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Efficacy of Slow-release Nifedipine, Talinolol and Combination in Angina Pectoris (NITAAP)*

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Efficacy of slow-release formulation of nifedipine (Corinfar[®] retard) and talinolol (Cordanum[®] 100), both as monotherapy and in combination, was investigated in 45 patients with effort-induced angina. The drugs were introduced/withdrawn in the following order:

- nifedipine monotherapy 20 mg then 2 × 20 mg daily;
- nifedipine/talinolol combination therapy 20 mg daily/100 mg daily then 2 × 20 mg/2 × 100 mg daily;
- talinolol monotherapy 2 × 100 mg daily.

Compared with baseline, the number of angina attacks, nitroglycerine consumption, and blood pressure all significantly decreased, while exercise tolerance increased during all treatments. The dose-related anti-anginal effect of nifedipine was demonstrated. The efficacy of nifedipine 40 mg and talinolol 200 mg monotherapies was similar; the maximal effect was seen in patients treated with the higher dose combination of nifedipine 40 mg and talinolol 200 mg. However, with this higher dose combination therapy, the incidence of adverse events was higher. In general, talinolol was well tolerated. The double product values (heart rate × systolic blood pressure/100) significantly decreased during high-dose combination therapy and talinolol monotherapy compared with baseline, but revealed differences between patients during high-dose nifedipine monotherapy. *J Clin Basic Cardiol 2000; 3: 29–34.*

Key words: nifedipine, talinolol, combination therapy, angina pectoris, beta-blockers

Angina pectoris is treated primarily with nitrates, beta-blockers and calcium channel blockers. For long-term treatment, preference is given to selective beta-blockers [1] and slow-release formulations of dihydropyridine calcium channel blockers [2]. Both drug classes have distinct modes of action. Selective beta-blockers slow heart rate and reduce myocardial contractility, thereby reducing myocardial oxygen demand. Dihydropyridine calcium channel blockers produce smooth muscle relaxation, which not only reduces myocardial oxygen demand, but also increases coronary blood flow. Such differences in mode of action have led to the use of combination treatments for symptom relief in stable angina. However, for an individual patient, the decision about the most appropriate therapy remains ambiguous.

Despite the undoubted benefits of these drugs, data on comparative efficacy (including slow-release nifedipine) are controversial. Quyyumi et al. [3] reported a higher efficacy of beta-blockers in comparison with calcium channel blockers. However, the TIBET study [4] demonstrated equal anti-anginal and anti-ischaemic efficacy of the calcium channel blocker, nifedipine (20 mg twice daily in a slow-release formulation), and the beta-blocker, atenolol (50 mg twice daily). This multicentre, double-blind study showed that these two drugs, both alone and in combination, significantly improved exercise parameters and significantly reduced ischaemic activity during exercise and daily activities. The results also suggested that there was only little advantage in giving these two drugs in combination.

The present study aims to provide further clarification of this situation by comparing two long-acting anti-anginal drugs – the beta-blocker talinolol and a slow-release formulation of the reference calcium channel blocker nifedipine. We assessed the clinical efficacy and the benefits of these two drugs, applied as monotherapy and in combination, in patients with stable effort angina pectoris.

Talinolol is a selective beta-1 adrenoceptor blocker without intrinsic sympathomimetic activity, which has been used both alone and in combination with other drugs for the treatment of hypertension since 1975 [5]. Other indications include coronary heart disease, acute myocardial infarction, tachycardias and hyperkinetic heart syndrome. Its beta-1 receptor selectivity is more favourable than that of atenolol and is approximately the same as that of metoprolol [5]. Talinolol has a favourable half-life. As with other beta-blockers, it has a biological half-life that is 2–3 times longer than the plasma half-life. Thus, talinolol, which has a plasma half-life of approximately 10–16 hours, has an effect for up to 24 hours when given at an appropriate dose [5]. In contrast, some other important beta-blockers, including propranolol and metoprolol, which have a plasma half-life of only 3–4 hours, and atenolol, which has a half-life of 6–9 hours, may be less effective over 24 hours.

The slow-release formulation of nifedipine used here also has a continuous effect throughout the day, when given twice daily, and avoids the fluctuation in plasma levels of active drug that are known to occur with certain other nifedipine formulations (such as drops). The pharmacokinetics of the nifedipine formulation in this study are comparable to those of a reference slow-release formulation of nifedipine [6].

Materials and methods

Patients

The study included 45 out-patients (42 males and 3 females) aged between 38 and 64 years (mean age was 48 ± 13 years). Informed consent was obtained from each patient. All patients had stable effort angina pectoris of functional class II–III (classification of Canadian Heart Association) with an angina attack rate of at least 3 per week and positive bicycle ergometric exercise test response. More than a year before inclusion into

this study, coronary artery bypass graft surgery had been performed in 2 patients, and percutaneous transluminal coronary angioplasty in 5 patients. Other conditions of note were:

- effort angina pectoris accompanied by angina attacks at rest – 12 patients
- myocardial infarction (MI) more than 6 months before the study began – 15 patients
- diagnosed arterial hypertension – 18 patients
- gastric and duodenal ulcer in remission – 9 patients
- chronic bronchitis – 1 patient
- diabetes mellitus type II – 2 patients.

None of the patients complained of intermittent claudication at the beginning of the investigation.

Exclusion criteria were:

- unstable angina;
- angina attacks accompanied by paroxysmal tachycardias or syncope;
- myocardial infarction;
- coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty less than 6 months before the beginning of the study;
- beta-blocker and calcium antagonist prescription contraindications;
- acute gastric or duodenal ulcer;
- atrial fibrillation;
- total left or right bundle branch block;
- no possibility to withdraw previous anti-anginal medication;
- the inability to fulfil an exercise test at a work load of at least 125 W without angina development and/or myocardial ischaemia (as determined by ECG).

Study design

The study was conducted in accordance with the Declaration of Helsinki.

Previous medication – except for sublingual consumption of nitroglycerine in anginal attacks – was withdrawn over 7 days. Patients received the study drugs – slow-release nifedipine (Corinfar® retard, ASTA Medica AG, Germany) and talinolol (Cordanum® 100, ASTA Medica AG, Germany) – in a stepped approach, either as monotherapy or in combination, as described in detail in Figure 1.

In order to determine the anti-anginal efficacy of the drugs at rest, patients recorded in diaries the rate of anginal attacks and consumption of nitroglycerine tablets both during the wash-out period and during each treatment. In addition, blood pressure measurements at rest, and ECG measurements at rest in 12 standard leads (with PQ interval measurement) were recorded during the last day of each of the following stages: baseline; high dose nifedipine monotherapy; high dose combination therapy; and talinolol monotherapy. Patients then underwent an exercise test (as described below) to assess the efficacy of the drugs during exercise.

This exercise test was conducted on a bicycle ergometer EM 840 (Germany) in an upright position. The initial workload was 50 W, and this was increased by 25 W every 3 minutes. ECG and blood pressure measurements were taken with each workload increase. During treatment, the exercise test was conducted 2 hours after nifedipine monotherapy and 3 hours after talinolol monotherapy or combination therapy. Nitroglycerine consumption was not permitted during the hour immediately before the exercise test. Patients continued to exercise until one of the indications for test discontinuation was shown. Discontinuation indicators were as follows:

- angina attack of moderate intensity, with or without ST-segment shift (a horizontal or down sloping depression of the ST-segment not less than 1 mm);

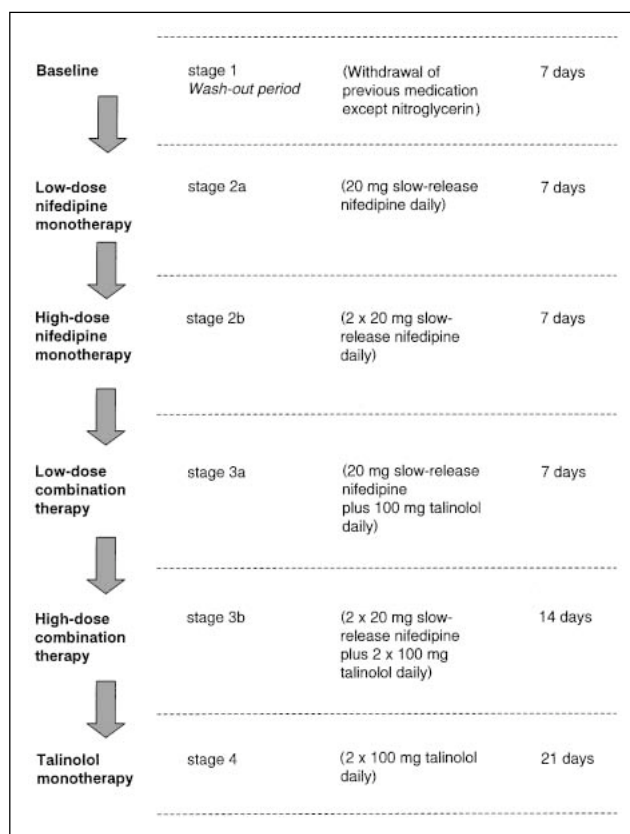


Figure 1. The drug application process

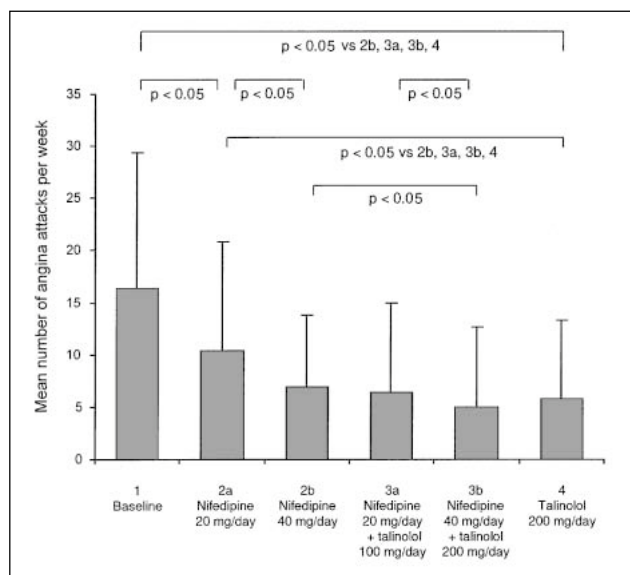


Figure 2. Angina attack rate at rest

- 'silent' ST-segment depression equal to 2 mm;
- achievement of submaximal heart rate;
- a blood pressure increase above 230/130 mmHg;
- cardiac rhythm and conduction disorders; and
- patient's refusal to continue the test due to excessive fatigue or dizziness.

We also evaluated duration of exercise, duration of exercise to onset of angina and 1 mm ST-segment depression, total workload, maximal ST segment depression. Double product was determined by calculating the heart rate \times systolic blood pressure/100 at peak load, to provide an indirect estimation of myocardial oxygen demand [7].

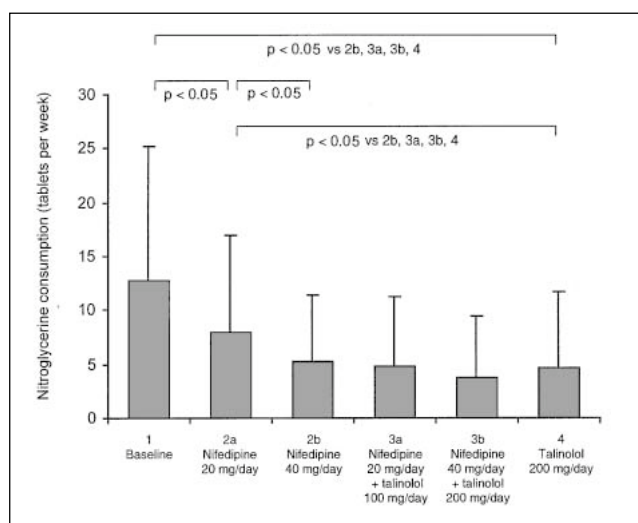
Table 1. Changes in blood pressure, heart rate and PQ interval at rest during treatment with nifedipine and talinolol alone and in combination

	Stage of study			
	Baseline 1	High-dose nifedipine monotherapy 2b	High-dose combination therapy 3b	Talinolol monotherapy 4
Systolic blood pressure (mmHg)	135 ± 15.2	121 ± 11.5*	118 ± 10.0*†	123 ± 15.2*#
Diastolic blood pressure (mmHg)	84.0 ± 7.2	78.0 ± 8.5*	76.0 ± 6.7*	80.0 ± 6.3*
Heart rate (bpm)	78.0 ± 15.1	76.0 ± 11.1	68.0 ± 8.7*†	66.0 ± 10.9*†
PQ interval (seconds)	0.151 ± 0.02	0.152 ± 0.02	0.158 ± 0.02*	0.164 ± 0.02*†#

* Significantly different from baseline (stage 1) $p < 0.05$

† Significantly different from high-dose nifedipine monotherapy (stage 2b) $p < 0.05$

Significantly different from high-dose combination therapy (stage 3b) $p < 0.05$

**Figure 3.** Nitroglycerine consumption at rest

The data obtained are expressed as mean ± standard deviation. The Student's *t*-test was applied for statistical analysis; values of $p < 0.05$ were regarded as statistically significant. The chi-square test was used to compare differences in proportions.

Results

Anti-anginal efficacy of nifedipine and talinolol at rest

Angina attack rate

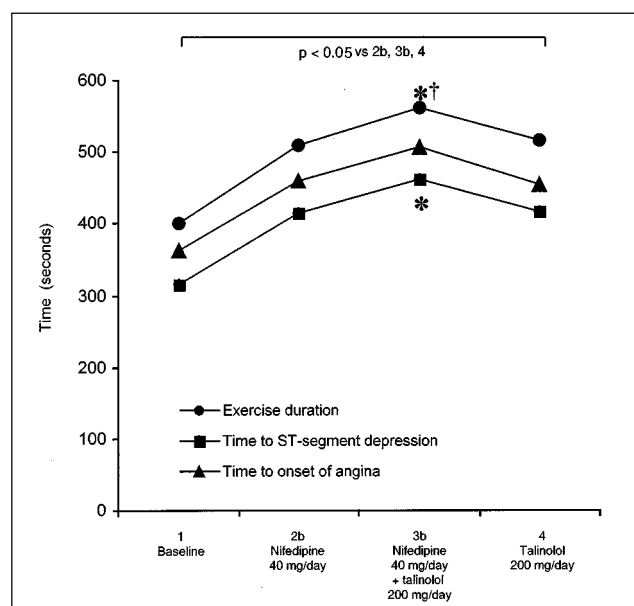
At the end of the wash-out period, the mean number of angina attacks per week was 16.4 ± 13.0 , and was significantly decreased during each subsequent treatment (Figure 2). There were significantly fewer anginal attacks with high-dose than with low-dose nifedipine monotherapy. Similarly, there were significantly fewer anginal attacks with high-dose than with low-dose combination therapy. During high-dose combination therapy, the number of anginal attacks was significantly lower than during all other therapies, except talinolol monotherapy.

Nitroglycerine consumption

Nitroglycerine consumption – and similarly the angina attack rate – significantly decreased during all treatments, compared with baseline values (Figure 3). Nevertheless, there were no significant differences in nitroglycerine consumption per week when comparing high-dose nifedipine monotherapy and all subsequent treatments.

Blood pressure

Compared with baseline values obtained after the wash-out period, systolic blood pressure significantly decreased during those three treatments where measurements were taken (Table 1). The lowest systolic blood pressure values were noted dur-

**Figure 4.** Exercise parameters at baseline and during treatment (* 3b significantly different from 4, $p < 0.05$; † 3b significantly different from 2b, $p < 0.05$)

ing high-dose combination therapy, although the values obtained were not significantly different from those seen during talinolol monotherapy. Similarly, diastolic blood pressure decreased during all three measured treatments compared with baseline values (Table 1) but, unlike systolic blood pressure, there was no significant difference between any of these therapies.

Heart rate

Heart rate at rest did not change during high-dose nifedipine monotherapy, but significantly decreased when patients received the high-dose combination therapy and also the talinolol monotherapy (Table 1). However, even in patients with baseline heart rate values less than 60 beats per minute, no marked bradycardia was noted. In only one case, heart rate at rest dropped to 46 beats per minute, so the talinolol dose was reduced.

PQ interval

The PQ interval significantly increased during both combination therapy and with talinolol monotherapy (Table 1). However, the maximal recorded value of PQ was 0.22 seconds, so pathological levels were not reached in any patient.

Efficacy of nifedipine and talinolol during exercise

Exercise parameters

Duration of exercise, time to ST segment depression, and time to onset of angina significantly increased during all treatments compared with baseline (Figure 4).

Exercise duration was significantly longer during high-dose combination therapy than during high-dose nifedipine monotherapy and talinolol monotherapy. Similarly, total workload significantly increased during all treatments compared with baseline (Figure 5). The greatest values for total workload were observed during combination therapy, these were significantly greater than those seen during nifedipine and talinolol monotherapy.

A significant decrease of ST-segment depression at the peak of exercise compared with the baseline (1.57 ± 0.71 mm) was noted only during high-dose nifedipine monotherapy (1.20 ± 0.91 mm) ($p < 0.05$) and high-dose combination therapy (1.11 ± 0.77 mm) ($p < 0.05$).

Double product and exercise tolerance

The double product values (heart rate \times systolic blood pressure/100) significantly decreased during high-dose combination therapy (187.6 ± 37.8) ($p < 0.05$) and talinolol monotherapy (179.7 ± 30.5) ($p < 0.05$) compared with baseline (234 ± 56.1). However, the mean double product during high-dose nifedipine monotherapy (240.2 ± 40.7) did not significantly change from baseline.

A closer analysis of the double product values obtained during high-dose nifedipine treatment revealed differences between patients (Figure 6).

Exercise tolerance was closely related to these double product value changes. Workload values increased by approximately 67 % in those patients where the double product increased by

14 units or more after nifedipine consumption, but by only approximately 22 % in patients with a change in double product value below 14 units. Baseline values for workload were similar in all patients.

Reasons for discontinuation of the exercise test

During exercise, the reasons for discontinuation of therapy were angina attacks, submaximal heart rate, and fatigue. At high-dose nifedipine monotherapy and at high-dose combination therapy, there was a significant reduction in exercise test discontinuations due to angina attacks accompanied by ST-segment depression of 1 mm or more, compared with baseline.

Fatigue was one reason for exercise test discontinuation during the three treatments, but not during wash-out. These discontinuation values were significantly different in all cases when compared with baseline values.

Drug safety and tolerability

Adverse events during treatment were noted in 24 patients, seven of them had more than one event. Adverse events fell into three categories: those not related to the therapy; those possibly related to the therapy; and those assessed as related to the therapy, which are detailed in Table 2.

Hypotension was noted during both nifedipine monotherapies and during high-dose combination therapy. A

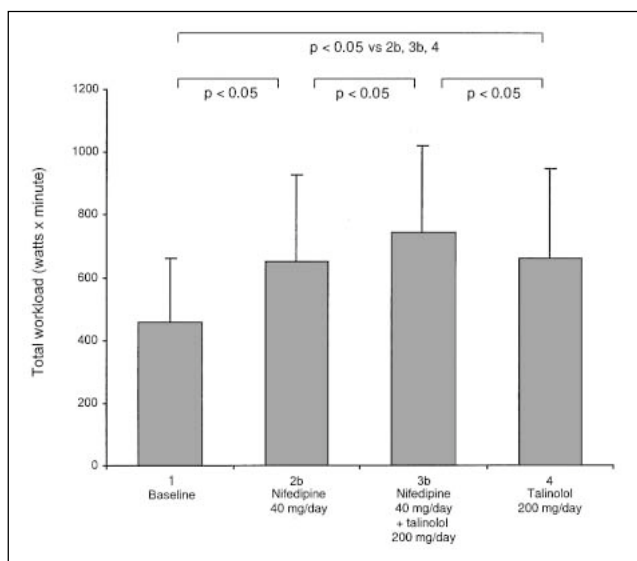


Figure 5. Total workload at baseline and during treatment

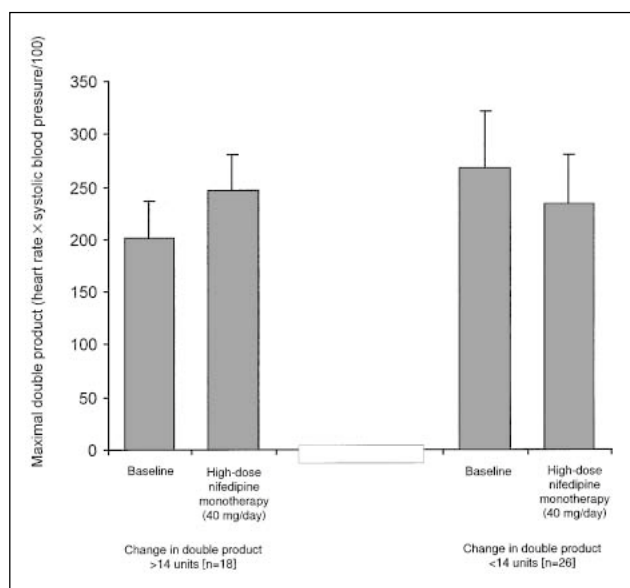


Figure 6. Change in double product in response to high-dose nifedipine monotherapy

Table 2. Adverse events assessed as related to therapy

Adverse events	Low-dose nifedipine monotherapy n = 45	High-dose nifedipine monotherapy n = 44	Low-dose combination therapy n = 43	High-dose combination therapy n = 41	Talinolol monotherapy n = 41
Hypotension	2	2	2	4	
Abdominal pain, nausea, heartburn	2	1	1	1	1
Palpitation	2				
Intermittent claudication				2	
Blurred vision		2			
Headache	1				
Oedema		1			
Dizziness				1	
Bradycardia				1	
Total	7	6	3	9	1

marked fall in blood pressure was the reason for decreasing the doses of both nifedipine and talinolol in two patients during high-dose combination therapy, and for stopping low-dose combination therapy in one patient. The best tolerated therapies were talinolol monotherapy and the low-dose combination therapy.

Only one patient was excluded from the study because of hypotension. Significant differences in adverse events between the different treatments could not be detected because of the small patient numbers.

Discussion

As with other calcium channel blockers and beta-blockers, nifedipine and talinolol are often prescribed together in cases of angina pectoris; the rationale being that when given together, their modes of action will be complementary, and will provide a greater therapeutic response than when used alone. In addition, synergy between the two classes of drugs may reduce the potentially harmful effects of each. The present study was designed to assess the efficacy of nifedipine and talinolol – as a monotherapy and when given in combination in different dosages – in patients with stable angina pectoris. It also provided an opportunity to compare the results with those from the TIBET study [4].

The multicentre, double-blind, randomised, parallel-group TIBET study was primarily designed to investigate whether the total ischaemic burden has important prognostic implications in patients with stable angina. Its secondary objective was to assess the anti-ischaemic effects of 6 weeks of therapy with atenolol (50 mg twice daily), and a slow-release formulation of nifedipine (20 mg twice daily), and their combination, using standardised exercise testing and ambulatory ST-segment monitoring. Thus there are a number of similarities in design between the TIBET study and the present study. The bioequivalence of the nifedipine preparations used in both studies was comparable [6]. The beta-blockers used – atenolol in the TIBET study, and talinolol in this study – belong to the same class. However, unlike the TIBET study, the present study used talinolol in two different doses (100 mg once daily or 100 mg twice daily) in combination with nifedipine. Atenolol (50 mg twice daily) and talinolol (100 mg twice daily) are considered to be approximately equally effective doses [Sourgens et al. Comparison of talinolol and atenolol effects on blood pressure in relation to lipid and glucose metabolic parameters. Results from the TALIP study. Submitted to Int J Clin Pharm].

In the main, results between the present study and the TIBET study were similar. In this study, heart rate at rest did not change during nifedipine treatment, but as expected, talinolol's beta-blocking activity significantly decreased heart rate when given alone, and in combination with nifedipine. At rest, both systolic and diastolic blood pressure decreased with all treatments. Systolic blood pressure was lowest during high-dose combination therapy, suggesting an additive effect of the two drugs for this parameter. These results are broadly in agreement with those in the TIBET study where atenolol decreased heart rate, but nifedipine did not, yet both drugs reduced blood pressure to a similar extent. The TIBET study also revealed a significantly more pronounced decrease in blood pressure during combination therapy.

Unlike the TIBET study, this study also monitored the anginal attack rate at rest. During all treatments, anginal attacks occurred significantly less often during rest, compared with baseline. Furthermore, the nitroglycerine consumption results are broadly in agreement with the reduction in anginal attack rates and provide further, objective evidence of thera-

peutic efficacy. We can confidently say, therefore, that all treatment regimens were effective at reducing these attacks. In addition, a comparative analysis of these anti-anginal effects at rest revealed a dose-response relationship between high and low-dose nifedipine monotherapy and high- and low-dose combination therapy. The most pronounced effect was produced by the high-dose combination of the two drugs and by talinolol monotherapy.

The anti-anginal efficacy of the two drugs seen at rest is also reflected in the increase in exercise tolerance. Duration of exercise, time to ST-depression, time to onset of angina attack, and total work load significantly increased during the three measured treatments. The most pronounced effect (although not significant for all parameters) was noted during the high-dose combination therapy. This is in marked contrast to the findings of the TIBET study, which showed no significant advantage in using the combination therapy of nifedipine with a beta-blocker over monotherapy.

Such differences in results between this study and the TIBET study may reflect differences in activities between the beta-blockers, talinolol and atenolol – particularly talinolol's higher beta-1 selectivity compared with atenolol. Differences in methodology and patient populations should also be considered. Unlike the present study, the parallel group structure of the TIBET study makes it impossible to state definitively that addition of a second drug results in further benefits.

Although the most marked anti-anginal effect at rest and during exercise was seen during high-dose combination therapy, this drug combination caused more adverse events than when the drugs were used alone. This factor may, therefore, limit the clinical applications of the combinations of nifedipine and talinolol in high doses, and consideration should be given to low-dose combinations, where, as this study demonstrates, adverse events are likely to be lower. It is noteworthy that the lowest adverse event rate was seen during talinolol monotherapy, despite its relatively high dose. Even at doses of 200 mg daily, this therapy did not lead to the development of critical bradycardia and/or atrio-ventricular conduction disorders that are sometimes observed with other beta-blockers [1].

Reducing myocardial oxygen demand is one of the prime targets of anti-anginal medications. However, direct measurement of this parameter is difficult because it depends upon a variety of factors [8, 9]. In this study, we have used the double product (which uses the readily measurable parameters of heart rate and systolic blood pressure) to ascertain oxygen demand, because the double product correlates well with oxygen demand both in angina pectoris patients and healthy individuals [10–12].

Our results indicate that the double product significantly decreased after talinolol consumption, which is consistent with a reduction in oxygen demand produced by a typical beta-blocker. However, after nifedipine consumption, the mean values of double product at peak load either remained the same or increased; effects that correspond well with published data [13]. Thus, with nifedipine, exercise tolerance increased at the same or even higher levels of oxygen demand. This suggests an increase in oxygen delivery to the ischaemic myocardium, which results from increased coronary perfusion and possibly a redistribution of blood flow between subepicardium and subendocardium [13].

Of particular clinical interest, we noted that during treatment with nifedipine, a significant increase of double product (by 14 units or more) occurred in some patients who also showed a marked increase in exercise tolerance. Such a pronounced response to nifedipine presumably reflects the considerable role played by coronary constriction in the develop-

ment of effort angina in some patients. The anti-anginal effect of nifedipine, therefore, may be at its greatest in this particular group of patients. Thus, in the clinical setting, an increase of double product of more than 14 units at peak exercise after nifedipine consumption may be a useful indicator of those patients who are likely to gain the most advantage from nifedipine anti-anginal therapy.

Overall, this study suggests that monotherapy with either the slow-release formulation of nifedipine or with talinolol provides anti-anginal and anti-ischaemic effects in patients with stable angina pectoris. This study also suggests greater efficacy with combination therapy. Therefore, in those patients where monotherapy is unable to provide satisfactory symptom relief, combination therapy with the two medications (particularly the high-dose combination of nifedipine 40 mg and talinolol 200 mg) is a viable alternative. However, the high-dose combination therapy appears to produce a greater incidence of adverse events, so a lower-dose combination therapy (nifedipine 20 mg and talinolol 100 mg) may provide an acceptable compromise between efficacy and tolerability in certain patients.

Acknowledgements

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