Combination of calcium channel blockers and β -adrenoceptor blockers for patients with exercise-induced angina pectoris: a double-blind parallel-group comparison of different classes of calcium channel blockers

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Aims The combination of calcium channel blockers and β -adrenoceptor blockers is more effective for the treatment of exercise-induced angina pectoris than β -adrenoceptor blocker monotherapy. As ischaemia in exercise-induced angina is preceded by increase in heart rate, calcium channel blockers with negative chronotropic properties may perform better for this purpose than nonchronotropic compounds.

Methods A 335 patient double-blind parallel-group study comparing 14 day treatment with amlodipine 5 and 10 mg, with diltiazem 200 and 300 mg, and mibefradil 50 and 100 mg added to baseline β -adrenoceptor blocker treatment was performed. Exercise testing (ETT) was performed by bicycle ergometry.

Results Although none of the calcium channel blockers improved duration of exercise or amount of workload, all significantly delayed onset of 1 mm ST-segment depression on ETT ($P < 0.001$ for any treatment *vs* baseline). In addition, mibefradil, both low and high dose treatment, produced the longest delays (low dose: different from diltiazem and amlodipine by 24.1 and 29.8 s, respectively, $P < 0.003$ and < 0.001 ; high dose: different from diltiazem and amlodipine by 33.7 and 37.0 s, respectively, $P < 0.001$ and < 0.001). These effects were linearly correlated with the reduction in rate pressure product (RPP). Serious symptoms of dizziness occurred significantly more frequently on mibefradil ($P < 0.05$), and 19 patients on mibefradil withdrew from trial.

Conclusions Calcium channel blockers with negative chronotropic properties provide greater delay of ischaemia in patients with exercise-induced angina, but the concomitant risk of intolerable dizziness attenuates this benefit.

Keywords: β -adrenoceptor blocker, angina pectoris, calcium channel blockers

Introduction

Numerous studies of drug–drug interactions between β -adrenoceptor blockers and calcium channel blockers in healthy volunteers, in patients with hypertension and in patients with ischaemic heart disease have given support to the concept of added benefit *vs* trade-off in adverse haemodynamics or symptoms. Several studies [1–8], although not all [9, 10], have shown that the combination of calcium channel blockers and β -adrenoceptor blockers are more effective for patients with exercise-induced

angina pectoris than is β -adrenoceptor blocker monotherapy. Although all of the classes of calcium channel blockers reduce afterload and produce coronary vasodilation, their chronotropic capacity is quite different [11, 12]: verapamil, diltiazem, and mibefradil reduce heart rate substantially, whereas dihydropyridine derivatives lack chronotropic property. As the ischaemic episodes in exercise-induced angina are preceded by increase in heart rate [7, 8], calcium channel blockers with negative chronotropic property might provide better benefit for the treatment of this condition than nonchronotropic compounds. However, so far studies directly comparing different classes are lacking or are small, and therefore inconclusive [13, 14].

The present study tests two hypotheses. First, we assumed

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that increased oxygen demand due to tachycardia is a major determinant in the pathogenesis of exercise-induced angina and, consequently, that calcium channel blockers with negative chronotropic properties may perform better in patients with this condition than calcium channel blockers devoid of such properties. Second, we assumed that the addition of a chronotropic calcium channel blocker to a β -adrenoceptor blocker may be limited by intolerable side-effects due to the further reduction in heart rate, in addition to reduction of afterload.

Amlodipine is a long-acting dihydropyridine calcium channel blocker devoid of chronotropic effects. Diltiazem, a benzothiazepine derivate, and mibefradil, a tetraline derivative, are both calcium channel blockers with important negative chronotropic properties. The first objective of this study was to study whether the latter two compounds would outperform the former during bicycle exercise testing, and whether such an effect would be associated with reduced myocardial oxygen demand. For that purpose linear regression analysis was used. The second objective was to test whether the combination of β -adrenoceptor blocker plus negative chronotropic calcium channel blocker would cause intolerable side-effects causing patients not to further comply with the protocol.

Methods

Patients

We included male and female outpatients, between 18 and 75 years of age, suffering from chronic stable angina pectoris and receiving stable β -adrenoceptor blocker treatment (heart rate at rest between 55 and 70 beats min^{-1}) for at least 2 weeks before the start of the study treatments. Patients were eligible when reproducible myocardial ischaemia occurred during exercise testing (ETT).

For ETT Lode bicycle ergometers, Type Corival, Groningen, Netherlands, and electrocardiographs, Siemens Minograf 410, Munich, Germany, were used. Reproducibility was warranted by a difference for maximal exercise duration of $\leq 15\%$ between two consecutive tests, performed with an interval of 5–10 days during the placebo-run-in period. In male patients, ischaemia was diagnosed if a persistent horizontal or downsloping of ≥ 1 mm of the ST-segment at 80 ms after the J-point occurred. Female patients had to have ≥ 2 mm depression of the ST-segment, or ≥ 1 mm ST-segment depression combined with other symptoms of ischaemia, including anginal symptoms and dysrhythmias.

Patients were excluded because of the following: myocardial infarction, coronary artery bypass surgery or angioplasty within 3 months prior to the study; cerebrovascular event within 12 months of the screening

visit; clinically significant valvular disease, hypertrophic obstructive or dilated cardiomyopathy, and heart failure (New York Heart Association class II–IV); 2nd- or 3rd-degree atrioventricular (AV)-block; uncontrolled hypertension (blood pressure (BP) $> 180/110$ mmHg) or hypotension (systolic blood pressure (SBP) < 100 mm (Hg); major systemic diseases; childbearing potential; concomitant antianginal therapy other than study medication or short-acting nitrates.

Study design

This was a randomized, double-blind, parallel-design trial involving 27 clinical centres in the Netherlands. The protocol was approved by the ethics committee of all participating centres and conducted in accordance with the revised Declaration of Helsinki [15].

After giving written informed consent patients entered a 1 to 2 week washout period, during which all of antianginal drugs were discontinued, except for β -adrenoceptor blockers and short-acting nitrates. Subsequently, patients were treated single-blind with placebo for 5–10 days, during which period two ETTs were performed. Whenever results between these baseline ETTs differed $> 15\%$, a third test was allowed within 3 days, which should not differ $> 15\%$ from the first ETT. ETTs were performed at ≈ 22 –24 h after the last drug intake, preferably in the morning, by means of a standardized bicycle exercise protocol. After measurement of sitting blood pressure (BP), by sphygmomanometer, using Korotkoff phases I and IV to identify systolic and diastolic values, and recording of a 12-lead ECG in resting conditions, exercise was started with a workload of 20 W for 1 min. Workload was increased each minute by 20 W increments until maximal exercise performance was achieved. Continuous ECG recording was initiated just before persistent 1 mm ST-segment depression occurred. At the end of each exercise interval and 5 min after completion of the ETT, BP and ECG were recorded once again. The ETT was terminated either by the patient due to chest pain or exhaustion, or on the investigators' clinical judgement.

To ensure inclusion of eligible patients as well as consistency in the evaluation of the ECG recordings and relevant ETT parameters, all of the ETTs were assessed by independent cardiologists. Whenever discrepancies occurred between the independent reviewer and the investigator, the principal investigator made the final judgement.

Qualified patients were randomly assigned to receive once daily mibefradil 50 mg, diltiazem slow release formulation (XR) 200 mg, or amlodipine 5 mg for 14 ± 3 days (low dose treatment), followed by a forced titration to mibefradil 100 mg, diltiazem XR 300 mg, or amlodipine 10 mg for another period of 14 ± 3 days (high

dose treatment). For randomization a blinded, computer-generated list was used. In order to ensure the double-blind character of the study, visually matching placebo tablets or placebo capsules—amlodipine and diltiazem were encapsulated—were appropriately dispensed. Tolerability of the study medication was evaluated by means of a self-administered questionnaire addressing questions about any adverse events, particularly symptoms of dizziness, at each visit. Physical examination and routine laboratory evaluation were performed at visits 2 and 4.

Statistics

For the primary analysis of the change from baseline for the ETT parameters the intention-to-treat (ITT) population was used, i.e. the patients who received at least one dose of the allocated trial medication and had a baseline ETT as well as one subsequent ETT that was obtained 22–24 h postdose. In the ITT analysis, of the patients discontinuing before the final visit, the last postrandomization visit was included in the overall analysis of the data. Under the assumption of a baseline standard deviation of 25% and between-group difference of 25% the study would have to include ≈ 300 patients to obtain a statistical power of 80% and a 5% significance level for testing between-group differences.

The primary efficacy parameter was the change from baseline in total exercise duration at day 28 ± 6 . In addition, total exercise duration after 14 ± 3 days as well as time to onset of symptoms, and onset of ischaemia (persistent 1 mm ST-segment depression), rate pressure product (RPP) (heart rate $\times$ systolic BP), at maximal comparable workload, ischaemic load during exercise, reason for stopping the exercise and vital signs after both the low and high dose intervals were assessed. All efficacy parameters were assessed by analysis of covariance, including treatment, centre, and treatment-by-centre interaction as fixed factors, and baseline ETT results as covariates. Results are expressed as means $\pm$ standard deviations (s.d.) unless indicated otherwise. A value of $P < 0.05$ was considered statistically significant.

Benefit/risk ratios defined as level of improvement of exercise tolerance (% increased time to onset ischaemia during ETT) level⁻¹ of reduced patient compliance (% of withdrawals due to dizziness) were calculated and tested statistically between the parallel-groups.

Results

Patients

A total of 393 patients entered into the placebo-run-in period. Of these, 58 failed to meet the final selection criteria with respect to ETT parameters, or were unable

to proceed for administrative or other reasons. The remaining 335 patients were randomized and received either mibefradil ($n=110$), diltiazem XR ($n=110$), or amlodipine ($n=115$). All of these 335 patients were included in the safety analysis whilst 35 randomized patients did not complete the study, 3 because of sudden death (2 on mibefradil, 1 on amlodipine), and 32 because of intolerable side-effects, mainly severe symptoms of dizziness. Of these 32 patients 9 were on amlodipine, 4 on diltiazem, and 19 on mibefradil. The data of the remaining 300 patients were used for efficacy analysis. There were no obvious differences between the three groups with regard to demographic and baseline characteristics (Table 1), as well as underlying conditions, previous medication and concomitant medications

Table 1 Baseline characteristics of the parallel-groups.

	Amlodipine n = 115	Diltiazem n = 110	Mibefradil n = 110
Gender (n), (m/f)	100/15	99/11	102/8
Age (years), (mean $\pm$ s.d.)	62.6 $\pm$ 7.6	63.7 $\pm$ 7.4	62.2 $\pm$ 7.5
Medical history			
Previous MI (n)	50	42	42
Previous CABG (n)	22	15	17
Previous PTCA (n)	15	29	23
Baseline treatment			
Hypolipaeemics (n)	65	55	63
Acetyl salicylic acid (n)	70	71	66
β -adrenoceptor blockers metoprolol/others (n)	82/33	79/31	75/35
Blood pressure (mean $\pm$ s.d.)			
Systolic (mmHg)	144 $\pm$ 21	145 $\pm$ 20	143 $\pm$ 20
Diastolic (mmHg)	81 $\pm$ 12	83 $\pm$ 10	81 $\pm$ 10
Heart rate (beats min ⁻¹) (mean $\pm$ s.d.)	64 $\pm$ 9	65 $\pm$ 10	64 $\pm$ 9
PQ-interval (ms) (mean $\pm$ s.d.)	163 $\pm$ 21	164 $\pm$ 27	165 $\pm$ 24
QTc (ms) (mean $\pm$ s.d.)	398 $\pm$ 26	396 $\pm$ 28	398 $\pm$ 29
RPP (mmHg beats min ⁻¹ 10 ⁻³) (mean $\pm$ s.d.)	22.7 $\pm$ 5.8	22.9 $\pm$ 5.5	22.9 $\pm$ 4.9
ETT variables (mean $\pm$ s.d.)			
Time to angina (s)	409 $\pm$ 128	388 $\pm$ 101	406 $\pm$ 97
Time to ischaemia (s)	336 $\pm$ 100	313 $\pm$ 87	338 $\pm$ 82

MI = myocardial infarction, CABG = coronary artery bypass graft, PTCA = percutaneous transluminal coronary angioplasty, QTc = QT-interval corrected, RPP = rate pressure product, ETT = exercise testing.

used. Heart rate at rest was 64 ± 7 , 65 ± 10 , and 64 ± 9 beats min^{-1} , for the amlodipine, diltiazem, and mibefradil groups, respectively, showing a similar level of β -adrenoceptor blockade between the groups. Also baseline exercise duration, and time to onset of ischaemia and anginal symptoms, as well as haemodynamics were well-matched (Table 1).

Exercise performance

The effects of the various treatments on ETT parameters are summarized in Table 2. The addition of a calcium channel blocker to unchanged β -adrenoceptor blocker treatment, did not improve duration of exercise or workload, maximal workload being 141 ± 43 W, 135 ± 31 W, and 141 ± 33 W for amlodipine 10 mg, diltiazem XR 300 mg, and mibefradil 100 mg, respectively. When compared with baseline, the time to onset of anginal symptoms increased insignificantly after addition of a calcium channel blocker, ranging from 15 to 20 s to 25–31 s compared with baseline, the time to onset of anginal symptoms increased insignificantly after

addition of a calcium channel blocker, ranging from 15–20 s to 25–31 s. The time to onset of persistent 1 mm ST-segment depression, however, improved significantly for all of the three classes of calcium channel blockers, and this was so both for low and high doses ($P < 0.001$ for any treatment *vs* baseline). Mibefradil both at low and high dose produced the largest anti-ischaemic effect as estimated by onset of 1 mm ST-segment depression with a difference between mibefradil 50 mg and diltiazem XR 200 mg being 24.1 s ($P < 0.003$; 95% confidence intervals (CI) 8.5, 39.6 s). At higher doses the difference between the two was even more pronounced (33.7 s, $P < 0.001$; 95% CI 6.3, 51.1 s). The differences between mibefradil and amlodipine were of similar magnitude; at low doses mibefradil improved time to ischaemia by 29.8 s more than amlodipine ($P < 0.001$, 95% CI 14.4, 45.2 s), whereas the difference between high dosages was 37.0 s ($P < 0.001$, 95% CI 19.9, 54.2 s). No statistically significant differences were observed between diltiazem XR and amlodipine, neither at the low dose (95% CI 9.5, 21.0 s) nor at high dose (95% CI 13.7, 20.4 s).

At rest, small effects of the three classes of calcium

Table 2 Haemodynamic and ETT variables after treatment with different classes of calcium channel blockers* (means $\pm$ s.d.).

	Amlodipine		Diltiazem		Mibefradil	
	5 mg	10 mg	200 mg	300 mg	50 mg	100 mg
<i>Rest</i>						
SBP (mmHg)	-6 ± 19	-9 ± 20	1 ± 20	-3 ± 10	-3 ± 9	-6 ± 10
DBP (mmHg)	-3 ± 9	-5 ± 10	-2 ± 9	-3 ± 10	-3 ± 9	-6 ± 10
HR (beats min^{-1})	1 ± 8	3 ± 10	-2 ± 7	-2 ± 10	-7 ± 8	-13 ± 8
RPP (mmHg beats $\text{min}^{-1} 10^{-3}$)	-0.2 ± 1.5	-0.2 ± 1.9	-0.1 ± 1.7	-0.3 ± 1.9	-1.1 ± 1.3	-1.9 ± 1.6
PQ-interval (ms)	164 ± 23	166 ± 23	170 ± 23	171 ± 23	166 ± 24	173 ± 27
QTc (ms)	404 ± 31	405 ± 35	402 ± 35	407 ± 35	395 ± 33	393 ± 33
<i>Onset of ischaemia</i>						
SBP (mmHg)	3 ± 25	1 ± 20	3 ± 22	1 ± 26	0 ± 23	-4 ± 23
DBP (mmHg)	-2 ± 9	-4 ± 10^x	-2 ± 10	$-3 \pm 10^\ddagger$	-1 ± 13	-7 ± 11
HR (beats min^{-1})	-1 ± 12^{xx}	0 ± 12^{xx}	-5 ± 11	$-7 \pm 14^\ddagger$	-6 ± 15	-18 ± 20
RPP (mmHg beats $\text{min}^{-1} 10^{-3}$)	0.3 ± 4.1	$0.1 \pm 3.5^\ddagger$	-0.6 ± 3.5	$-1.1 \pm 4.6^\ddagger$	-1.1 ± 4.6	-3.4 ± 5.1
<i>Maximal workload</i>						
SBP (mmHg)	3 ± 22	0 ± 23	2 ± 21	1 ± 24	-2 ± 23	-4 ± 19
DBP (mmHg)	-2 ± 11	-4 ± 11^x	-2 ± 11	$-3 \pm 10^\ddagger$	-2 ± 12	-7 ± 12
HR (beats min^{-1})	0 ± 9^{xx}	-1 ± 13^{xx}	$-5 \pm 10^\ddagger$	$-8 \pm 11^\ddagger$	-15 ± 14	-25 ± 16
RPP (mmHg beats $\text{min}^{-1} 10^{-3}$)	$0.3 \pm 3.7^\ddagger$	-0.2 ± 3.9^{xx}	-0.7 ± 3.7^x	$-1.3 \pm 4.0^\ddagger$	-2.8 ± 4.3	-5.1 ± 4.3
Time to onset of angina (s)	16 ± 46	25 ± 56	20 ± 47	31 ± 69	16 ± 57	30 ± 64
Time to onset of ischaemia (s)	$25 \pm 50^\ddagger$	$33 \pm 63^\ddagger$	$30 \pm 64^\ddagger$	$39 \pm 70^\ddagger$	54 ± 55	70 ± 62

ETT = exercise testing, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, RPP = rate pressure product, QTc = corrected QT-interval.

^x $P < 0.03$ *vs* mibefradil at comparable dosage. ^{xx} $P < 0.003$ *vs* mibefradil at comparable dosage. [†] $P < 0.02$ *vs* mibefradil at comparable dosage.

[‡] $P < 0.001$ *vs* mibefradil at comparable dosage. [¶] $P < 0.003$ *vs* diltiazem at comparable dosage.

*Changes from baseline are presented, except for the PQ interval and QTc that are described in terms of absolute measurements.

channel blockers on haemodynamic variables including RPP were observed. However, at onset of ischaemia amlodipine did not reduce RPPs, whereas diltiazem and mibefradil decreased RPP significantly mainly by a pronounced effect on heart rate.

Linear regression analysis revealed a highly significant linear correlation between the amount of RPP reduction by the calcium channel blockers and their potential to beneficially influence onset of ischaemia ($r = -0.5$, $P < 0.001$).

Benefit/risk analysis

Except for symptoms of dizziness, adverse effects were generally mild and did not lead to patient withdrawal. During the trial two patients died, one after 4 and 15 days treatment with mibefradil 50 mg, the other after 10 days on amlodipine 10 mg. Serious symptoms of dizziness occurred in up to 14% of randomised patients, and caused 19 patients treated with mibefradil to withdraw from the study. Table 3 compares improvement of exercise tolerance as estimated by delayed onset of ischaemia during exercise, compared with the risk of intolerable symptoms of dizziness as estimated by percentage of withdrawals due to dizziness. Although the calcium channel blockers with negative chronotropic property better delayed ischaemia, the accompanying decrease in compliance largely offset this benefit. The benefit/risk ratios of these two variables were calculated separately for different classes of calcium channel blockers. Table 3 shows that, according to this approach, diltiazem low dose performed significantly better than did low dose mibefradil, and tended to perform better than did low dose amlodipine.

Discussion

Calcium channel blockers are frequently added to β -adrenoceptor blocker therapy in patients with exercise-induced angina pectoris in order to further reduce the frequency and severity of anginal episodes [1–10], although information is lacking on whether this combination also reduces morbidity and mortality. From a hypothetical point of view the addition of a slow-acting dihydropyridine calcium channel blocker to β -adrenoceptor blocker therapy may seem to be the most reasonable option, since the potentially beneficial effects of such combination is complementary: the combination should reduce heart rate and afterload, and, in addition, dilate coronary arteries [7, 8]. Non-dihydropyridine calcium channel blockers like verapamil and diltiazem have also been combined with β -adrenoceptor blockers [13, 14]. It may be hypothesized that the addition of such compounds to β -adrenoceptor blocker maintenance therapy offers the benefit of further reducing heart rate. Exercise-induced angina is commonly preceded by increase of heart rate, suggesting the need for optimal reduction of heart rate. This combination has generally been tolerated well but studies are small [13, 14].

The current 335 patient double-blind parallel-group comparison of three classes of calcium channel blockers allows for some relevant conclusions. First, in patients with exercise-induced angina treated with β -adrenoceptor blockers, further reduction of heart rate is significantly associated with better anti-ischaemic effect. Second, however, in such patients calcium channel blockers with negative chronotropic property cause major symptoms of dizziness sufficient to cause patients to withdraw from therapy. Nonetheless, with small doses of such calcium

Table 3 Improved exercise tolerance as estimated by percentage increased time to onset of ischaemia during ETT, reduced patient compliance as estimated by percentage of withdrawals due to symptoms of dizziness, and their ratios.⁶

	<i>Amlodipine</i>		<i>Diltiazem</i>		<i>Mibefradil</i>	
	5 mg	10 mg	200 mg	300 mg	50 mg	100 mg
Improved exercise tolerance	7.5 ^{xxx}	9.9 ^{xxx}	9.6 ^{xx}	12.4	16.0	20.8
95% CI	–7.5, 22.5	–9.1, 29.1	–10.9, 30.1	–9.9, 34.9	0.0, 32.0	2.3, 38.8
Reduced patient compliance	3.5	4.5	0.9 ^x	3.0 ^x	7.3	10.8
95% CI	0.9, 8.9	1.5, 10.4	0, 5.0	0.8, 8.7	3.2, 13.9	5.8, 18.3
Ratio improved exercise tolerance/reduced patient compliance	2.1 ^(x)	2.2	10.7 ^x	4.1	2.2	1.9
95% CI	0.4, 7.2	0.4, 7.3	5.7, 18.3	1.4, 10.1	0.4, 7.5	0.2, 6.4

ETT = exercise testing, 95% CI = 95% confidence intervals. ^(x)0.05 < P < 0.1 *vs* diltiazem comparable dose. ^x P < 0.05 *vs* mibefradil comparable dose. ^{xx} P < 0.02 *vs* mibefradil comparable dose. ^{xxx} P < 0.001 *vs* mibefradil comparable dose.

channel blockers, both risks of side-effects may be acceptable and additional benefits may be significant. In the current trial this was particularly so with low dose diltiazem which, according to the ratio of improved exercise tolerance *vs* reduced patient compliance, performed better than did low dose mibefradil, and tended to perform better than did low dose amlodipine.

The pronounced reduction in heart rate on mibefradil may partly be a consequence of interaction of the compound with metoprolol used concomitantly in the majority of the patients. Both of these compounds are metabolized through inhibition of isoenzyme CYP 2D6 [16]. However, of the patients who received other β -adrenoceptor blockers in addition to mibefradil, the negative chronotropic effect was equally great as with the other classes of calcium channel blockers. So, these data do not support a major influence of a pharmacokinetic drug interaction in our study.

The current paper also addresses the more general issue of more potent treatment regimens giving rise to more potent adverse effects. Although serious risks such as death or major illness, are routinely accounted for in drug trials, the risk of minor side-effects that may be very unpleasant to individual patients are rarely weighed against benefits. The present study presents a novel approach to estimation of benefit/risk ratios. Although untested for reproducibility, sensitivity and specificity to estimate patients' satisfaction with treatment, this approach, using the most important endpoints of the study, gives some clue about relationship between major positive and negative effects of the study, and provides arguments in favour of more frequent weighing procedures to that end.

In the period after the completion of the current study, mibefradil was withdrawn by the manufacturer because of drug interactions at the cytochrome P 450 3 A4 and 2D6 enzymes. Withdrawal of mibefradil makes much of the specific conclusions on this medication somewhat academic. However, it does not invalidate the overall conclusions of this report, because alternative calcium channel blockers with negative chronotropic property are available and new compounds are in the process of development [16].

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