Nicardipine: pharmacokinetics and effects on carotid and brachial blood flows in normal volunteers

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1 The effects of nicardipine, 20 mg, three times daily, nicardipine slow release, 30 mg, twice daily and a placebo on brachial and carotid arteries diameters and flows have been investigated by the pulsed Doppler technique during a single blind and cross-over study performed in six healthy volunteers. Simultaneously, nicardipine plasma levels and relative bioavailability were determined.

2 Nicardipine significantly increased brachial and carotid arteries diameters (by 16 and 10% respectively) and flows (by 60 and 35% respectively). These effects peaked after 4 h and lasted no longer than 6 h. Forearm vascular resistance was significantly decreased. Hence nicardipine dilated both large and small arteries.

3 Nicardipine slow release elicited the same effects on brachial and carotid arteries diameters and flows as nicardipine. These effects peaked at 6 h and lasted up to 10 h.

4 Although the profiles of the pharmacodynamic effects and of the kinetics of nicardipine were almost parallel in each individual after administration of both nicardipine formulations, there was no correlation between the nicardipine plasma relative bioavailability and its effects on brachial and carotid arteries blood flows when considering all subjects together.

Keywords pulsed Doppler nicardipine arterial blood flows pharmacokinetics

Introduction

Calcium channel blocking drugs are presently used in a number of indications, including angina pectoris, arterial hypertension and Raynaud's phenomenon, because of their peripheral vascular dilating and relaxing effects (McAllister, 1982).

Thus, it has been shown in hypertensive patients, that nifedipine and diltiazem do increase arterial diameters and flows and decrease peripheral vascular resistances (Simon *et al.*, 1983).

Nicardipine is a new calcium channel blocking agent (Takenaka *et al.*, 1976; Hof, 1983)

endowed with peripheral vasodilating properties, especially for the cerebral vascular territory (Takenaka & Handa, 1979; Yamamoto *et al.*, 1983).

However this drug has in man a relatively short elimination half-life ($t_{1/2}$) approximately 2 h (Seki & Takenaka, 1977). Hence, the present study had three major goals: (a) investigate in the normal subject the kinetics of nicardipine effects on brachial and carotid blood flows, assessed by the pulsed Doppler technique, (b) compare these kinetics to those of a slow release nicardipine formulation and (c) investi-

gate a possible relationship between the clinical effects and the pharmacokinetics of nicardipine, during a single blind and cross-over trial performed in six healthy volunteers.

Methods

Subjects

Six volunteers (three women and three men), aged 20–28 years, weighing 48–77 kg, with normal ECG and healthy on the basis of medical history and physical examination, took part in the study. All of them gave written informed consent for the study which was approved by the Hospital Ethical Committee. They were given orally and under single blind conditions nicardipine, nicardipine slow release (SR) and a placebo in a random order at 2 week intervals. The drugs were administered over a 4 day period according to the following schedule: nicardipine, 20 mg, or placebo at 9.00, 17.00 and 23.00 h, and nicardipine SR, 30 mg, at 09.00 and 21.00 h. Randomization was based on a latin square design. None of the subjects was receiving any other medication throughout the study.

Parameters investigated

The following parameters were investigated before initiating any treatment and at regular intervals on the fourth day of drug administration (experimental day):

Heart rate (HR) was obtained from an electrocardiogram and systolic and diastolic blood pressures (SAP and DAP) were measured by means of a brachial cuff sphygmomanometer. The values shown for blood pressure are the means of three consecutive determinations. Mean arterial pressure (MAP) was calculated as:

$$\text{MAP} = \text{DAP} + \frac{\text{SAP} - \text{DAP}}{3}$$

Arterial haemodynamics (diameter and flow) of the brachial and carotid arteries were measured using a bidimensional pulsed Doppler system (Echovar Doppler pulsé, Alvar Electronic) as previously described by Safar *et al.* (1981) (see below).

Biological parameters: plasma renin activity (PRA) was measured by radioimmunoassay according to Ménard *et al.* (1972). Plasma aldosterone (PA) was measured by radioimmunoassay according to Pham Hu *et al.* (1974). Plasma noradrenaline (NA) and

adrenaline (A) were determined by the double isotope radioenzymatic method described by Brown & Jenner (1981).

Nicardipine pharmacokinetics: blood and urine levels of nicardipine were measured after extraction and oxidation with nitrous oxide by a gas chromatographic method with electron capture detector (Higuchi *et al.*, 1975). The area under blood drug concentration/time curve (AUC_C) was calculated using the trapezoidal method in order to estimate nicardipine relative bioavailability.

Measurement of arterial haemodynamics

The Echovar pulsed Doppler system (pulsed emission characteristics: 8 MHz, 0.5–2 μs , every 15–30 μs) has two main original characteristics: (a) an electronic gate which selects the signals reflected at a given time from the emission (reception time delay t) and the reception duration (d). Adjustment (by 0.5 μs steps) of t and d allows determination of the distance between red cells and the transducer and of the thickness of the sample volume, respectively. In these conditions, with the smallest sample volume size (1 μs for an emission duration of 1 μs), the depth of the gate is progressively increased to cross the lumen vessel. The time delays of the first (t_1) and of the last (t_2) velocity waves correspond respectively to the proximal and distal vessel walls and the diameter of the vessel is calculated as:

$$D = \frac{C}{2(t_2 - t_1) \sin \Theta},$$

where Θ is the angle between the ultrasonic beam and the vessel axis and C the ultrasonic speed in the tissues (1540 m/s); (b) a double transducer which allows the precise measurement of Θ : two transducers forming a $\alpha = 120^\circ$ angle are symmetrically located at the extremity of the exploring probe. Thus, by adjusting the probe position so that the two velocity curves become equal in amplitude, i.e., when the probe is perpendicular to the vessel axis, the Θ angle between each ultrasonic beam and the vessel axis equals $\frac{\alpha}{2}$, i.e. a 60° angle.

The subjects are investigated in the supine position after a preliminary rest period of 40 min. The Doppler signals are monitored throughout the study by loudspeaker and recorded on a Hewlett-Packard apparatus (HP 7754 A). After determining by palpation the pathway of the brachial or carotid artery, the probe is positioned so that the two velocity

curves, successively recorded for a duration of ten cardiac cycles, are equal in absolute values. Proximal and distal arterial walls are located by moving the depth of the sample volume as described above. Then, arterial blood velocity through the vessel cross section is obtained by adjusting the electronic gate to the corresponding arterial depth and width. The calibration voltage of the apparatus corresponds to a velocity of 38 cm/s for an incidence angle of 60°. Mean velocity (V_m , cm/s) in the vessel is calculated by electronic integration of the velocity curve (mean of 10 successive cardiac cycles for each transducer). All determinations are repeated six times in each patient. The estimated vessel mean volumic flow Q (ml/min) is calculated as: $Q = (D^2/4 \times V_m) \times 60$, and the areas under blood flows/time curves (AUC_F) are calculated using the trapezoidal method.

Finally, the brachial vascular resistance (expressed in mm Hg/ml.s) is calculated as the MAP/ Q ratio.

Design of the study

On day 1 and after overnight fasting, the subjects arrived at the laboratory at 8.00 h.

After a rest period of 40 min in the supine position, the control clinical parameters (CP): HR, AP, carotid blood flow (CBF) and brachial blood flow (BBF), were measured, and blood samples for biological parameters: PRA, PA, NA and A determinations were collected. Then, nicardipine or nicardipine SR or the placebo were administered, starting at 09.00 h (t -72) and according to the previously mentioned schedule on days 1, 2 and 3 under ambulatory conditions. The volunteers but not the Doppler investigator knew the nature of the treatment administered.

On day 4, the subjects arrived at the laboratory at 07.45 h after overnight fasting. An indwelling intravenous catheter with a heparinized lock was inserted into a forearm vein and the subjects rested for a 40 min period in the supine position. At 08.45 h (t 0), CP were recorded and blood samples for determination of biological parameters and nicardipine blood levels were collected, after which the treatment was immediately administered (09.00 h). CP were again determined 1, 2, 4, 6, 8 and 12 h and biological parameters 1, 2, 3 and 4 h after the 09.00 h drug intake. Additional blood samples for nicardipine plasma levels determination

Table 1 Effects of nicardipine (N), nicardipine slow release (NSR) and placebo (P) on systolic and diastolic arterial pressures and heart rate at t -72 (Day 1) and from t 0 to t 12 (Day 4).

		Day 1				Day 4				
		t -72	t 0	t 1	t 2	t 4	t 6	t 8	t 10	t 12
Systolic arterial pressure (mmHg)	P	105 ± 3	106 ± 3	109 ± 2	109 ± 4	103 ± 3	107 ± 4	107 ± 4	107 ± 5	111 ± 4
	N	105 ± 8	106 ± 4	114 ± 4	111 ± 6	106 ± 3	109 ± 4	112 ± 4	107 ± 2	109 ± 2
	NSR	111 ± 5	108 ± 3	118 ^a ± 4	114 ± 4	107 ± 4	113 ± 4	114 ± 3	109 ± 4	111 ± 4
Diastolic arterial pressure (mmHg)	P	67 ± 3	65 ± 4	63 ± 4	64 ± 4	65 ± 4	57 ± 3	64 ± 3	62 ± 3	66 ± 3
	N	68 ± 2	69 ± 3	70 ± 4	64 ± 5	66 ± 3	63 ± 3	67 ± 3	67 ± 2	63 ± 2
	NSR	71 ± 2	75 ± 4	72 ± 3	71 ± 2	73 ± 4	66 ± 3	71 ± 2	70 ± 4	65 ± 3
Heart rate (beats/min)	P	60 ± 2	58 ± 2	68 ± 4	70 ± 3	60 ± 3	68 ± 2	63 ± 3	62 ± 2	66 ± 2
	N	64 ± 2	63 ± 3	76 ± 7	72 ± 4	67 ± 3	73 ± 3	67 ± 3	67 ± 2	66 ± 3
	NSR	67 ± 2	63 ± 3	72 ± 4	75 ± 3	66 ± 4	70 ± 2	66 ± 3	61 ± 2	70 ± 5

Values are means ± s.e. mean. ^a: $P < 0.05$ vs placebo.

were drawn 1, 2, 4, 6, 8, 9, 10, 12, 14, 15, 16, 18, 20 and 22 h after the 09.00 h nicardipine or placebo administration and 1, 2, 4, 6, 8, 10, 12, 13, 14, 16, 18, 20, 22 and 24 h after nicardipine SR administration. Urine was collected during the 12 h period preceding day 1 (control) and at day 4, every 8 h after the 09.00 h nicardipine or placebo administration and every 12 h after the 09.00 h nicardipine SR intake. Finally, subjects were asked to fill out a questionnaire as to their general tolerance to the drugs.

Light meals were served at 09.15 h, 13.30 h and 19.30 h. No tea, coffee, alcoholic beverages or smoking were allowed during the entire trial period.

Drugs used

Nicardipine formulations used were either 20 mg tablets or 30 mg slow release capsules, supplied by Laboratoires Sandoz, France. Doses refer to nicardipine hydrochloride.

Statistical analysis

Results are given as means $\pm$ s.e. mean. Statistical analysis between the three different groups was performed on the differences *vs* pre-

drug values using analysis of variance followed by comparison of means by Student's *t*-test.

Correlations between nicardipine plasma levels and regional blood flows, and between AUC_C and AUC_F were calculated by means of linear regression analysis.

Results

Arterial blood pressure and heart rate

Table 1 shows that throughout the experiment there were no differences between the three treatments as to their effects on systolic and diastolic blood pressure and heart rate.

Brachial artery haemodynamics

Control values of brachial blood flow (BBF) before initiating any treatment (day 1, *t*-72) were respectively 105 ± 9 (placebo), 110 ± 12 (nicardipine) and 103 ± 9 (nicardipine SR) ml/min. Figure 1 illustrates the kinetics of the variations of brachial blood flow from these control values induced on day 4 by the three treatments.

On day 4 at *t*0, BBF values in the nicardipine, nicardipine SR and placebo treated subjects were almost identical to the corresponding

Figure 1 Kinetics of the brachial blood flow variations (ml/min) as compared with pretreatment (*t*-72) values, induced by nicardipine (●), nicardipine SR (▲) and placebo (○) during the 12 h following the first drugs administration on day 4. Significant variations as compared to placebo **P* < 0.05; ***P* < 0.01. ↑: drug administration.

values on day 1 (t -72). Nicardipine-induced increase in BBF was significant 2, 4 and 6 h after drug intake with a peak increase (+ 61%) at 4 h. After 8 h, just before the second nicardipine administration, BBF value was still slightly but not significantly increased but the second nicardipine administration induced the same increases in BBF as the first. Nicardipine SR also significantly increased BBF and this effect (+50-+65%) lasted up to 10 h after drug intake. Nicardipine as well as nicardipine SR significantly increased brachial artery diameter with a maximal effect at 4 h (nicardipine) or 6 h (nicardipine SR) (Table 2). At these times, and as compared to t -72, forearm arterial resistance had decreased by 34% ($P <$

0.01) with nicardipine and by 32% ($P < 0.01$) with nicardipine SR.

The overall increases in BBF [AUC_F from t_0 to t_8 ($AUC_{FO \rightarrow 8\text{ h}}$) for nicardipine, 20 mg and AUC_F from t_0 to t_{12} ($AUC_{FO \rightarrow 12\text{ h}}$) for nicardipine SR, 30 mg] induced by the two treatments were almost identical ($426.2\text{ ml min}^{-1}\text{ h}$ and $488.2\text{ ml min}^{-1}\text{ h}$ respectively).

Carotid artery haemodynamics

Control values of carotid blood flow (CBF) before initiating any treatment (day 1, t -72) were respectively 455 ± 19 (placebo), 507 ± 24 (nicardipine) and 537 ± 16 (nicardipine SR) ml/min. Figure 2 illustrates the kinetics of the

Figure 2 Kinetics of the carotid blood flow variations (ml/min) as compared with pretreatment (t -72) values, induced by nicardipine (●), nicardipine SR (▲) and placebo (○) during the 12 h following the first drugs administration on day 4. Significant variations as compared to placebo: * $P < 0.05$; ** $P < 0.01$. ↑ : drug administration.

variations of CBF from these control values induced on day 4 by the three treatments.

On day 4 at t_0 , CBF values in the nicardipine and placebo treated subjects were almost identical to those observed on day 1 at t_{-72} . In contrast, in the nicardipine SR treated subjects, CBF value on day 4 at t_0 (618 ± 38 ml/min) was increased as compared to the corresponding value (537 ± 16 ml/min) on day 1 at t_{-72} . However the difference, which was mainly due to two subjects in whom CBF was increased by respectively 60 and 20%, did not reach significance ($P = 0.07$). Nicardipine-induced increase in CBF was significant 1, 2 and 4 h after drug intake with a peak increase (+34%) at 2 h. After 8 h, just before the second nicardipine administration, CBF had returned to its t_0 value but the second nicardipine administration induced the same increases in CBF as the first.

Nicardipine SR also increased significantly CBF and this effect (30–40%) lasted up to 10 h after drug intake. Nicardipine as well as nicardipine SR significantly increased carotid artery diameter with a maximal effect at 4 h (nicardipine) or at 6 h (nicardipine SR) (Table 2).

The overall increase in CBF induced by nicardipine SR, 30 mg ($AUC_{FO \rightarrow 12\text{ h}} 1120.3$ ml min^{-1} h) was greater, although not significantly than that induced by nicardipine, 20 mg ($AUC_{FO \rightarrow 8\text{ h}} = 695.0$ ml min^{-1} h).

Biological parameters (Table 3)

Both nicardipine and nicardipine SR transiently but significantly increased PRA 1 h after their administration. One hour later, this effect had disappeared. PA, NA and A were not drug affected.

Table 3 Effects of nicardipine (N), nicardipine slow release (NSR) and placebo (P) on plasma renin activity, plasma aldosterone, plasma noradrenaline and adrenaline observed at t_{-72} (Day 1) and from t_0 to t_4 (Day 4).

		Day 1 t_{-72}	t_0	t_1	Day 4 t_2	t_3	t_4
Plasma renin activity (ng l^{-1} min^{-1})	P	16.2 ± 3.7	17.8 ± 4.9	23.7 ± 5.9	21.2 ± 5.9	22.7 ± 7.7	18.2 ± 4.3
	N	14.5 ± 2.5	16.7 ± 3.5	58.3 ^a ± 10.8	24.5 ± 2.3	23.8 ± 5.6	—
	NSR	13.3 ± 3.5	17.5 ± 3.8	23.8 ^a ± 5.2	29.7 ± 10.8	23.0 ± 6.8	22.8 ± 5.8
Plasma aldosterone (ng/100 ml)	P	8.1 ± 3.3	8.7 ± 2.1	7.3 ± 1.8	4.2 ± 0.9	4.7 ± 0.7	5.6 ± 1.2
	N	8.2 ± 1.4	9.2 ± 1.9	9.7 ± 2.1	8.1 ± 1.1	6.2 ± 1.1	—
	NSR	9.2 ± 2.5	10.7 ± 1.0	8.4 ± 1.0	7.1 ± 1.1	8.5 ± 2.1	12.3 ± 2.7
Plasma noradrenaline (pg/ml)	P	419 ± 52	464 ± 89	422 ± 63	472 ± 41	404 ± 45	365 ± 27
	N	412 ± 53	435 ± 86	437 ± 85	355 ± 60	432 ± 57	—
	NSR	396 ± 36	450 ± 93	—	501 ± 46	451 ± 46	404 ± 41
Plasma adrenaline (pg/ml)	P	26 ± 7	23 ± 6	12 ± 3	22 ± 7	13 ± 4	15 ± 4
	N	31 ± 10	30 ± 9	21 ± 7	10 ± 3	21 ± 5	—
	NSR	34 ± 5	30 ± 7	—	25 ± 6	29 ± 10	17 ± 4

Values are means $\pm$ s.e. mean. ^a: $P < 0.05$ vs placebo.

Figure 3 Kinetics of nicardipine plasma levels measured on day 4 after administration of nicardipine (●) and nicardipine SR (▲). ↑: drug administration.

Nicardipine pharmacokinetics

Figure 3 illustrates the kinetics of nicardipine plasma levels during the 24 h period following drug intake on day 4 at t_0 .

After nicardipine, $t_{\max}$ value was 1 h after each of the three administrations but $C_{\max}$ values showed some variations: 68.7 ± 15.1 ng/ml (range 13.5–102.1) on the first dose; 21.8 ± 6.4 ng/ml (range 3.7–45.9) on the second dose and 29.4 ± 8.1 ng/ml (range 6.3–58) on the third dose. Nicardipine plasma relative bioavailability (AUC_C) after the second and third administrations was reduced by approximately 40% as compared to that after the first administration. Nicardipine plasma levels could be measured in all subjects up to 8 h after administration.

After nicardipine SR, $t_{\max}$ was 1 h after the 09.00 h administration and 4 h after the 21.00 h administration. $C_{\max}$ values were respectively: 17.8 ± 6.3 ng/ml (range 8.3–48.8) on the first dose and 9.3 ± 2.7 ng/ml (range 1.9–20.9) on the second dose. Nicardipine plasma relative bioavailability (AUC_C) after the second administration was reduced by approximately 30% as compared to that after the first administration. Nicardipine plasma levels could be measured up to 12 h after nicardipine SR administration in five out of the six subjects.

Mean AUC_C values were respectively: for nicardipine $AUC_{C0 \rightarrow 22\text{ h}} = 370.9 \pm 59.1$ mg

$\text{ml}^{-1}\text{ h}$ and for nicardipine SR $AUC_{C0 \rightarrow 24\text{ h}} = 155.2$ $\text{ng ml}^{-1}\text{ h}$ indicating that nicardipine plasma relative bioavailability after administration of the SR formulation was reduced by approximately 60% as compared to that observed after the ordinary formulation.

Urinary elimination of unchanged nicardipine during the 24 h period starting on day 4 at t_0 was very low, ranging from 1.6 to 3.5 $\mu\text{g}/24\text{ h}$ after nicardipine and from 0.6 to 2.1 $\mu\text{g}/24\text{ h}$ after nicardipine SR, indicating a low renal clearance of the drug.

Correlations

The profiles of the pharmacodynamic effects (CBF and BBF) and of the kinetics of nicardipine were almost parallel in each individual after administration of either nicardipine or nicardipine SR. However, considering all subjects together, there was no correlation:

either between nicardipine plasma relative bioavailability ($AUC_{C0 \rightarrow 8\text{ h}}$) and the drug overall effects ($AUC_{F0 \rightarrow 8\text{ h}}$) on BBF ($r = 0.095$, NS) and CBF ($r = 0.730$, NS) after nicardipine administration, or between nicardipine plasma relative bioavailability ($AUC_{C0 \rightarrow 12\text{ h}}$) and the drug overall effects ($AUC_{F0 \rightarrow 12\text{ h}}$) on BBF ($r = 0.101$, NS) and CBF ($r = 0.218$, NS) after nicardipine SR administration.

General tolerance

The side effects encountered in this study on day 4 were as follows: (a) facial flushing in five subjects on nicardipine (two marked, three moderate) and in three subjects on nicardipine SR (two marked, one moderate), (b) headache in five subjects on nicardipine (two marked, three moderate) and in one subject on nicardipine SR (moderate), (c) palpitations in three subjects (nicardipine) and (d) asthenia in one subject (nicardipine) and in three subjects (nicardipine SR). The subjects reported that these side effects were almost identical to those encountered on the 3 previous days.

Discussion

Calcium channel blocking drugs are known to exert vasodilating properties and to reduce arterial blood pressure in hypertensive patients (Guazzi *et al.*, 1979; Taylor *et al.*, 1982). However, in this study performed in normotensive volunteers, nicardipine, 20 mg, and nicardipine SR, 30 mg, did not affect blood pressure, a result in agreement with those by Iliopoulou *et al.* (1983) with nicardipine and by Lederballe-Pedersen *et al.* (1980) with nifedipine. But, the use of the pulsed Doppler technique in this study enabled us to demonstrate that the vasodilating effects of nicardipine did indeed develop in the normotensive subject, as evidenced by the increases in brachial and carotid arteries diameter and by the decrease in forearm vascular resistance. In our study, the vasodilating effects of nicardipine were probably counteracted by (a) the simultaneous drug-induced increase in cardiac output, which led to augmented brachial and carotid blood flows, and (b) the transient stimulation of the renin-angiotensin system, thus resulting in a non-modified blood pressure. Furthermore, our data clearly indicate that nicardipine dilates the large peripheral arteries and increases arterial compliance since peripheral arteries dilated without any simultaneous change in pressure. The drug-induced increase in peripheral flows is consistent with (a) the previous data by Takenaka & Handa (1979) who, using the ^{133}Xe clearance technique, demonstrated that nicardipine increases carotid blood flow without affecting arterial blood pressure, P_{CO_2} , P_{O_2} , and pH, and (b) with similar results obtained with the pulsed Doppler technique with other calcium channel antagonists, e.g. diltiazem and nifedipine (Simon *et al.*, 1983). Furthermore, our data show that forearm vascular resistance was

decreased by nicardipine, which indicates that at least in this vascular territory the drug also significantly dilates the small arteries. Thus it appears that, like nifedipine and diltiazem (Simon *et al.*, 1983), nicardipine dilates both large and small arteries. From another point of view, comparison of our brachial and carotid arteries data indicate that CBF is increased earlier than BBF but that BBF is increased to a larger extent than CBF (by 60 and 33%, respectively, vs $t=72$ at the peak effect). Finally, it appears from this study that administration of nicardipine every 8 h results in qualitatively and quantitatively reproducible effects as well on BBF as on CBF, indicating that at least in short term experiments no tolerance develops upon repeated nicardipine administration.

Nicardipine SR exhibited in this study the same effects on CBF and BBF as nicardipine, but the kinetics of these effects were as expected different for the two formulations. Thus, whereas nicardipine-induced increases in BBF and CBF did not exceed 6 and 4 h, respectively, the nicardipine SR-induced ones were still significant 10 h after drug intake for both parameters. This finding, together with the remaining effect of nicardipine SR observed in some subjects on CBF 12 h after the last administration demonstrates the longer duration of action of this formulation. However, when comparing the overall vasodilating effects of nicardipine, 20 mg ($\text{AUC}_{\text{F0} \rightarrow 8 \text{ h}}$) and nicardipine SR, 30 mg ($\text{AUC}_{\text{F0} \rightarrow 12 \text{ h}}$), it appears that regarding BBF, the two AUC_{F} are almost similar which indicates that the SR formulation was on a weight basis approximately 2/3 as active as the normal formulation. This was not the case for CBF since the $\text{AUC}_{\text{F0} \rightarrow 12 \text{ h}}$ for nicardipine SR was almost 1.6-fold that of $\text{AUC}_{\text{F0} \rightarrow 8 \text{ h}}$ for nicardipine, indicating similar potencies for the two formulations. The reasons for this discrepancy between the different activities of the two formulations on BBF and CBF respectively remain unknown.

The lower peak plasma levels and the reduced nicardipine plasma relative bioavailability observed after the second (nicardipine and nicardipine SR), and third (nicardipine) daily doses on the fourth day of chronic oral treatment with either nicardipine, three times daily, or nicardipine SR, twice daily, as compared to those observed after the first administration were not expected. In regard of other experiments (Higuchi & Sasaki, 1980; other unpublished results), it seems that these decreases might be related either to circadian rhythms or to the dosage regimen. Further investigation of these findings are presently in progress. Finally, it appears from our data that nicardipine

plasma relative bioavailability after the SR formulation was strongly decreased as compared to that obtained after the normal formulation. This might be due to the fact that when high plasma levels are reached, as occurs after oral nicardipine administration, some biotransformation processes become saturated. This would not occur after nicardipine SR administration, hence resulting in a reduced plasma relative bioavailability.

There was no correlation in this study between AUC_{SC} and AUC_{SF} . This is not surprising since (a) the effects of nicardipine on BBF and CBF were identical upon the two first administrations whereas the plasma levels achieved were not, (b) nicardipine and nicardipine SR induced identical effects on BBF and CBF whereas nicardipine plasma levels after the SR formulation were much lower than after the normal formulation, (c) there was in some subjects, after nicardipine SR but not after nicardipine a remanent increase in CBF just before the first drug administration on day 4 while the plasma levels achieved with both formulations were identical and (d) with both formulations, nicardipine plasma levels decreased rapidly whereas the drug effects on BBF and CBF were much more long lasting. These observations could partially be explained (a) either by the *in*

vivo formation of an active metabolite of nicardipine, (b) or by a prolonged blockade of calcium channels by nicardipine, (c) or by the fact that nicardipine plasma concentrations as low as those achieved after the second or third administrations on day 4 are sufficient to elicit maximal increases in BBF and CBF. Although the first hypothesis can probably be ruled out since nicardipine metabolites have been shown to be much less pharmacologically active than the parent drug, further experiments are needed to investigate these possibilities.

In conclusion, this study demonstrates (a) that nicardipine dilates both large (increase in arterial diameter) and small (reduction in forearm vascular resistance) arteries, increasing significantly brachial and cerebral blood flows in normal volunteers, (b) that nicardipine SR duration of action is approximately 1.6 that of nicardipine and could thus be administered twice daily instead of three times a day and (c) that in the doses used, there is no correlation between the nicardipine plasma levels achieved and the magnitude of the elicited effects on BBF and CBF.

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References

- Brown, M. J. & Jenner, D. A. (1981). Novel double isotope technique for the enzymatic assay of plasma catecholamines, permitting high precision, sensitivity and sample capacity. *Clin. Sci.*, **61**, 591–598.
- Guazzi, M., Olivari, M. T., Polese, A., Fiorentini, C., Magrini, F. & Moruzzi, P. (1979). Nifedipine, a new antihypertensive with rapid action. *Clin. Pharmac. Ther.*, **22**, 528–532.
- Higuchi, S. & Sasaki, H. (1980). Pharmacokinetic studies on nicardipine hydrochloride, a new vasodilator, after repeated administration to rats, dogs and humans. *Xenobiotica*, **10**, 897–903.
- Higuchi, S., Sasaki, H. & Sado, T. (1975). Determination of a new cerebral vasodilator 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 (YC 93) in plasma by electron capture gas chromatography. *J. Chromatog.*, **110**, 301–307.
- Hof, R. P. (1983). Calcium antagonist and the peripheral circulation: differences and similarities between PY 108-068, nicardipine, verapamil and diltiazem. *Br. J. Pharmac.*, **78**, 375–394.
- Iliopoulou, A., Turner, P. & Warrington, S. J. (1983). Acute haemodynamic effects of a new calcium antagonist, nicardipine, in man. A comparison with nifedipine. *Br. J. clin. Pharmac.*, **15**, 59–65.
- Lederballe-Pedersen, O., Christensen, N. J. & Ramsch, K. D. (1980). Comparison of acute effects of nifedipine in normotensive and hypertensive man. *J. cardiovasc. Pharmac.*, **2**, 357–366.
- McAllister, R. G. (1982). Clinical pharmacology of slow channel blocking agents. *Prog. cardiovasc. Diseases*, **25**, 83–102.
- Ménard, J., Corvol, P., Allegrini, J. & Bremiener, J. (1972). Méthode de mesure de l'activité rénine plasmatique de l'homme par dosage radioimmunologique de l'antiotensine I. In *Techniques Radioimmunologiques*, INSERM ed., Paris, pp. 459–469.
- Pham Hu, U., Trusc, M. & Corvol, P. (1974). Aldosterone radioimmunoassay. *Steroids*, **24**, 587–598.
- Safar, M. E., Peronneau, P. A., Levenson, J. A., Toto-Moukoko, J. A. & Simon, A. C. (1981). Pulsed Doppler: diameter, blood flow velocity and volumic flow of the brachial artery in sustained essential hypertension. *Circulation*, **63**, 393–400.
- Seki, T. & Takenaka, T. (1977). Pharmacological evaluation of YC 93, a new vasodilator in healthy volunteers. *Int. J. clin. Pharmac.*, **15**, 267–274.
- Simon, A. C., Safar, M. E., Levenson, J. A., Bouthier, J. E. & Benetos, A. (1983). Action of vasodilating drugs on small and large arteries of hypertensive patients. *J. cardiovasc. Pharmac.*,

- 5, 626–631.
- Takenaka, T. & Handa, J. (1979). Cerebrovascular effects of YC 93, a new vasodilator, in dogs, monkeys and human patients. *Int. J. clin. Pharm. Biopharm.*, **17**, 1–11.
- Takenaka, T., Usuda, T., Nomura, T., Maeno, H. & Sado, T. (1976). Vasodilator profile of a new 1,4-dihydropyridine derivative, 2,6-dimethyl 4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-[2-(*N*-benzyl-*N*-methyldamino)]-ethyl ester 5-methyl ester hydrochloride (YC 93). *Arzneim. Forsch.*, **26**, 2172–2178.
- Taylor, S. H., Silke, B., Ahuja, R. C. & Okoli, R. (1982). Influence of nicardipine on the blood pressure at rest and on the pressor responses to cold, isometric, exertion, and dynamic exercise in hypertensive patients. *J. cardiovasc. Pharmac.*, **4**, 803–807.
- Yamamoto, M., Ohia, T. & Toda, N. (1983). Mechanisms of relaxant action of nicardipine a new Ca^{++} -antagonist, on isolated dog cerebral and mesenteric arteries. *Stroke*, **14**, 270–275.

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