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Comparison of Diltiazem Standard Formulation and Diltiazem Controlled Release in Patients with Stable Angina Pectoris: A Randomized, Double-blind, Cross-over, Multicenter Study

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Summary: In a randomized, double-blind, cross-over, multicenter study with a placebo run-in phase, the efficacy and safety of two oral formulations of diltiazem, standard three or four times daily (t.i.d. or q.i.d.) and controlled release twice daily (b.i.d.), were compared in 49 patients with stable angina pectoris. ST-segment depression at maximum exercise 12 h after tablet intake was less frequently observed with diltiazem controlled release than with standard diltiazem (34 of 49, 69% vs. 43 of 49, 88%, p = 0.007). In patients with ST-segment depression after both treatments (n = 33), the average time to 1-mm ST-segment depression was 55.4 ± 19.9 s longer with diltiazem controlled release than with standard diltiazem [476 ± 195 vs. 422 ± 163 s, p = 0.009; 95% confidence interval (CI) 14.8–96 s]. Reduction in mean number of anginal attacks and nitroglycerin (NTG) intake was not significantly different between treatment with standard diltiazem and diltiazem controlled release. The incidence of side effects was low and not different between the two treatments. Both formulations are equally effective in reducing the number of anginal attacks and are well tolerated. Diltiazem controlled release is more effective than standard diltiazem in preventing myocardial ischemia 12 h after tablet intake. Thus, diltiazem controlled release allows twice-daily intake frequency and may therefore be preferable to standard diltiazem in treatment of stable angina pectoris. **Key Words:** Diltiazem—Diltiazem controlled release—Monotherapy—Angina pectoris—Exercise electrocardiography.

Diltiazem, a benzothiazepine derivative, is a potent calcium antagonist widely used in treatment of angina pectoris. Diltiazem decreases oxygen consumption of the myocardium by reducing afterload and decreasing heart rate (HR) (1–3). Diltiazem increases oxygen supply to the myocardium by dilating the coronary arteries, resulting in an increase in myocardial blood flow at rest as well as during exercise with no disturbance in autoregulation (4–8). The efficacy of diltiazem in treatment of angina pectoris is documented in several short- and long-term placebo controlled trials (9–12).

The major drawback of the standard diltiazem formulation is its short half-life (t½) of 3–4 h, necessitating a dose schedule of three to four administrations daily. The recently available controlled release tablet is claimed to require fewer daily doses and may therefore improve patient compliance.

The efficacy of diltiazem controlled release in treating angina pectoris was previously established in placebo-controlled studies (13,14), in short-term comparative studies versus isosorbide-5-mononitrate (15) and versus metoprolol (16), and in a long-term comparative study versus metoprolol

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(17). Monotherapy with diltiazem controlled release appeared to be more effective than monotherapy with isosorbide-5-mononitrate and at least as effective as metoprolol. Furthermore, in both short- and long-term comparative studies versus metoprolol, a favorable effect on exercise capacity was observed after treatment with diltiazem controlled release formulation (16,17).

Recently, a significant reduction in frequency and duration of ST-segment depression was observed on 72-h ECG Holter recordings in patients with stable coronary artery disease after treatment with diltiazem controlled release (18). Moreover, the beneficial effects of diltiazem controlled release in this study were maintained throughout the circadian cycle.

In this randomized, double blind, cross-over, multicenter study, the efficacy, tolerance, and safety of monotherapy with two oral preparations of diltiazem (standard and controlled release) in individually determined dosages, were compared in patients with stable angina pectoris. Special interest was focused on drug efficacy 12 h after tablet intake, allowing detection of the presumed prolonged efficacy of diltiazem controlled release as compared with standard diltiazem.

PATIENTS AND METHODS

Patient selection

Patients who met the following criteria were included: age between 30 and 70 years; typical stable effort-induced angina pectoris with a duration of at least 3 months, relieved by sublingual nitrates; at least three anginal attacks during the single-blind placebo week; and a reproducible positive exercise test (at the beginning and end of the placebo week). A positive exercise test was defined as at least 1-mm horizontal or downsloping ST-segment depression as compared with the reference ECG and persisting at least 0.08 s after the J-point, in combination with anginal pain and occurring between a workload of at least 60 W and at most 150 W. Reproducibility of the positive exercise test was defined as <15% variation in time to ischemic threshold (time to 1-mm ST-segment depression). Women had to have additional proof of coronary artery disease by angiographic demonstration of >70% obstruction in one or more major coronary arteries, documented myocardial infarction (MI), or a positive thallium perfusion test during exercise. Written or witnessed informed consent was required.

Patients were not eligible for entry into the study if one of the following conditions existed: unstable angina; angina occurring only under special circumstances such as cold, anxiety, or emotions; valvular heart disease mimicking symptoms of angina pectoris; congestive heart failure (grade III or IV New York Heart Association, NYHA); second- or third-degree atrioventricular (AV) block; sick sinus syndrome or bradycardia <55 beats/min; MI in the previous 3 months; severe or complicated hypertension [diastolic blood pressure (DBP) >120 mm Hg and/or systolic BP (SBP) >250 mm Hg]; coronary angioplasty in the previous 3 months; coronary artery bypass surgery <6 months earlier; clinically significant hepatic dysfunction; renal insufficiency (creatinine >160 μM); anemia or any other serious chronic disease; a history of alcoholism (whether the patient was undergoing detoxication or not); weighing 20% more or 20% less than standard weight for height; a history of severe adverse events to calcium antagonists; inability to understand the study or follow-up treatment; inability to complete effort test (e.g., due to arteriopathy); abnormal ECG results precluding interpretation of exercise test (e.g., complete left bundle branch block, Wolff-Parkinson-White phenomenon, digitalis treatment); concomitant medication likely to interfere with study results; premenopausal status in women of childbearing potential not receiving oral contraceptives or nursing mothers; or predominant rhythm other than sinus rhythm.

Study design

The study was a randomized, double-blind, double-dummy, cross-over, multicenter study preceded by a placebo run-in phase and a dose-titration period (Fig. 1). Patients receiving antianginal treatment underwent a treatment tapering-off phase before being included in the study. A 7-day tapering-off period was necessary for

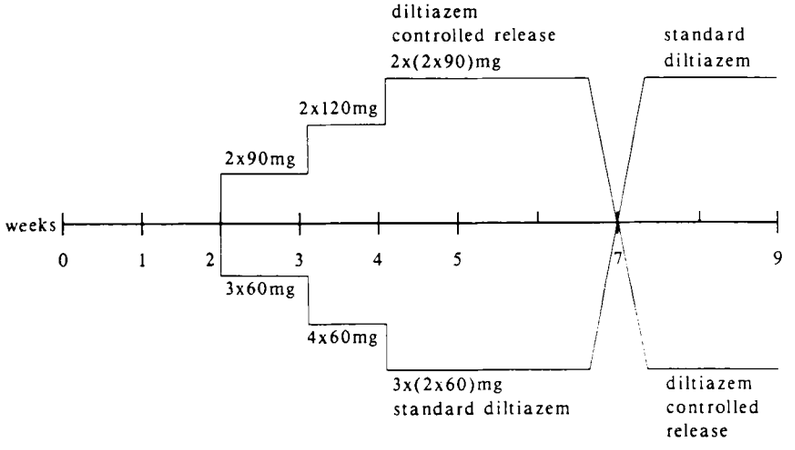

FIG. 1. Study design. During the dose-titration period, efficacy was defined as a reduction of more than two thirds in the number of anginal attacks per week as compared with frequency during placebo treatment. Depending on the required dosage, total duration of the active treatment period ranged from 5 to 7 weeks.

β-blockers and a 3-day tapering-off period was required for calcium antagonists. Long-acting nitrates could be discontinued 1 day before the single-blind placebo week. During both periods, patients received two placebo tablets three times a day (t.i.d.). Sublingual nitroglycerin was permitted as acute antianginal treatment throughout the study. Prophylactical use of sublingual nitroglycerin was not allowed, nor was use of any other antianginal medication.

At completion of the baseline period, eligible consenting patients entered into the double-blind portion of the study and were randomly assigned to one of the two treatment-order groups. To determine efficacious dose of standard diltiazem or diltiazem controlled release, the two times 2 weeks cross-over period was preceded by a dose-titration period in which efficacy was defined as a reduction of more than two thirds in the number of anginal attacks each week as compared with baseline.

Half of the patients were randomized to start the active treatment period with 60 mg diltiazem standard formulation three times daily (t.i.d.). If this dose was not effective at the end of the first week, the dosage was increased to 60 mg four times daily (q.i.d.). The last dosage was increased to 120 mg t.i.d. if the required efficacy as described was not reached (Fig. 1). When the effective dose was determined, this group received this dosage of standard diltiazem for 2 weeks followed by the same dose of diltiazem controlled release in the next 2 weeks followed by the same dose of diltiazem controlled release for the subsequent 2 weeks.

The other half of the patients received 90 mg diltiazem twice daily (b.i.d.) controlled release. If this dose was not effective, it was increased to 120 mg b.i.d. and 180 mg b.i.d., respectively. When the effective dose was determined, this group received this dosage of diltiazem controlled release for 2 weeks followed by the same dose of standard diltiazem for the subsequent 2 weeks. A daily dosage of 360 mg that was not effective was regarded as an endpoint, and the patient had to be excluded from the study.

To respect the double-blind character of the study, the method of double placebo was used. Matched identical tablets were provided, containing either diltiazem 60 mg standard formulation, diltiazem 90 mg controlled release formulation, diltiazem 120 mg controlled release formulation, or placebo. Patients were asked to take their evening trial medication after 10 p.m. A diary card was provided for each patient to record frequency of anginal attacks and use of sublingual nitroglycerin (NTG). The diary card was checked and approved by the investigator at each visit.

No dose adjustment of trial medication was permitted after the dose-titration period. Use of β-blockers, long-acting nitrates, and calcium antagonists other than the study medication was not permitted. The same applied to drugs likely to affect AV conduction (e.g., amiodarone), or drugs likely to interfere with the absorption or efficacy of diltiazem (e.g., aluminum salts).

Compliance was checked by questioning each patient and by counting tablets at every visit. Samples for diltiazem blood level determination were taken in a subset of 13 patients on the final day of each cross-over period ~12 h after tablet intake just before the exercise test and before the morning dose. Lithium-heparin tubes with 10 ml venous blood were immediately frozen at −20°C and kept at this temperature until analysis. The times of blood sampling and intake of the last dose were recorded carefully.

Patients received consecutive numbers and were randomized with a blocking factor of six just before the start of the double-blind phase. Each participating center was provided with six prepacked boxes of study medication with sealed code envelopes for emergency cases only. After the trial, all code envelopes were collected and checked by the study monitor. The study was approved by the medical ethical committee in each participating center and was performed according to the Declaration of Helsinki.

Exercise test

Exercise tolerance was assessed by a symptom-limited bicycle exercise test performed at the beginning and end of the baseline period, after 2 weeks of treatment with the effective dose of standard diltiazem, and after 2 weeks of treatment with the effective dose of diltiazem controlled release. The tests had to be performed at approximately the same time in the morning in the presence of the same investigator.

Patients were asked not to take their study medication on the morning of the test so that the controlled release properties 12 h after tablet intake could be assessed. If patients had to use sublingual NTG, the test had to be postponed until at least 1 h after NTG intake.

An electronically braked bicycle ergometer was used. The exercise was performed with the patient in sitting position. Starting at a workload of 30 W with increments of 10 W every minute, patients performed the test until maximum workload was reached. Maximum workload was reached when patients either experienced the same degree of anginal pain that would have forced them to stop activity in daily life or when they reached physical exhaustion. Twelve-lead ECG recordings were performed before exercise was started, at the end of each exercise stage, at the beginning of ST-segment changes, at occurrence of angina, at maximum effort, and 1, 3, and 6 min postexercise or longer if the ECG had not returned to baseline levels. The exercise test had to be interrupted when the following symptoms occurred: dizziness, severe dyspnea, lowered consciousness, signs of vasoconstriction (pallor, cold skin), decrease in SBP >20 mm Hg; SBP >250 mm Hg and/or DBP >120 mm Hg, atrial fibrillation, atrial flutter or other forms of supraventricular tachycardia, ventricular tachycardia (VT, three or more successive beats of ventricular origin), ST-segment decrease or increase of >2 mm or additional ST-segment decrease or increase of >2 mm as compared with baseline, widening of QRS complexes, and onset of AV conduction disturbances.

Safety evaluation

Adverse events were assessed and recorded, regardless of the relation to the study drug, by a standard nonleading question at each visit. A questionnaire with 22 possible side effects was also presented to the patients. The severity of side effects was scored with the following classification: minor, the patient experiences a few symptoms, but these are quite tolerable; moderate, the symptoms affect the patient slightly in daily activity; and severe, the patient experiences disturbance in daily activity.

Chest roentgenograms were obtained before study entry if none had been available in the previous 6 months. Routine physical examination was performed during each visit.

Laboratory evaluations

Laboratory tests were performed before study entry and at the end of each of the 2-week treatment periods with the efficacious dose. Hematology (including blood cell count and platelet count) and serum chemistry were assessed.

Criteria for effectiveness

The primary outcome measures were time to 1-mm ST-segment depression and time to onset of angina pectoris during the symptom-limited bicycle exercise test ~12 h after tablet intake. Secondary exercise test variables were total exercise time and maximum workload. In addition, in a subset of 13 patients, diltiazem blood levels were determined just before the start of the exercise test. Finally, efficacy of treatment was assessed by the number of anginal attacks and NTG intake.

Statistical analysis

Statistical analyses were performed with the SPSS/PC+ and EGRET packages. Equality of the carryover (residual) effects was tested by comparing the within-patient period totals between the two treatment-order groups, taking the baseline (placebo) measurement as a covariate if imbalance resulted from the randomization. If there was no evidence of different carryover effects, equality of the two treatments was tested by comparing the within-patient period differences between the two treatment-order groups. The two-sample *t* test was used for symmetrical distribution. The Mann-Whitney test was used for skewed distributions. For dichotomous (yes/no) variables, within-patient period differences were compared between the two treatment-order groups in a 3×2 crosstable and tested with an exact trend test. Equality of placebo and either one of the two treatments was tested by means of the one-sample *t* test or the one-sample Wilcoxon test (for skewed distributions); for dichotomous variables, the McNemar's test was used. If the *t* test was applied, mean and SD are reported. If the Mann-Whitney or Wilcoxon test was applied, mean, median, and range are reported. For each test, $p < 0.05$ (two-sided) was considered statistically significant. Ninety-five percent confidence intervals (CIs) are given for the main treatment effects.

RESULTS

One hundred ten patients were screened in 13 centers, and 55 of them were excluded before entering the double-blind active treatment period. The most common exclusion factor was failure to exhibit ST-segment depression within the prescribed workloads during the exercise test. Four patients were randomized but could not be included in the analysis because of protocol violations (1 patient without placebo week data, 1 lost to follow-up, and 2 because of poor quality of the case record forms allowing no interpretation of results). Two patients were withdrawn prematurely from the study. One patient receiving standard diltiazem experienced acute myocardial infarction in the third week of the dose-titration phase. One patient receiving diltiazem controlled release was withdrawn in the first week of the dose-titration phase because of relapse of preexisting paroxysmal runs of premature ventricular contractions.

Forty-nine patients completed the study. Characteristics of the study population at entry are shown in Table 1. Twenty-five patients started the titration phase with standard diltiazem, and 24 started with diltiazem controlled release.

No differences in the number of dosage increase steps during the titration phase between standard diltiazem and diltiazem controlled release could be demonstrated. In the group that started the dose-titration phase with standard diltiazem, 14 were treated with 60 mg t.i.d., 10 were treated with 60 mg q.i.d., and 1 was treated with 120 mg t.i.d. In the group that started with diltiazem controlled release, 12 patients were treated with 90 mg b.i.d., 10 were treated with 120 mg b.i.d., and 2 were treated with 180 mg b.i.d. No patient was excluded from the study as a result of treatment failure.

Because the study was a cross-over study, all patients served as their own controls. No carryover effects could be demonstrated. Data on the treatment periods with standard diltiazem and diltiazem controlled release were pooled.

Anginal episodes and NTG consumption

The frequency of anginal attacks per week decreased from a mean of 6.61 (range 3–24) in the placebo period to 1.14 (range 0–8) during treatment with standard diltiazem and to 1.53 (range 0–7) during treatment with diltiazem controlled release ($p < 0.0001$ for both treatments vs. placebo; no significant difference between the two treatments). Use of sublingual NTG tablets decreased from a mean of 2.14 (range 0–11) during the placebo period to 0.53 (range 0–8) during standard diltiazem and to 0.57 (range 0–5) during diltiazem controlled release ($p < 0.0001$ for both treatments vs. placebo, no significant difference between the two treatments).

Adverse effects

The frequency of spontaneously reported adverse effects was low and was not different between the two formulations (Table 2). Neither did the number of side effects per patient, according to the questionnaire, show any significant difference between placebo and the two treatments (Table 3).

Hemodynamic, ECG, and laboratory assessments

Physical examination showed that both formulations, as compared with placebo, caused a significant reduction in heart rate (HR): from 77.6 ± 11.7 beats/min during placebo to 73.3 ± 9.05 with standard diltiazem ($p = 0.001$) and to 71.0 ± 11.7 with

TABLE 1. *Characteristics of study population at entry into study*

Parameter	Mean ± SD[a]	Range
Clinical		
Age (yr)	57.3 ± 9.09	(35–70)
Sex (n)		
M	46	
F	3	
Weight (kg)	76.1 ± 8.61	(56–93)
Height (cm)	175 ± 7.93	(155–191)
Duration of coronary artery disease (mo)	59.7 ± 72.8	(3–366, median 24.5)
Previous myocardial infarction (n)	26	
Previous hypertension (n)	15	
Diabetes mellitus (n)	2	
Smokers (n)	26	
Hypercholesterolemia (n)	25	
Coronary bypass surgery >6 mo earlier (n)	4	
Angioplasty >3 mo (n)	7	
Functional class[b] (n)		
II	16	
II à III	25	
III	8	
Angiographic		
With coronary angiography (n)		
One-vessel disease	21	
Two-vessel disease	11	
Three-vessel disease	3	

[a] Values are means ± SD when applicable. Values in parentheses are minimum–maximum.
[b] Functional class according to New York Heart Association.

diltiazem controlled release ($p < 0.0005$ for both formulations vs. placebo, no significant difference between the two treatments). Rate-pressure product (RPP) at rest decreased from 11,129 ± 2,359 min^{-1} mm Hg during placebo to 10,286 ± 2,354 min^{-1} mm Hg during standard diltiazem ($p = 0.001$) and to 9,852 ± 2,413 min^{-1} mm Hg during diltiazem controlled release ($p < 0.0005$, no significant difference between the two treatments).

Both formulations increased the P-R interval of the ECG from 0.159 ± 0.031 s at baseline to 0.163 ± 0.029 s during standard diltiazem ($p = 0.059$) to 0.166 ± 0.030 s ($p = 0.008$) during diltiazem controlled release treatment (no significant difference between the two treatments). No effects on hematology or biochemistry parameters could be demonstrated for either treatments.

In a subset of 13 patients, diltiazem blood levels were measured ~12 h after tablet intake. Median blood levels with diltiazem controlled release treatment were significantly higher than with standard diltiazem treatment: 69.2 μg/L (range 30.4–198.5 μg/L) versus 45.9 μg/L (range 22.9–146 μg/L), respectively, ($p = 0.019$).

TABLE 2. *Adverse effects spontaneously reported by 49 patients*

Effect	Treatment		
	Placebo	Diltiazem	Diltiazem controlled release
Dizziness	1	1	0
Tiredness	0	2	2
Palpitations	0	0	1
Stomach complaints	0	1	1[a]
Skin reaction	0	2	1[a]
Flushing	0	2	0
Nausea	0	1	0
Headache	1	0	1
Paresthesias	1	0	0
Total	3	9	6

[a] Same patient for diltiazem as well as diltiazem controlled release treatment.

Exercise test results

Table 4 shows ECG, clinical, and hemodynamic results of the exercise tests performed at the end of the placebo week and after both treatment periods. Significant ST-segment depression occurred in 43 patients during standard diltiazem treatment and in 34 during diltiazem controlled release treatment ($p = 0.007$). In patients with ST-segment depression on both treatments ($n = 33$), the average time to occurrence of 1-mm ST-segment depression was 55.4 ± 19.9 s longer with diltiazem controlled release than with standard diltiazem treatment (476 ± 195 vs. 422 ± 163 s) ($p = 0.009$, 95% CI 14.8–96 s). In patients with ongoing angina pectoris after both treatments ($n = 23$), the average time to occurrence of angina pectoris was 35.2 ± 19.2 s longer with diltiazem controlled release than with standard diltiazem treatment (569 ± 137 vs. 528 ± 159 s) ($p = 0.081$, 95% CI −4.80–75.2 s).

TABLE 3. *Number of side effects in all patients scored according to a questionnaire with 22 possible side effects*

	Treatment		
Severity cutoff	Placebo	Standard diltiazem	Diltiazem controlled release
Minor, moderate, and severe	1.74 (0–0–14)	1.37 (0–0–10)	1.24 (0–0–11)
Only moderate and severe	0.61 (0–0–5)	0.33 (0–0–4)	0.37 (0–0–5)
Only severe	Once flushing	Once stomach pain	0

Values are means. Values in parentheses are minimum, median, and maximum. No statistical differences were observed.

Total exercise time improved by 12% with standard diltiazem (from 563 ± 180 s to 631 ± 195 s, $p < 0.0005$) and by 14% with diltiazem controlled release (to 642 ± 189 s, $p < 0.0005$; no significant difference between the two treatments) (Fig. 2). RPP at rest decreased equally during both treatments as compared with placebo. RPP at maximum exercise was not different as compared with placebo during treatment with either formulation, despite the increase in maximum workload (from 116 ± 30.6 to 126 ± 32.3 W with standard diltiazem treatment and to 129 ± 31.8 W with diltiazem controlled release treatment) ($p < 0.0005$, no significant difference between the two treatments).

DISCUSSION

In this study, the efficacy, tolerance, and safety of monotherapy with two preparations of diltiazem, standard and controlled release, were compared in

TABLE 4. *Results of exercise testing ~12 h after intake*

	Treatment								
Parameter	Placebo	Standard diltiazem	p-Value versus placebo	Diltiazem controlled release	p-Value versus placebo	Treatment effect diltiazem controlled release versus standard diltiazem[a]	p-Value of diltiazem controlled release versus standard diltiazem	95% CI Lower	95% CI Upper
ECG									
No. of patients with ≥1 mm ST-depression	49	43	0.031	34	0.000	−9	0.007		
Time to 1 mm ST-depression (s) n = 33	419 ± 156	422 ± 163	0.833	476 ± 195	0.002	55.4 ± 19.9	0.009	14.8	96.0
Clinical									
Time to angina pectoris (s) n = 23	489 ± 143	528 ± 159	0.202	569 ± 137	0.005	35.2 ± 19.2	0.081	−4.80	75.2
Total exercise time (s) n = 49	563 ± 180	631 ± 195	0.000	642 ± 189	0.000	11.2 ± 9.22	0.231	−7.35	29.7
Maximum workload (W) n = 49	116 ± 30.6	126 ± 32.3	0.000	129 ± 31.8	0.000	2.63 ± 1.52	0.089	−0.422	5.69
Hemodynamic									
Rest									
HR (min^{-1}) n = 49	82.6 ± 14.3	76.8 ± 11.7	0.000	74.8 ± 14.9	0.000	−1.91 ± 1.47	0.201	−4.88	1.05
SBP (mm Hg) n = 48	148 ± 20.0	139 ± 16.7	0.003	141 ± 18.2	0.027	2.37 ± 2.42	0.332	−2.50	7.25
RPP (min^{-1} mm Hg) n = 48	12,273 ± 2,731	10,744 ± 2,421	0.000	10,629 ± 2,649	0.000	−115 ± 304	0.707	−726	497
Maximum exercise									
HR (min^{-1}) n = 49	139 ± 20.1	137 ± 17.8	0.348	137 ± 19.4	0.313	−0.011 ± 1.26	0.993	−2.55	2.53
SBP (mm Hg) n = 45	194 ± 24.9	196 ± 28.2	0.443	192 ± 27.8	0.545	−2.66 ± 3.18	0.407	−9.08	3.75
RPP (min^{-1} mm Hg) n = 45	27,232 ± 6,083	27,257 ± 6,071	0.970	26,532 ± 6,109	0.335	−545 ± 478	0.260	−1,508	417

Values are means; ± is mean ± SD.

[a] A positive value indicates diltiazem controlled release greater than standard diltiazem.

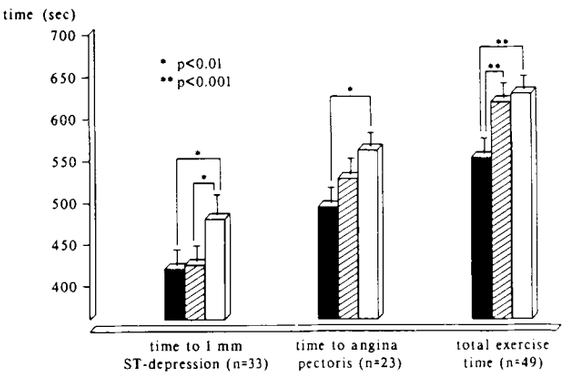

FIG. 2. Results of exercise testing ~12 h after tablet intake (mean ± SEM). Placebo (solid bars), standard diltiazem (hatched bars), diltiazem controlled released (open bars).

49 patients with stable angina pectoris. The strict exercise test inclusion criteria were meant to establish a homogeneous population for study; this was only partially achieved, as shown by the wide range in number of anginal attacks (3–24) during the placebo period. The therapeutic effect of diltiazem is evident with daily doses between 180 and 360 mg (19). The results of this study show that most patients can be effectively and safely treated with diltiazem 240 mg/day. It is remarkable that no patient had to be withdrawn because of inefficacy. With regard to data derived from the angina pectoris diaries, diltiazem controlled release is as potent as standard diltiazem in reducing the number of anginal attacks and NTG consumption.

Standard diltiazem as well as diltiazem controlled release has proven to be well tolerated. The incidence and severity of side effects in this study were not different from those reported in the literature (20,21). Although no statistically significant differences were observed between the two treatments, there appears to be a trend toward fewer side effects during treatment with diltiazem controlled release (Table 3). Fewer side effects during treatment with controlled release preparations are to be expected as a result of relatively lower plasma peaks. However, the beneficial side effect profile of the diltiazem molecule would require a large study population to detect a possible significant difference in side effects between the two preparations.

ECG and clinical exercise test parameters ~12 h after tablet intake showed greater beneficial effects of diltiazem controlled release as compared with standard diltiazem (Table 4). This is not surprising because treatment with diltiazem controlled release leads to higher blood levels 12 h after tablet intake as a result of continuous release of the drug from the matrix tablet (22), as was confirmed in a subset of 13 patients in this study. Twelve hours after tablet intake, however, RPP at maximum exercise was not different as compared with placebo during treatment with either formulations, indicating that there were no differences in oxygen consumption.

The favorable effect on ECG exercise parameters of treatment with diltiazem controlled release as compared with standard diltiazem in this study therefore could result from increased oxygen supply. Diltiazem may increase coronary blood flow only above a certain plasma level at steady state. Support for this hypothesis was provided by Remme and colleagues (23), who reported a similar blood level-dependent relation for diltiazem administered intravenously. The reduced number of daily doses necessary for optimum effect in treatment with diltiazem controlled release may improve patients' compliance with treatment. Pullar and coworkers (24) showed significantly improved compliance in patients receiving tablets once or twice a day as compared with patients receiving tablets three or four times a day; in their study, it was remarkable that no significant difference in patient compliance was noted between once- or twice-daily tablet intake.

An important advantage of twice-daily dosing may be more sustained 24-h protection against ischemic periods, whether silent or not, because current literature data increasingly show the deleterious effects of ischemic periods on morbidity and mortality (25,26). In addition, the circadian pattern of ischemic episodes with a peak in the early morning hours may also be an argument in favor of the controlled release formulation (27–29).

We conclude that both standard diltiazem and diltiazem controlled release formulations are effective in patients with stable angina pectoris and have few side effects. Diltiazem controlled release is more effective than standard diltiazem in preventing myocardial ischemia 12 h after tablet intake. Thus, diltiazem controlled release allows twice-daily intake frequency and may therefore be preferable to standard diltiazem in treatment of stable angina pectoris.

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