concentration, blood pressure, heart rate, and systolic time intervals were measured before dosing and at frequent intervals between 1 and 360 min post dosing.

5 At 160 $\mu\text{g kg}^{-1}$, adequate plasma levels of nicardipine were obtained to permit analysis of individual pharmacokinetic variables, and significant and consistent haemodynamic effects were seen.

6 After injection of nicardipine, systolic BP and the QS_2 (measure of total electromechanical systole) and QT intervals were not altered.

7 The changes in BP and heart rate were consistent with arteriolar vasodilatation.

8 The changes in PEP and LVET suggest an increase in cardiac contractility, which is unlikely to be a direct effect of nicardipine on the myocardium but rather a result of afterload reduction.

9 The close correlation of nicardipine plasma level with haemodynamic effect should permit accurate dose titration.

10 The net increase in contractility should allow nicardipine to be administered safely with β -adrenoceptor blocking drugs.

Keywords blood pressure calcium antagonist concentration effect modelling
heart rate nicardipine systolic time intervals

Introduction

Calcium antagonists or calcium (slow) channel blocking drugs are being introduced into clinical practice as anti-hypertensive and anti-anginal agents (Guazzi *et al.*, 1977; Lederballe Pedersen & Mikkelsen 1978; Subramanian *et al.*, 1980). They interfere with excitation–contraction coupling in cardiac and vascular smooth muscle by blocking flux of calcium ions into cells during phase III of the action potential (Cranefield *et al.*, 1974; Singh, 1972). Their direct effect on myocardium, *in vitro*, is depression of contractility

or a negative inotropic effect. However, individual drugs vary in their tissue specificity. The dihydropyridine derivatives are relatively selective for vascular smooth muscle (Millard *et al.* 1982), causing arteriolar vasodilatation. The resulting fall in blood pressure causes reflex, sympathetically-mediated cardiac stimulation, which may overcome any direct myocardial depressant effect of the drug (Bellocci *et al.*, 1981). Therefore, these drugs also may have a place, as offloading agents in the treatment of cardiac failure.

Nicardipine (2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[2-(*N*-benzyl-*N*-methylamino)] ethyl ester 5-methyl ester hydrochloride) is a new calcium antagonist which is currently being evaluated in angina and hypertension. Compared with nifedipine, it has been shown to have enhanced *in vitro* specificity for peripheral vascular smooth muscle (Clarke *et al.*, 1983). Both oral and intravenous formulations of nicardipine have been made. There is preliminary evidence that an increase in cardiac performance accompanies the reduction in blood pressure occurring after nicardipine treatment (Iliopoulou *et al.*, 1983). The purpose of the present study was to establish an intravenous dose of nicardipine that would produce significant haemodynamic effects in normotensive man, measurable by noninvasive techniques, and to determine its pharmacokinetics and concentration-effect relationships.

Methods

Fourteen normotensive male volunteers, aged 21–40 years and on unrestricted sodium intake, were studied in two phases. In the dose-finding phase I, nicardipine or inert vehicle was administered to ten subjects in a randomised double-blind design in which nicardipine doses of 10, 20, 40, 80, and 160 $\mu\text{g kg}^{-1}$ were given intravenously over 1 min. Two subjects were studied at each dose, beginning with the lowest dose and with increasing doses being given sequentially. Treatments were separated by at least 1 week. Each subject fasted from 22.00 h on the prestudy day. Smoking, alcohol, and caffeine-containing beverages were prohibited in the 24 h before each study.

Subjects were admitted to the Clinical Pharmacology Research Unit at 08.30 h. Intravenous cannulae were inserted into each forearm to permit drug administration and sampling of blood. The subjects then rested supine for 30 min. Blood pressure (BP), heart rate (HR), and systolic time intervals (STI) were measured (supine) before drug administration and at 1, 2, 3, 4, 5, 10, 15, 20, 30, 60, 90, 120 min and thereafter every 60 min until 360 min after dosing. Blood was withdrawn from the contralateral arm for nicardipine measurement at 0, 3, 5, 10, 20, 30, 60, 90, and 120 min and thereafter every 60 min to 360 min. Subjects were given a standard snack lunch at 13.00 h. Blood pressure

was measured by a semi-automatic sphygmomanometer (Bosomat II, Bosch and Sohn) and heart rate by electrocardiogram; systolic time intervals were determined by an on-line computerized signal averaging program based on 30 s of recording. The STI indices obtained were corrected for heart rate, employing the technique described by Kelman *et al.* (1981).

Blood samples were received into lithium heparin tubes in melting ice, and, following separation, plasma was stored at -20°C until assayed. Nicardipine was assayed using an h.p.l.c. method which allowed separation of the parent drug and its haemodynamically inactive metabolite (Wu *et al.*, 1984).

During phase I, clear haemodynamic changes were seen in both subjects who received 160 $\mu\text{g kg}^{-1}$ of nicardipine. Consequently, in the second phase of the study another four subjects were given either this dose or placebo in a randomised double-blind design.

Routine haematological, biochemical, and electrocardiographic screening was undertaken both before and after the study. The study was approved by the Research and Ethics Committee of the Northern District of the Greater Glasgow Health Board, and only subjects giving written, informed consent to participate were studied.

Results

Side effects were limited to sensations of flushing and slight palpitation in the first 3–4 min after injection of the drug, although these effects sometimes were noted even at low dose. One subject who received 40 $\mu\text{g kg}^{-1}$ experienced nausea in the evening of the study day, but this was not obviously related to nicardipine. Screening of clinical laboratory data revealed no unfavourable effects.

At doses between 10 and 80 $\mu\text{g kg}^{-1}$, some evanescent, inconsistent haemodynamic changes did occur, in particular slight shortening of the pre-ejection period (PEP) and prolongation of the left ventricular ejection time (LVET). In addition, the plasma concentrations of nicardipine following these doses did not permit adequate characterisation of individual pharmacokinetic variables. Accordingly, individual pharmacokinetics were calculated only for the six subjects who received 160 $\mu\text{g kg}^{-1}$ nicardipine. These kinetic values were then employed in defining drug concentration-effect relationships for blood

Table 1 Fitted pharmacokinetic parameter values (s.e. mean)

Subject	Dose (mg)	A (ng/ml)	λ_1 (h^{-1})	B (ng ml $^{-1}$)	λ_2 (h^{-1})	r 2
1	11.2	783.3 (136.7)	28.1 (3.8)	129.0 (10.9)	1.20 (0.16)	0.99
2	11.5	765.6 (143.2)	18.2 (4.0)	119.6 (26.9)	0.85 (0.31)	0.99
3	10.2	332.5 (28.2)	5.3 (0.9)	36.2 (19.8)	0.46 (0.38)	0.99
4	10.9	1061.0 (23.0)	21.0 (0.4)	132.0 (5.1)	1.27 (0.11)	0.99
5	10.9	1408.0 (291.0)	42.6 (4.4)	103.1 (6.1)	1.23 (0.12)	0.99
6	9.6	331.1 (13.9)	3.74 (0.5)	42.8 (2.4)	0.37 (0.04)	0.99

Table 2 Derived pharmacokinetic parameter values

Subject	k_{12} (h^{-1})	k_{21} (h^{-1})	Clearance		V_{ss} (l)	$t_{1/2}$ (min)
			k_{10} (h^{-1})	(l h^{-1})		
1	17.6	5.0	6.7	83.0	55.6	34.6
2	11.0	3.2	4.8	62.7	57.7	49.1
3	2.2	0.9	2.6	72.3	92.5	89.8
4	11.1	3.5	7.7	70.6	38.4	32.7
5	26.8	4.1	12.9	93.3	54.3	33.8
6	1.5	0.8	1.8	47.1	76.8	112.0

pressure, heart rate, PEP, LVET, QS $_2$ and QT. The calculations were made using a Nodecrest V77/600 computer.

Pharmacokinetics

The fitted kinetic values for the six subjects who

Figure 1 Plasma concentration following intravenous bolus administration (160 μ g kg^{-1}) in a representative subject ($t_1 = 2.3$ min $t_{1/2} = 4.9$ min).

received 160 μ g kg^{-1} nicardipine are shown in Table 1. Plasma kinetics were described satisfactorily by the bi-exponential equation:

$$C_p = Ae^{-\lambda_1 t} + Be^{-\lambda_2 t}.$$

Excellent fitting was obtained, and the coefficient of determination (r^2) was not less than 0.99 in all six subjects. From this, inter-compartmental constants and other pharmacokinetic parameters were derived, and these are shown in Table 2. The results obtained from a representative individual are shown in Figure 1. For the six subjects, t_1 , λ_1 was 4.3 ± 4.1 min (mean $\pm$ s.d.) and represented a distribution phase. $t_{1/2}$ was also fairly rapid at 58.7 ± 34.0 min. Clearance was high at 71.5 ± 16.1 l h^{-1} , and the apparent volume of distribution at 62.6 ± 19.1 l reflected fairly low tissue binding of nicardipine. These mean values were constrained by the relatively high apparent volume of distribution and the relatively low clearance in subject 6; the reason for this was not apparent.

Figure 2 Concentration-effect model. C = central compartment. P = peripheral compartment. ED = effect compartment. k_{12} , k_{21} , and k_{1e} are inter-compartmental rate constants. k_{10} = the elimination rate constant. k_{eq} = the elimination rate constant from the effect-compartment.

Table 3 Effect modelling parameters – diastolic blood pressure

Subject	m (mmHg $\mu\text{g}^{-1} \text{ml}^{-1}$)	k_{eq} (min^{-1})	r^2
1	-0.037	0.734	0.68
2	-0.058	0.115	0.69
3	-0.033	0.422	0.29
4	-0.047	0.201	0.54
5	-0.018	0.364	0.31
6	-0.182	0.012	0.52

Table 4 Effect modelling parameters – heart rate

Subject	m (beats $\text{min}^{-1} \mu\text{g}^{-1} \text{ml}^{-1}$)	k_{eq} (min^{-1})	r^2
1	0.121	0.638	0.94
2	0.055	0.634	0.89
3	0.101	1.560	0.91
4	0.051	0.784	0.92
5	0.155	0.172	0.88
6	0.050	0.112	0.98

Blood pressure and heart rate

In these normotensive subjects only small changes in systolic blood pressure were observed, and these did not achieve statistical significance (ANOVA). By contrast, diastolic pressure fell rapidly and was reduced significantly between 1 and 30 min post-dosing ($P < 0.01$), the average maximum reduction being 22.3 mm Hg. This reduction in diastolic blood pressure was accompanied by a brisk rise in heart rate that was highly significant between 1 and 30 min ($P < 0.001$), the average maximum increase being 34.6 beats min^{-1} . No significant changes in blood

Figure 3 Changes in heart rate and diastolic blood pressure following nicardipine ($160 \mu\text{g kg}^{-1}$) intravenously in a representative subject.

pressure or heart rate were observed following placebo.

Concentration-effect modelling was undertaken using the model shown in Figure 2 (Sheiner *et al.*, 1979). Using the kinetic values already obtained, the effects on diastolic blood pressure and heart rate were satisfactorily described by an equation having the form

$$E = m \cdot C_E + i,$$

where E = effect, m = change in effect/unit change in drug concentration in the effect-compartment, and $C_E = f(A, \lambda_1, B, \lambda_2, k_{eq}, t)$, described by the equation

$$C_E = \frac{A \cdot k_{eq}}{\lambda_1 - k_{eq}} \cdot e^{-k_{eq}t} - e^{-\lambda_1 t} + \frac{B \cdot k_{eq}}{\lambda_2 - k_{eq}} \cdot e^{-k_{eq}t} - e^{-\lambda_2 t}$$

The intercept, i , represents the 'effect' at time zero; that is, before drug administration, $E = i$. In considering the changes in effect produced by the drug, it therefore may be regarded as zero.

The effect of nicardipine on diastolic blood pressure of the six subjects is shown in Table 3. The r^2 values are only moderately good, reflecting the relative variability of diastolic blood pressure

Table 5 Mean effect parameters – LVET and PEP

	m (m^2 , $\mu g^{-1} ml^{-1}$)	k_{eq} (min^{-1})	r^2
Left ventricular ejection time	80.0	2.32	0.77
Pre-ejection period	-83.0	0.14	0.69

there was a tendency to reduction in QS_2 . However, this was somewhat variable and, when corrected for heart rate, did not show significant alteration.

QT interval With increasing doses of nicardipine, T wave amplitude was reduced making measurement difficult. Others have noted a similar effect following nicardipine (Iliopoulou *et al.*, 1983). When corrected for heart rate, measured changes in QT did not achieve statistical significance.

LVET, when corrected for heart rate, was prolonged between 1 and 30 min following nicardipine, which was significant ($P < 0.01$). The maximum prolongation (26.9 ms) occurred very early, 2 min post-injection.

PEP was shortened significantly ($P < 0.01$), between 1 and 30 min; the maximum reduction (17.3 ms) occurred 10 min after injection of nicardipine. LVET and PEP changes in a representative subject are illustrated in Figure 4.

Concentration–effect relationships for these changes in systolic time intervals were satisfactorily modelled in five of the six subjects, and the mean values for m , k_{eq} and r^2 are shown in Table 5. Approximately 70% of the observed changes in both indices are accounted for by measured changes in plasma nicardipine. The values of m are equivalent to 0.013 ng ml^{-1} of nicardipine in the effect compartment per ms change in LVET and 0.012 ng ml^{-1} per ms change in PEP.

Discussion

The pharmacokinetics, haemodynamic effects, and concentration–effect relationships of the calcium antagonist nicardipine were studied following intravenous injection over 1 min in normotensive subjects. At a dose of $160 \mu g \text{ kg}^{-1}$, individual kinetics could be adequately char-

Figure 4 Changes in left ventricular ejection time and pre-ejection period following nicardipine ($160 \mu g \text{ kg}^{-1}$) intravenously in a representative subject.

measurement, even with automated equipment. The mean slope, $m = 0.062$, represents $16.1 \mu g \text{ ml}^{-1}$ nicardipine in the effect-compartment per 1 mm Hg fall in diastolic blood pressure. A k_{eq} of $0.308/\text{min}$ (mean) represents a minimal 'lag' between plasma concentration and haemodynamic effect.

Heart rate change was modelled similarly, and the results are shown in Table 4. The slope, $m = 0.089$, represents $11.2 \mu g \text{ ml}^{-1}$ nicardipine in the effect-compartment per 1 beat min^{-1} heart rate change. Again there was little lag in effect ($k_{eq} = 0.65/\text{min}$). The r^2 values were higher, probably reflecting greater accuracy in heart rate measurement. They suggest that measured changes in plasma nicardipine accounted for about 92% of observed heart rate change. Changes in diastolic blood pressure and heart rate in a representative subject are shown in Figure 3.

Systolic time intervals

QS_2 is a measure of total electromechanical systole. As would be expected, changes following nicardipine broadly mirrored heart rate, that is,

acterized, and consistent, significant haemodynamic changes were produced.

Plasma kinetics of nicardipine were described by a two-compartment model. $t_{1/2, \lambda_1}$ was very short, probably representing a distribution phase. Of greater interest is the $t_{1/2, \lambda_2}$, the terminal elimination half-life. Nicardipine is cleared from plasma quite rapidly, with a terminal elimination half-life averaging less than one hour.

Plasma concentration of nicardipine and changes in blood pressure, heart rate, and myocardial function, as reflected in systolic time interval measurements, correlated quite closely. Because of this, bolus intravenous injection does not appear to be a suitable route of nicardipine administration. Firstly, the effects are short lived, and secondly, it is also likely that the high peak concentrations achieved following bolus administration were responsible for the transient side effects of flushing and palpitation.

On the other hand, the results mean that close titration of drug administration to achieve desired haemodynamic effects should readily be possible during continuous intravenous infusion. This would be of particular value in several clinical applications, including hypertensive crisis and acute heart failure. If clearance were found to be equally rapid following oral dosing, this characteristic would be less advantageous.

Reduction of diastolic blood pressure with accompanying tachycardia, even when the subjects were supine, is typical of a drug acting principally as a dilator of arteriolar resistance vessels, and this is in keeping with the marked selectivity for peripheral vascular smooth muscle already noted *in vitro*. The absence of a significant effect on supine systolic blood pressure in these normotensive subjects is not surprising and results from the baroreceptor-mediated compensatory changes which are manifested in part by the tachycardia.

Such mechanisms are probably also responsible for the changes in myocardial function seen following nicardipine in this study; these are of potential therapeutic importance. We assessed left ventricular performance non-invasively by STI measurement, employing a computer program. Complete analysis of STI indices measured at all time points from two subjects was undertaken in about half an hour. Using this methodology, repeated measurements of LV function over time following drug administration

can be undertaken readily and can be analysed easily.

Following correction for heart-rate changes, LVET was prolonged significantly and PEP was shortened significantly during the time when diastolic blood pressure was reduced. These changes reflect increased myocardial contraction. It has been shown that taken together, LVET and PEP measurements can provide approximately 90% of the information on left ventricular ejection fraction that can be obtained by cardiac catheterisation (Weissler *et al.*, 1978). Maximum discrimination may be obtained by calculation of the PEP/LVET ratio, but it is difficult to regard this as an independent index of myocardial function. Myocardial contraction must be distinguished from contractility, which only can be measured *in vitro*. Depression of contractility is the direct effect of calcium antagonists on myocardium *in vitro*.

In the present study, however, the changes in PEP and LVET suggest a marked net increase in myocardial performance. Such a change could be mediated either by a direct positive inotropic drug effect or reflexly by an increase in preload or a reduction in afterload, secondary to dilatation of the resistance vessels. Systolic time interval measurement cannot separate these potential influences. A direct positive inotropic effect is obviously unlikely. The pronounced changes in diastolic blood pressure suggest that the major factor responsible for the potentially favourable inotropic effects seen in this study is the sympathetically-mediated increased drive to the heart secondary to afterload reduction.

Nicardipine is a new calcium antagonist available for intravenous and oral use whose haemodynamic effects following intravenous administration are closely related to plasma drug concentration. It appears to lower blood pressure by arteriolar dilatation. It is likely that this marked afterload reduction promotes sympathetically-mediated positive inotropic (as well as chronotropic) effects on the myocardium; these more than compensate for any direct depressant effect on myocardial contractility. In contrast with some other calcium antagonists, it is therefore likely that nicardipine can safely be administered together with β -adrenoceptor blocking drugs in anti-hypertensive and anti-anginal regimens.

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