Twenty-four hour efficacy of two dose levels of a once daily sustained-release diltiazem formulation in stable angina: a placebo-controlled trial

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- 1 This placebo-controlled study assessed once daily sustained-release (SR) diltiazem, 200 and 300 mg, in 182 stable angina patients with positive exercise test.
- 2 Exercise testing was performed at baseline after a 7 day placebo run-in period, and repeated after 7 days of treatment, 25.0 ± 0.1 h postdose.
- 3 Diltiazem (200 and 300 mg) produced respectively a 68% and a 64% decrease in weekly angina episodes, and placebo a 15% decrease ($P < 0.05$). Similarly, both dose levels produced a 70% decrease in nitroglycerin consumption, whereas no difference was obtained with placebo ($P < 0.01$). The increase in time to ischaemic threshold was significantly superior for 200 mg and 300 mg diltiazem when compared with placebo (75.2 and 91.5 s respectively vs 47.0 s) ($P < 0.05$); increase in time to anginal threshold was also significantly greater for diltiazem when compared with placebo (84.6 and 85.9 s respectively vs 43.9 s) ($P < 0.05$).
- 4 Only one patient experienced worsening of angina and had to be withdrawn from the study.
- 5 This study demonstrates 200 and 300 mg SR diltiazem is effective when given once-a-day in the prophylaxis of stable exertional angina. This once daily formulation should improve patients' compliance and comfort.

Keywords stable angina pectoris diltiazem once daily sustained-release formulation exercise tolerance

Introduction

The effectiveness of diltiazem, a calcium-channel antagonist, in the treatment of stable exertional angina has been well documented for its multiple-dose formulation [1] over the past 15 years. A more recently available controlled-release tablet used in the United States, designed to be given twice-daily has proven efficacy in placebo-controlled studies [2, 3], in short-term comparative studies against metoprolol [4] and isosorbide-5-mononitrate [5], and in a long-term study against metoprolol [6]. In addition, controlled-release diltiazem has been shown to be more effective than the standard formulation in preventing myocardial ischaemia 12 h after ingestion, both formulations being equally effective in reducing number of anginal attacks [7].

Pharmacokinetic data have shown a new galenic formulation to present smaller blood level daily

fluctuations than those after multiple doses of the standard formulation (data on file, Synthélabo Recherche). These results validate the safe use of once daily sustained-release (SR) diltiazem in angina.

This study was undertaken to evaluate the 24 h efficacy and the safety of this new once daily SR preparation of diltiazem in patients with exertional angina, using two different dosages, in a controlled protocol.

Methods

This was a multicentre, European, double-blind, placebo run-in, parallel-group trial comparing two dose levels, 200 and 300 mg, of once daily SR diltiazem.

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azem with placebo. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent of all patients and approval by each local Hospital Ethics Committee were obtained prior to study.

Patients

Patients 30 to 70 years old, suffering from typical stable exertional angina for at least 3 months and presenting with reproducible exercise tests performed 7 days apart could be enrolled. A positive exercise test was defined by at least a 1 mm horizontal or a down-sloping 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. Women had to have additional proof of coronary artery disease by angiographic demonstration of >75% obstruction in one or more major coronary arteries, or documented myocardial infarction. Time to ischaemic threshold (TIT) had to be between 3 and 12 min. Reproducibility of tests was defined as <15% variation in total exercise time (TET).

Patients were excluded in case of myocardial infarction, or coronary angioplasty or aortocoronary by-pass grafting within the last 3 months, unstable angina, severe valvular disease, congestive heart failure, severe hypertension, sinus rhythm disorders, 2nd or 3rd degree atrioventricular block or left bundle-branch block, hypertrophic cardiomyopathy, or any evidence of major systemic disease. Concomitant medications likely to interfere with study results were not allowed. Previous antianginal drugs had to be tapered off during the wash-out period preceding placebo run-in. Sublingual nitroglycerin was authorized during the study.

Study schedule

A 1 week single-blind placebo period was used as baseline for measuring frequency of anginal attacks and short-acting nitrates consumption. Exercise testing on a bicycle ergometer was performed upon pre-selection (day -7) and at baseline (day 0). Patients who fulfilled inclusion criteria were then randomized to one of the three treatment arms: 200 mg once daily SR diltiazem, 300 mg once daily SR diltiazem, or placebo. After the 1 week active treatment period, an exercise test was performed (day 7) 22 to 26 h post-dosing. Clinical examinations were performed at each visit. Routine laboratory tests took place at day -7 and at study completion, and plasma samples were assayed at day 7, prior to exercise test and to morning dose for diltiazem level determination. Investigators documented all treatment emergent adverse events reported spontaneously by the patients, regardless of assessment of causality.

Exercise test

Exercise performance was assessed by a bicycle test initiated at a workload of 30 watts with increments of 30 watts every 3 min. The patients exercised to an endpoint of clinical or electrical myocardial

ischaemia, signs of circulatory failure, severe hypertension, rhythm disorders, achievement of maximum theoretical heart rate or muscle exhaustion. Twelve-lead ECG recordings were monitored before the test was started, every minute during the test, at ischaemic and anginal thresholds, at maximal exertion, and 1, 3, 7 and 10 min post-exercise. Blood pressure and heart rate were measured at each exercise level, at ischaemic and anginal thresholds, at end of exercise and 10 min post-exercise. The following variables were analyzed from test: TIT, time to anginal threshold (TAT), TET, peak ST depression. Rate-pressure product (RPP) was calculated as the product of heart rate (HR) and systolic blood pressure.

Statistical analysis

Analysis has been conducted on all patients having performed an exercise test under active treatment. The main objective efficacy criteria were TIT, TAT, TET. Weekly anginal episodes and nitroglycerin consumption were also evaluated. For patients who did not achieve ischaemic and anginal thresholds, parameters at these times were replaced by parameters measured at maximal exertion. Analysis was performed on raw data at day 7 and on changes between day 0 and day 7, results being presented as mean (s.e. mean). The three treatment groups were compared using an analysis of variance. Two-tailed tests were used with a significance level of 5%. Differences between dose changes are presented as mean (95% CI).

Results

Patients' characteristics

One hundred and ninety-two patients were screened in 26 centres of three European countries (investigators of the DILDURANG study group); ten of them were excluded during the placebo run-in period yielding 182 eligible patients for randomization. Three patients withdrew prematurely from the study during the active treatment period and did not have an evaluation at day 7: one patient in the 200 mg diltiazem group experienced worsening of angina, the outcome of which was favorable under treatment, one patient in this same group was excluded for bad compliance with the protocol and one patient receiving placebo underwent emergency surgery for a strangulated inguinal hernia. Therefore, 179 patients were taken into account for efficacy analysis, 59 received placebo, 54 diltiazem 200 mg and 66 diltiazem 300 mg.

No between-group differences were noted, at baseline, in demographic features, risk factors and coronary artery disease characteristics (Table 1).

Exercise test results

No between-group differences were noted in ergometric parameters at baseline. All exercise test parameters were improved by both dose levels of SR diltiazem (Table 2), exercise tests being performed

Table 1 Demographic and other baseline features for all enrolled patients

	Placebo n = 60	Sustained-release diltiazem	
		200 mg day ⁻¹ n = 56	300 mg day ⁻¹ n = 66
Men/women	57/3	51/5	57/9
Mean age (years)	61.1 (1.0)	61.8 (1.0)	60.4 (1.0)
Mean weight (kg)	72.5 (1.3)	74.7 (1.0)	72.8 (1.2)
Mean height (cm)	168.5 (0.7)	170.5 (0.9)	167.7 (0.7)
Duration of coronary disease (months)	49.5 (6.5)	49.1 (5.6)	58.0 (6.9)
Previous myocardial infarction (n)	26	21	23
Hypertension (n)	24	18	26
Diabetes mellitus (n)	8	6	8
Smokers (n)	34	30	41
Hypercholesterolaemia (n)	37	32	45
Family coronary disease (n)	18	19	25
Coronary by-pass grafting (n)	7	10	12
Weekly anginal episodes (n)	2.0 (0.4)	2.8 (0.7)	2.5 (0.4)
Weekly nitroglycerin intake (n)	1.4 (0.4)	1.7 (0.4)	1.6 (0.3)

Results are expressed as mean (s.e. mean) when relevant.

Table 2 Changes in ergometric parameters presented as mean (s.e. mean)

	Placebo n = 59	Sustained-release diltiazem	
		200 mg day ⁻¹ n = 54	300 mg day ⁻¹ n = 66
TIT (s)			
day 0	427 (21)	459 (22)	426 (22)
day 7	464 (21)	533 (24)*	524 (21)*
Δ TIT	47.0 (13.1)	75.1 (14.5)	91.5 (15.0)*
TAT (s)			
day 0	457 (22)	473 (22)	476 (25)
day 7	507 (20)	573 (23)*	581 (23)*
Δ TAT	43.9 (11.5)	84.6 (13.2)*	86.0 (11.9)*
TET (s)			
day 0	510 (21)	534 (20)	531 (22)
day 7	543 (21)	595 (23)	603 (23)
Δ TET	37.3 (10.2)	64.0 (12.1)	71.4 (10.5)*
SE segment depression (mm)†			
day 0	-1.81 (0.12)	-1.48 (0.08)	-1.63 (0.10)
day 7	-1.74 (0.12)	-1.29 (0.11)**	-1.42 (0.11)*
Δ ST segment depression (mm)	0.08 (0.12)	0.20 (0.10)	0.20 (0.08)

TIT, time to ischaemic threshold; TAT, time to anginal threshold; TET, total exercise time.

* $P < 0.05$ compared with placebo, ** $P < 0.01$ compared with placebo.

†At maximum exertion.

25.0 ± 0.1 h on average, after last drug intake. TIT and TAT increases were significant for both dose levels in comparison with placebo ($P < 0.05$). No statistical significant difference was shown against placebo for TET increase. Amplitude of ST segment depression was significant against placebo for both 200 and 300 mg dose levels ($P < 0.01$ and $P < 0.05$, respectively); however, no statistical difference was shown between both diltiazem groups.

Analysis of differences having occurred between day 0 and day 7 showed 300 mg diltiazem significantly increased TIT, TAT and TET in comparison with placebo ($P < 0.05$), while a significant increase in TAT and a tendency to an increase in TIT and TET was observed with 200 mg diltiazem (Table 2 and

Figure 1). No statistically significant difference was seen between both dosages of SR diltiazem.

Differences between dose levels presented as mean (95% confidence intervals) were consistent with the above results (Table 3); 300 mg diltiazem yielded statistically significant differences against placebo for differences in TIT, TAT and TET; 200 mg diltiazem yielded a statistically significant difference for the difference in TAT; no difference was shown between both diltiazem dose levels.

A descriptive analysis of changes in the reasons for stopping exercise test between day 0 and day 7 shows that the decrease in the number of patients who stopped the test because of anginal pain together with ST segment depression was greater in patients on

Figure 1 Changes in ergometric parameters after placebo (□), 200 mg once daily SR diltiazem (▨) and 300 mg once daily SR diltiazem (▩). TIT: time to ischaemic threshold, TAT: time to anginal threshold, TET: total exercise time.

diltiazem (−13 on 200 mg and −21 on 300 mg diltiazem) than in those on placebo (−9). An inverse relationship in the course of patients stopping the test because of muscle exhaustion was noticed (+4 on placebo, +9 on 200 mg and +23 on 300 mg diltiazem).

Angina episodes and nitroglycerin consumption

Mean number of weekly angina attacks decreased to 1.7 ± 0.4 with placebo and to 0.9 ± 0.2 with both dose levels of diltiazem ($P < 0.05$ in comparison with placebo). Similarly, mean number of weekly nitroglycerin intake decreased to 1.4 ± 0.4 with placebo and to 0.5 ± 0.2 with both dosages of once daily SR diltiazem ($P < 0.01$ in comparison with placebo). Baseline data of these variables are shown in Table 1.

Table 3 Differences between doses for ergometric parameters presented as mean (95% CI)

Δ TIT (s)		
200 mg diltiazem – placebo	28	(−13; 69)
300 mg diltiazem – placebo	45	(5; 84)*
300 mg – 200 mg diltiazem	16	(−24; 56)
Δ TAT (s)		
200 mg diltiazem – placebo	41	(6; 76)*
300 mg diltiazem – placebo	42	(9; 75)*
300 mg – 200 mg diltiazem	1	(−33; 35)
Δ TET (s)		
200 mg diltiazem – placebo	27	(−5; 56)
300 mg diltiazem – placebo	34	(4; 64)*
300 mg – 200 mg diltiazem	7	(−23; 38)
Δ ST segment depression (mm)		
200 mg diltiazem – placebo	0.12	(0.17; 0.41)
300 mg diltiazem – placebo	0.11	(0.16; 0.39)
300 mg – 200 mg diltiazem	−0.01	(−0.29; 0.27)

TIT, time to ischaemic threshold; TAT, time to anginal threshold; TET, total exercise time.

*Comparisons significant at the 0.05 level.

†At maximum exertion.

Haemodynamic parameters

At rest as well as at ischaemic threshold and at maximum exercise, no difference was seen for haemodynamic parameters between both dose levels of SR diltiazem and placebo. Only HR at rest was significantly decreased with 300 mg diltiazem in comparison with placebo ($P < 0.05$), however without modifying the RPP (Table 4).

Differences between dose levels presented as mean (95% confidence intervals) confirm these results (Table 5).

Table 4 Mean (s.e. mean) haemodynamic measurements at rest, ischaemic threshold and peak exercise on day 7

	Placebo n = 59	Sustained-release diltiazem	
		200 mg day ^{−1} n = 54	300 mg day ^{−1} n = 66
At rest			
HR (beats min ^{−1})	77 (2)	72 (1)*	73 (2)*
SBP (mm Hg)	138 (3)	141 (2)	140 (2)
DBP (mm Hg)	81 (2)	82 (1)	81 (1)
RPP (beats min ^{−1} mm Hg 10 ^{−2})	107 (3)	102 (3)	102 (3)
At ischaemic threshold			
HR (beats min ^{−1})	128 (3)	123 (2)	125 (2)
SBP (mm Hg)	183 (4)	185 (3)	185 (3)
DBP (mm Hg)	94 (2)	93 (2)	93 (2)
RPP (beats min ^{−1} mm Hg 10 ^{−2})	236 (8)	229 (7)	233 (7)
At peak exercise			
HR (beats min ^{−1})	137 (2)	130 (2)	132 (3)
SBP (mm Hg)	193 (4)	188 (3)	192 (3)
DBP (mm Hg)	97 (2)	95 (2)	94 (2)
RPP (beats min ^{−1} mm Hg 10 ^{−2})	266 (8)	246 (7)	256 (8)

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPP, rate-pressure product.

* $P < 0.05$ compared with placebo.

Table 5 Differences between doses for haemodynamic parameters presented as mean (95% CI)

	<i>At rest</i>	<i>At ischaemic threshold</i>	<i>At peak exercise</i>
<i>Δ HR (beats min⁻¹)</i>			
200 mg diltiazem – placebo	-2 (-6; 2)	-3 (-8; 2)	-4 (-8; 0.6)
300 mg diltiazem – placebo	-1 (-5; 3)	-1 (-6; 3)	-3 (-7; 1)
300 mg – 200 mg diltiazem	0 (-4; 4)	2 (-3; 6)	0.6 (-3; 5)
<i>Δ SBP (mm Hg)</i>			
200 mg diltiazem – placebo	-2 (-8; 5)	-2 (-9; 4)	-6 (-13; 1)
300 mg diltiazem – placebo	-2 (-8; 3)	-3 (-10; 4)	-6 (-12; 1)
300 mg – 200 mg diltiazem	-1 (-4; 2)	-0.5 (-3; 4)	0.4 (-7; 7)
<i>Δ DBP (mm Hg)</i>			
200 mg diltiazem – placebo	0 (-3; 4)	-2 (-5; 2)	-3 (-7; 1)
300 mg diltiazem – placebo	0 (-4; 3)	-1 (-5; 3)	-4 (-8; -0.3)
300 mg – 200 mg diltiazem	-1 (-4; 2)	0.5 (-3; 4)	-1 (-5; 3)
<i>Δ RPP (beats min⁻¹ mm Hg 10⁻²)</i>			
200 mg diltiazem – placebo	-4 (-13; 4)	-9 (-24; 5)	-15 (-29; 1)*
300 mg diltiazem – placebo	-5 (-13; 3)	-7 (-21; 7)	-11 (-25; 1)
300 mg – 200 mg diltiazem	-1 (-9; 8)	3 (-11; 17)	3 (-10; 16)

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPP, rate-pressure product.

*Comparison significant at the 0.05 level.

Plasma concentration of diltiazem

Concentrations of diltiazem 24.6 ± 0.8 h after daily doses of 200 and 300 mg were respectively 55 ± 6 ng ml⁻¹ and 77 ± 6 ng ml⁻¹.

Tolerability

Distribution of adverse events was comparable between the three treatment groups and showed a low number of patients with complaints (one on placebo, two on 200 mg and four on 300 mg diltiazem). One of these patients, in the 200 mg group, experienced worsening of angina on day 5 and was withdrawn from the study. Treatment with nitroglycerin, heparin and a β -adrenoceptor blocker led to a favourable outcome within 3 days. Other effects were mild, of the vasodilator type or of gastrointestinal origin. In this study population, 32% of patients were over 65 years and only one patient in this subgroup experienced an adverse event (lower limb oedema). No unexpected side-effect occurred.

Electrocardiographic parameters showed no difference between groups, especially the PR interval (158 ± 2.7 and 157 ± 2.7 for placebo, 161 ± 3.4 and 167 ± 3.7 for 200 mg diltiazem and 162 ± 3.1 and 164 ± 3.4 for 300 mg diltiazem at baseline and day 7, respectively). No case of sinus bradycardia <45 beats min⁻¹ or 2nd or 3rd degree atrioventricular block was reported. Minor abnormalities occurred in laboratory values evenly distributed in the three groups; none of the changes resulted in clinical manifestations or study withdrawals.

Discussion

This study protocol was drawn especially to evaluate, with objective parameters, the 24 h anti-ischaemic and antianginal protection of both dose levels of a new galenic formulation of once daily SR diltiazem; therefore exercise tests were scheduled to take place at the end of the dosing interval. On average, tests were performed 25 h after drug administration and showed, after 1 week of treatment, a significantly increased exercise capacity for both diltiazem dosages in comparison with placebo. Changes in ergometric parameter values observed between day 0 and day 7 were significantly greater with 300 mg in comparison with placebo. For the 200 mg dose level, trends were noted for an increase in TIT and TET, and a significant change for TAT. These results suggest a dose-effect relationship could possibly apply to the anti-ischaemic activity of diltiazem. However study conditions were not designed for this particular goal, as tests were performed at trough rather than peak concentrations. Blood samples showed diltiazem determinations to be dose-dependent, and consistent with plasma concentrations reported with this same formulation [8]. Improvements in TIT and TET seem to be of a comparable order of magnitude as those reported in a trial comparing respectively once daily diltiazem with the standard formulation (17% and 20% improvement for TIT, 12% and 15% for TET) [8].

Subjective improvement was also significant for both dose levels of SR diltiazem, with a 68% decrease in weekly anginal attacks with 200 mg, a 64%

decrease with 300 mg and only a 15% decrease with placebo. A 70% decrease in nitroglycerin consumption was achieved with both dose levels, whereas no difference appeared from baseline in the placebo group. Reasons for stopping exercise after the 1 week active treatment changed considerably in the diltiazem groups, as pain with ST segment depression decreased in favour of an increase in number of muscle-exhaustion endpoints.

As for haemodynamic variables, no changes in HR and RPP were noted as previously described in some other studies [4, 6, 7], suggesting an important vasodilating component in the anti-ischaemic activity of diltiazem.

Tolerability has been very satisfactory with respect to clinical data, ECG, and laboratory findings, in the whole population as well as in the elderly subgroup and in accordance with the literature.

These study results show 200 mg and 300 mg once daily SR diltiazem to be active and well-tolerated over the 24 h period in the prevention of exertional stable angina. Treatment with diltiazem can be started

at the lowest 200 mg dose level, then safely increased to 300 mg according to the patient's response. The once-a-day regimen should improve patients' compliance and comfort.

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