Development of tolerance to nifedipine in patients with stable angina pectoris

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- 1 The possibility of development of tolerance to the anti-ischaemic and anti-anginal effects of nifedipine during sustained administration for 2 months was studied in 15 patients with stable angina pectoris by means of repeated exercise tests on a treadmill.
- 2 After acute administration of nifedipine (20–30 mg) substantial anti-ischaemic and anti-anginal effects lasted for at least 4 h in all patients.
- 3 During sustained nifedipine treatment with a dose schedule which provided continuous anti-ischaemic effect during a day (mean daily dose 82.7 ± 6.0 mg, range 60–120 mg) a substantial attenuation of this effect was registered. The duration of the anti-ischaemic effect was 5.4 ± 0.3 h after acute administration, decreasing significantly to 3.6 ± 0.4 h during sustained administration.
- 4 The attenuation of the nifedipine effect was not associated with worsening of the patients' condition.
- 5 Plasma concentrations of nifedipine and its metabolite were similar after acute administration and during sustained treatment. Protein binding of nifedipine also remained constant during the study.
- 6 There was marked interindividual variation in the degree of attenuation of the nifedipine effect during sustained administration. In five patients nearly complete loss of nifedipine efficacy was registered. Eight to ten days after stopping regular administration of nifedipine only partial restoration of nifedipine effect was observed.
- 7 We conclude that during sustained nifedipine administration tolerance to its anti-ischaemic, anti-anginal and circulatory effects develops in a substantial number of patients with stable angina pectoris.

Keywords nifedipine angina pectoris exercise tests plasma concentration tolerance

Introduction

Nifedipine has been shown to be effective in the management of different cardiovascular disorders, and in particular ischaemic heart disease. The results of several clinical studies have clearly demonstrated the efficacy of nifedipine in patients with angina pectoris (Crake *et al.*, 1987; Stone *et al.*, 1983). It has been established that

the anti-anginal effectiveness of nifedipine is well maintained with sustained therapy (Mueller & Chahine, 1981; Vetrovec *et al.*, 1987), although no special investigations have been conducted to compare the efficacy of nifedipine during acute and chronic administration in patients with stable angina pectoris. It has been

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demonstrated that tolerance to nifedipine develops in patients with arterial hypertension (Kleinbloesem *et al.*, 1987) and in patients with migraine (Meyer *et al.*, 1985). In view of this, the present study was undertaken to determine whether sustained administration of nifedipine would result in a significant attenuation of its efficacy in patients with stable angina pectoris.

Methods

Patients

The study was performed in 15 patients (mean age 52, range 45–57 years) with stable angina pectoris. Nine patients were in Canadian Cardiovascular Society functional class 2, and six patients were in class 3. Angina had been present from 6 months to 8 years. Eight patients had a history of myocardial infarction at least 6 months prior to the study. All patients except two had undergone coronary angiography, which in all cases demonstrated $\geq 75\%$ narrowing of the luminal diameter of at least one major coronary artery. Angina pectoris was documented by a positive exercise test with both typical symptoms of angina and horizontal or down-sloping ST-segment depression of more than 1 mm in all the patients. Patients with rest angina, hypertension or heart failure were not included into the study. No patient received β -adrenoceptor blockers or calcium antagonists prior to entry into the study.

Study protocol

The study was approved by the Pharmacological Committee of the Ministry of Public Health of the USSR. Informed consent was obtained from all the patients.

To analyse the efficacy of nifedipine, pharmacodynamic studies on a treadmill were performed to assess the duration and the extent of the anti-ischaemic and anti-anginal effects (Martsevich & Metelitsa, 1986; Metelitsa *et al.*, 1987; Nazarenko & Nikolenko, 1981).

One week before examination all anti-anginal therapy was stopped except sublingual nitroglycerin to relieve anginal pain. First, all patients performed a standard graded exercise test on a computer-assisted treadmill (ICR Stress Test System), at a speed of 4 km h⁻¹ and with the gradient increasing every 3 min by 4%. Exercise was discontinued when the patient experienced angina of moderate severity. After that individual work loads were adjusted for each patient so that angina pectoris developed between the 3rd and the 6th min of exercise. The adjusted work load was studied 3–4 times and only patients with well-reproduced angina were admitted to the study.

Each pharmacodynamic study included exercise tests on a treadmill before and repeatedly after drug (or placebo) administration. On the day of investigation, 2.5 h after a light breakfast, each patient exercised at the previously adjusted individual work load (control work load). Then 20 mg of nifedipine or placebo was given in a random order and the same work load was repeated after 1, 2, 3, 5 and 6 h. If the effect (see below) persisted 6 h after drug administration, additional work loads were performed at 7 and 8 h.

If the efficacy of nifedipine 20 mg did not satisfy the desired criteria (see below), an additional pharmacodynamic study was carried out with nifedipine 30 mg (Figure 1).

After the effective dose of nifedipine was determined sustained administration of nifedipine began and was continued for 2 months. The frequency of administration was chosen to

Figure 1 Study design. SGET—standard graded exercise treadmill test; WLA—work load adjustment; PL—placebo; NF—nifedipine; *—study was done only in cases when nifedipine 20 mg was ineffective; **—was done in cases with marked effect attenuation during sustained nifedipine administration; ▽—pharmacodynamic study: similar work loads on a treadmill prior to and 1, 2, 3, 5 and 6 h after drug administration.

Table 1 A rating scale of angina intensity during exercise

Scale	
0	No pain
1	Mild pain which does not need exercise cessation
2	Moderate pain usually requiring the cessation of exercise
3	Severe pain, requiring nitroglycerin administration

provide a fairly constant anti-ischaemic effect during a day. At the end of nifedipine treatment the pharmacodynamic study was repeated according to the same protocol. On the day before the pharmacodynamic study during sustained nifedipine treatment the drug was given at 22.00 h.

In all cases when substantial attenuation of nifedipine efficacy during the pharmacodynamic study at the end of sustained administration was registered (a decrease in duration of anti-ischaemic effect by two times or more), the drug was withdrawn for 8–10 days and a repeated pharmacodynamic study according to the same protocol was carried out thereafter.

ECG at rest and during exercise was recorded using 12 standard leads. The magnitude of ST-segment depression was assessed from the net curves of ST-level drawn by a computer based system. The intensity of angina during exercise was assessed by a 3-point rating scale which the patients were accustomed to use (Table 1). Exercise tests were stopped when the severity of angina reached scale 2.

Evaluation of the effect

Anti-ischaemic drug effect was assessed by the reduction in the maximal ST-segment depression during exercise after drug administration as compared with the ST-segment depression during control work load on the same day; it is expressed as $\Delta\text{ST}\%$. The results of each study were plotted and the overall duration of anti-ischaemic effect was calculated. Anti-ischaemic effect duration was calculated as the period over which ST-segment depression during exercise after drug administration was at least 20% less than that during the control work load. The anti-ischaemic efficacy of nifedipine was considered sufficient if its duration was at least 4 h, and the maximal extent of the effect was more than 50%.

In every patient duration of complete anti-anginal effect, i.e. the period over which angina during exercise after drug administration was absent, was also calculated.

Determination of plasma nifedipine concentration

Venous blood samples were collected 2, 3 and 6 h after administration of the drug. Plasma concentrations of nifedipine and its initial metabolite B-4759 were determined by gas liquid chromatography according to a previously described technique (Rumiantsev *et al.*, 1986).

Statistical analysis

The results are presented as mean $\pm$ s.e. mean. The significance of differences was assessed by Student's paired *t*-test with the Bonferroni modification. Differences were considered significant for a probability (*P*) of less than 0.05.

Results

Acute nifedipine administration

Acute placebo administration caused no significant changes in the extent of ST-segment depression and in the intensity of angina during repeated exercise treadmill tests as compared with control (Table 2).

The desired anti-ischaemic effect after acute administration of nifedipine was obtained in all 15 patients (see Table 5). The effective dose of nifedipine was 20 mg in eight patients and 30 mg in seven patients. Significant anti-ischaemic effect of nifedipine was observed at 1 h, was maximal at 3 h and persisted at 6 h (Table 2). Changes in angina intensity during exercise after nifedipine administration closely paralleled changes in ST-segment depression.

Sustained nifedipine administration

Frequency of nifedipine administration ranged from three to four times a day, and the daily dose ranged from 60 to 120 mg, with a median daily dose of 82.7 ± 6.0 mg (Table 5). In one patient unstable angina developed 1.5 months after commencing nifedipine therapy 30 mg

Table 2 Effects of acute and chronic nifedipine administration on maximal ST-segment depression during similar work loads on treadmill in 14 patients with stable angina pectoris

Drug	Exercise duration (min)	↓ ST during control work load (mm)	Changes of ↓ ST (Δ%) Time after drug administration (h)				
			1	2	3	5	6
Placebo ac.	4.2 ± 0.3	1.6 ± 0.1	+3 ± 5	-4 ± 6	-12 ± 6	+8 ± 8	+10 ± 7
Nifedipine ac.	4.5 ± 0.3	1.7 ± 0.1	-50 ± 8***	-69 ± 6***	-71 ± 4***	-35 ± 6**	-26 ± 5**
Nifedipine chr.	4.6 ± 0.4	1.8 ± 0.2	-37 ± 8**	-52 ± 7***	-39 ± 7***	-7 ± 6	+14 ± 7
P placebo-nifedipine ac.	NS	NS	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
P nifedipine ac.-nifedipine chr.	NS	NS	NS	< 0.05	< 0.05	< 0.05	< 0.01

↓ ST—maximal ST-segment depression; ac.—acute administration; chr.—chronic administration; NS—non-significant. Significance of differences with control work load: *— $P < 0.05$, **— $P < 0.01$, ***— $P < 0.001$.

Table 3 Effects of acute and chronic administration of nifedipine on resting systolic blood pressure (BP) in 14 patients with stable angina pectoris

Drug	BP before drug administration (mm Hg)	Changes of BP (Δ%) Time after drug administration (h)				
		1	2	3	5	6
Placebo ac.	121 ± 3	-1 ± 2	-3 ± 3	-2 ± 1	-2 ± 2	0 ± 3
Nifedipine ac.	121 ± 2	-10 ± 3**	-14 ± 2***	-14 ± 3***	-7 ± 3*	-3 ± 2
Nifedipine chr.	121 ± 4	-7 ± 2**	-10 ± 2**	-8 ± 2**	-5 ± 2*	-2 ± 3
P placebo-nifedipine ac.	NS	< 0.01	< 0.01	< 0.01	< 0.05	NS
P nifedipine ac.-nifedipine chr.	NS	NS	NS	< 0.05	NS	NS

Abbreviations—see Table 2.

three times daily. The patient was withdrawn from the study.

The duration of control exercise (4.6 ± 0.4 min), i.e. exercise performed 12 h after the last administration of nifedipine during chronic administration, in 14 patients did not differ significantly from the exercise duration prior to acute placebo administration (4.2 ± 0.3 min) and prior to acute nifedipine administration (4.5 ± 0.3 min). Similarly, maximal ST-segment depression during these exercise tests differed insignificantly (Table 2).

The extent of the nifedipine anti-ischæmic effect during sustained administration was attenuated at 2, 3, 5 and 6 h as compared with that in the acute study. The effect of nifedipine 5 and 6 h after administration during sustained treatment was insignificant. The overall anti-

ischæmic effect duration during sustained administration decreased significantly from 5.4 ± 0.3 h to 3.6 ± 0.4 h ($P < 0.01$). Similarly, the duration of nifedipine complete anti-anginal effect decreased from 4.3 ± 0.5 h during the acute study to 2.6 ± 0.4 h on sustained administration.

A considerable reduction in the extent and the duration of systolic blood pressure reduction after nifedipine administration was also observed during sustained nifedipine administration (Table 3).

Nifedipine plasma concentrations and effect

Plasma concentrations of nifedipine and its metabolite were similar during acute and sustained administration. Plasma protein binding

Table 4 Plasma concentrations of nifedipine and its metabolite (B-4759) after acute and sustained administration

	Acute administration			Sustained administration		
	2 h	3 h	6 h	2 h	3 h	6 h
C_{NF}	53 ± 6	49 ± 5	22 ± 3	61 ± 9	49 ± 7	28 ± 4
C_{NF-f}	0.92 ± 0.11	0.89 ± 0.12	0.39 ± 0.09	1.25 ± 0.17	1.01 ± 0.13	0.58 ± 0.09
C_m	23 ± 4	18 ± 2	8 ± 1	25 ± 3	20 ± 3	10 ± 1

C—concentration (ng ml⁻¹); NF—nifedipine; NF-f—free (unbound) fraction; m—metabolite.

Table 5 Individual data on the efficacy of nifedipine during acute and sustained administration in 15 patients with stable angina pectoris

Patient	Effective single dose (mg)	Frequency of administration (times/day)	Daily dose (mg)	Duration of anti-ischaemic effect (h)		Duration of complete anti-anginal effect, (h)	
				Acute	Sustained	Acute	Sustained
1	20	3	60	7	3	7	4
2	20	3	60	6	3	7	4
3	20	4	80	4	3	1	0
4	20	3	60	5	5	3	2
5	30	4	120	4	5	6	5
6	30	4	120	4	5	4	3
7	20	4	80	4	3	5	2
8	20	3	60	7	5	4	2
9	20	3	60	6	3	4	4
10	30	4	120	5	2	1	0
11	30	3	90	6	4	5	3
12	30	3	90	6	0	3	0
13*	30	3	90	6	—	5	—
14	20	3	60	6	5	5	4
15	30	3	90	6	4	5	3
Mean	24.6		82.7	5.4	3.6	4.3	2.6
± s.e. mean	±1.4		±6.0	±0.3	±0.4	±0.5	±0.4
				└P < 0.01┐		└P < 0.001┐	

*—patient who developed unstable angina; mean data are given without patient 13.

of nifedipine was of the same order during acute and sustained administration (Table 4).

After acute nifedipine administration a significant relationship between nifedipine plasma concentration and the extent of the anti-ischaemic effect was registered ($r = +0.686$, $P < 0.001$). This relationship was weaker during sustained nifedipine administration ($r = +0.314$, $P < 0.05$). Six hours after nifedipine administration during sustained treatment there were no signs of anti-ischaemic and anti-anginal effects, although the plasma nifedipine concentration was quite high (28 ± 5 ng ml⁻¹).

Individual analysis

Large interindividual differences in the degree of attenuation of the nifedipine effect during sustained administration were registered (Table 5). In five patients a substantial reduction of anti-ischaemic and anti-anginal efficacy was observed despite a considerable concentration of the drug in the plasma. The extent and duration of nifedipine effects and plasma nifedipine concentrations after acute administration in these patients did not differ greatly from the values recorded in the whole group of patients.

Figure 2 Anti-ischaemic effects ($\Delta ST\%$) and plasma concentrations (ng ml^{-1}) of nifedipine in five patients with marked effect of attenuation during sustained nifedipine administration. $\square$ —acute study, $\blacksquare$ —study during sustained nifedipine administration, $\hatched$ —study 8–10 days after withdrawal of nifedipine. Significance of differences with acute study: *— $P < 0.05$, **— $P < 0.01$.

Eight to ten days after withdrawal of nifedipine only partial restoration of anti-ischaemic effect was recorded in these five patients (Figure 2). It should be noted that the duration of the control work load in these five patients remained constant during the study.

Side effects

In five patients peripheral oedema was registered during nifedipine treatment. Body mass remained constant during the study.

Discussion

The present study provides direct evidence that continuous administration of nifedipine intended to yield sustained therapeutic efficacy leads to development of tolerance with respect to anti-ischaemic, anti-anginal and circulatory effects. The attenuation of the nifedipine effect was not associated with worsening of the patients' condition, since the duration of control exercise test and the magnitude of ST-segment depression during it remained unchanged for the whole investigation period.

A decrease of nifedipine effect on ST-segment depression during exercise paralleled reduction of the drug effect on angina intensity during exercise and on systolic blood pressure. This excludes the possibility of any specific influence of nifedipine or its metabolites during sustained administration on the level of the ST-segment and confirms that there was a true attenuation of nifedipine effect.

No previous studies have examined the possibility of development of tolerance to calcium blocking agents in patients with stable angina pectoris. However, a number of papers report evidence of signs of the effect of these drugs waning during sustained administration. Thus McCans (1986) reported no increase in exercise tolerance compared with placebo 10 h following the last dose of diltiazem on chronic treatment despite significant plasma concentrations. Furthermore, the author reported that the relationship between circulating drug level and treadmill response appeared to be altered during sustained diltiazem therapy. Eldridge *et al.* (1987) demonstrated a lack of improvement in exercise performance 3–5 h after the last dose of nifedipine at the end of 4 weeks of therapy with 30–90 mg day⁻¹. The authors suggested that at the doses used nifedipine failed to exert a significant anti-ischaemic effect in the later part of the dosing interval, but it cannot be excluded that a primary nifedipine effect disappeared or was greatly attenuated at the end of treatment due to the development of tolerance.

It is unknown when the attenuation of the effect of nifedipine appears. Kleinbloesem *et al.* (1987) suggested that the nifedipine effect attenuated during the first days of nifedipine use, but then remained quite stable. Tolerance may take a different time to develop in different patients. This is supported by the fact that 2 months after the beginning of therapy with nifedipine the extent of the development of tolerance differed between individuals in our study.

The reasons for attenuation of nifedipine efficacy during sustained therapy are obscure. Our results disagree with those of Kleinbloesem

et al. (1987) who found that the pharmacokinetics of nifedipine were altered after 6 weeks of chronic treatment. In our previous study (Rumiantsev *et al.*, 1989) we did not find any significant change in the pharmacokinetics of nifedipine during chronic administration in comparison to acute administration. In the present study we also demonstrated similar concentrations of nifedipine and its metabolite during acute and sustained administration. Plasma nifedipine binding was also unchanged during sustained administration. Therefore we conclude that the attenuation of nifedipine effects are not due to changes of pharmacokinetics of the drug but to something else.

Similar attenuation of the anti-ischaemic and circulatory effects of nifedipine is analogous to that observed during sustained administration of nitrates and, there may be some similarity in the mechanism of development of tolerance. However, we have found distinctions in the development of tolerance to nifedipine and to nitrates. It is well known that tolerance to nitrates rapidly disappears after their withdrawal (Parker *et al.*, 1983). In the case of nifedipine we did not find complete restoration of the effect even 8–10 days after stopping sustained administration of nifedipine. It is necessary to study whether tolerance to nifedipine is reversible and, if no, what time is required for restoration of sensitivity to nifedipine.

Further studies are obviously needed to clarify the clinical significance of the development of tolerance to nifedipine. It was reported previously that nifedipine can increase angina frequency (Jariwalla & Anderson, 1978). This was ascribed to a reflex tachycardia or to induction of a steal phenomenon (Stone *et al.*, 1983) but it is possibly a consequence of the development of tolerance to nifedipine.

Thus it can be concluded that during chronic nifedipine administration tolerance may develop to its anti-ischaemic, anti-anginal and circulatory effects. Whether this is true for all patients with stable angina pectoris and whether it is possible to prevent this phenomenon by special schedules of nifedipine administration remains to be tested in future studies.

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