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Effects of a New Calcium Antagonist, Mibefradil (Ro 40-5967), on Silent Ischemia in Patients With Stable Chronic Angina Pectoris: A Multicenter Placebo-Controlled Study

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Objectives. **The purpose of this study was to evaluate the effects of mibefradil (Ro 40-5967) on the frequency and duration of episodes of asymptomatic ischemia in patients with stable angina pectoris and to determine the most efficient single therapeutic dose of this drug.**

Background. **Mibefradil is a novel calcium channel antagonist that shows a high bioavailability, induces no reflex tachycardia and has no negative inotropic effects.**

Methods. **In a multicenter, double-blind, placebo-controlled, parallel-design trial, 126 patients with chronic stable angina pectoris were studied. After 1 week of a placebo run-in period, patients were randomized to receive 25, 50, 100, 150 mg of mibefradil or placebo for 2 weeks. Ambulatory 48-h electrocardiographic (ECG) monitoring was performed at the end of both the placebo run-in period and the active treatment period.**

Results. **Compared with placebo, mibefradil was associated with significantly less ischemia as manifested during ambulatory ECG monitoring. In the 150- and 100-mg groups, respectively, the drug resulted in a 73% and 63% reduction in the frequency of episodes of ST segment depression and a 78% and 58% reduction in the total duration of ST segment depression. Highly significant linear dose-response relations were present across all treatment groups for ischemic episodes and ischemia duration ($p < 0.001$). Electrocardiographic abnormalities related to treatment were first-degree atrioventricular block, sinus bradycardia and short Wenckebach episodes, observed during sleep on Holter monitoring. All ECG events were dose related.**

Conclusions. **Mibefradil is a new, safe, well tolerated and very effective dose-dependent anti-ischemic calcium channel antagonist.**

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The phenomenon of silent transient ischemia recorded during ambulatory electrocardiographic (ECG) monitoring has attracted a great deal of clinical and investigative interest (1–4). Recent reports (5–8) of 48-h ST segment monitoring in patients with stable angina pectoris receiving standard medical therapy suggest that between 40% and 47% of these patients have ischemic episodes, the majority without angina, during daily activities. Transient ischemia occurs predominantly in patients with positive exercise test results at low work loads (6,9). A variety of anti-ischemic drugs have been studied as treatment for episodes of ambulatory asymptomatic ischemia, but those controlled, double-blind trials included only a small number of patients, and there was a lack of definitive comparisons (10).

Mibefradil (Ro 40-5967) is a novel calcium channel blocker that combines the properties of high bioavailability, a once-daily regimen without galenic manipulation, the absence of reflex tachycardia or edema, or both, and a lack of negative inotropic effects (11–20). The purpose of this study was to determine the effects of mibefradil on the frequency and duration of episodes of asymptomatic ischemia in patients with stable exertional angina pectoris, as well as to determine the most efficient single therapeutic dose of this agent.

Methods

Study design. A multicenter, double-blind, placebo-controlled, parallel-design study was performed in 11 centers in 8 countries (Austria, Finland, France, Germany, Israel, The Netherlands, Sweden and Switzerland) after approval by the local ethics committees. It was conducted according to the Helskini Declaration as amended in Tokyo and Venice.

Patients were eligible for inclusion if they satisfied all of the following criteria. 1) They had coronary artery disease documented by at least one of the following: coronary angiogram indicating at least one or more major coronary arteries or major branches with ≥60% reduction in lumen diameter; documented myocardial infarction; reversible perfusion defect

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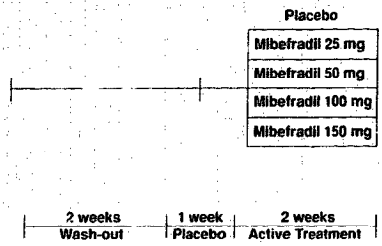

Figure 1. Study design.

during stress-redistribution thallium-201 scintigraphy; or ≥1.0-mm horizontal or a downsloping ST segment depression on an exercise test; 2) they had a stable pattern of angina pectoris for ≥3 months before screening; 3) they had effort-induced angina pectoris on a bicycle exercise test; and 4) they were able to exercise ≥3 min at a work load of 25 W. The results of the exercise tests have been reported elsewhere (21).

Patients were excluded if they had any of the following: 1) myocardial infarction or cardiac surgery within 3 months, or coronary angioplasty within 6 months, of the screening visit; 2) congestive heart failure; 3) bradycardia, atrioventricular (AV) block or any clinical significant arrhythmia; 4) uncontrolled hypertension (blood pressure >180/105 mm Hg) or hypotension (blood pressure <100/60 mm Hg); 5) major systemic disease; 6) a history of alcohol or drug abuse; or 7) childbearing potential.

Study protocol (Fig. 1). During a 2-week washout period, previously ingested anti-anginal medications (beta-adrenergic blocking agents, long-acting nitrates and calcium antagonists) were gradually discontinued, and only short-acting sublingual nitrates for aborting anginal attacks were allowed during the study period. Patients entered a 1-week placebo run-in period in which three exercise tests were performed on 3 different days. If patients were randomized to one of the five study groups (placebo or 25, 50, 100, or 150 mg of the study drug) for 2 weeks of active treatment, exercise tests were performed at the end of each week at the same time of day. Patients were asked to complete a diary every week throughout the study to assess the number of anginal episodes and total nitroglycerin consumption.

Ambulatory ECG monitoring. Ambulatory ECG recordings were performed with the use of ACS-8500 cassette recorders. Electrodes were applied to record a modified lead V_5 and a modified lead aVF. After the leads were connected to the patient but before the ambulatory recording session was initiated, a cable from the recorder was inserted into a standard ECG machine. Recordings were made in different positions to ensure that artificial ST segment deviation did not occur. The recordings were analyzed by the Holter ECG Cor Laboratory (Lausanne, Switzerland). The technician and the physician were unaware of medication assignment or treatment regimen. An ischemic episode was defined as transient ischemic ST segment depression ≥1.0 mm and lasting ≥1 min. The variables evaluated included the number of episodes of ST segment depression and the total duration (in minutes) of ischemia. Ambulatory 48-h ECG monitoring was performed at the end of both the placebo run-in period and the active treatment period. Episodes of ischemia identified by ambulatory ECG were correlated with symptoms identified in the patient's diary to determine whether the ischemic events were silent or associated with angina.

Statistical analysis. Statistical analysis was performed on the differences between the results of the ambulatory ECG recorded at baseline and at week 2. To show the dose-response relation, a linear trend test was performed by applying the appropriate linear hypothesis in the analysis of variance with the treatment effect. To show the individual dose effect, a pairwise comparison of each dose group with placebo was made by using the appropriate contrast of the linear model. The Jonckheere-Terpstra test (22) was used to test the previously mentioned hypotheses. A close test (23) was applied to ensure that the normal significance level was kept at 5%.

Results

Patient characteristics. Of 245 patients with angina pectoris who were screened for eligibility to participate in the study, 171 entered the placebo run-in period. During this period, 45 patients either did not qualify for randomization or discontinued treatment for administrative reasons. A total of 126 were randomly assigned to the five treatment groups. Five patients were classified as protocol violators and three patients did not complete the active treatment period because of adverse events. All 126 patients had ambulatory baseline ECG recordings and were eligible for analysis. Of these 126 patients, 45 patients (37%) showed evidence on the first ambulatory ECG recording of having had at least one episode of silent ischemia. The average age of the study population was 59.3 ± 8.0 years; 82% were men.

Effect of mibefradil on heart rate and blood pressure. The administration of mibefradil was associated with a slight but highly significant dose-dependent decrease in heart rate and systolic and diastolic blood pressure (Table 1).

Effect of mibefradil on episodes of ambulatory ischemia (Table 2). Symptomatic episodes of ischemia detected on ambulatory ECG monitoring were excluded for the subsequent analyses. Mibefradil was associated with significantly less ischemia as manifested during ambulatory ECG monitoring than was placebo (Fig. 2). In the 150- and 100-mg groups, respectively, the drug resulted in a 73% and 63% reduction in the frequency of episodes of ST segment depression and a 78% and 58% reduction in the total duration of ST segment depression. There was a significant linear dose trend (dose-response relation) toward a decrease in ischemic episodes and ischemia duration in the ambulatory ECG recordings ($p < 0.001$).

Effect of mibefradil on episodes of angina pectoris. Mibefradil was associated with significantly fewer anginal episodes than was placebo. In the 150- and 100-mg groups, respectively, it resulted in a 51% and 50% reduction in the frequency of

Table 1. Changes From Baseline in Hemodynamic Variables at Rest

	Placebo (n = 27)	Mibefradil 25 mg (n = 25)	Mibefradil 50 mg (n = 25)	Mibefradil 100 mg (n = 25)	Mibefradil 150 mg (n = 23)	p Value (by linear trend test)
SBP (mm Hg)	−1 ± 12	−3 ± 15	−6 ± 10	−8 ± 16	−8 ± 12	0.005
DBP (mm Hg)	0 ± 6	−2 ± 7	−4 ± 6	−5 ± 7	−7 ± 8	0.001
HR (beats/min)	1 ± 9	−1 ± 8	−1 ± 9	−5 ± 10	−6 ± 10	0.001

Values are expressed as mean value ± SD. DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

anginal episodes/week and a 79% and 61% reduction in nitroglycerin consumption/week. A dose-dependent decrease in the number of anginal episodes and the rate of nitroglycerin consumption/week was observed across the active treatment groups. However, although no improvement was observed in the 25-mg dose group of mibefradil, all other groups did better than the placebo group (linear trend test, $p < 0.01$).

Tolerability and safety. Mibefradil was well tolerated. When all nontreatment-related and treatment-related adverse events were considered, no differences were observed between patients taking mibefradil and those receiving placebo (27% vs. 30% for all adverse events combined and 18% vs. 22% for treatment-related adverse events alone). Aggravated angina was reported in 14% of the placebo group and in 2% of the mibefradil groups. The most frequently occurring adverse events observed in the patients treated with mibefradil or placebo were, respectively, dizziness (7% vs. 3.7%), gastralgia (2% vs. 0%), flushing (2% vs. 0%) and headaches (3.7% vs. 3.0%).

When ECG abnormalities related to treatment were considered, the main events observed in the mibefradil groups were first-degree AV block (8%, maximal PQ interval 240 ms), sinus bradycardia (5%) and short Wenckebach episodes, observed during sleep on Holter ambulatory ECG monitoring (5%). All ECG events were dose related (Table 3).

Discussion

Our results indicate that mibefradil was effective in reducing the frequency and duration of asymptomatic ischemic episodes in patients with stable exertional angina pectoris and asymptomatic ischemia.

The significant linear trends observed throughout the five treatment groups with regard to 1) the number of events and duration of silent ischemia, and 2) the decrease in weekly anginal attacks and nitroglycerin consumption clearly indicate that the increase in the dose of mibefradil from 0 (placebo) to 150 mg/day, after 2 weeks of active treatment, is associated with a significant improvement in the clinical condition of patients with chronic, stable exertional angina pectoris. Treatment with the three higher dose levels of mibefradil was associated with a significant improvement in all the evaluated indexes of ischemia (21). However, the differences between the 100- and the 150-mg doses of mibefradil were small and clinically nonsignificant, suggesting that the 150-mg dose is at the plateau of the dose-response curve and may be the highest effective dose.

Comparison with other calcium channel antagonists. Although calcium channel antagonists have been demonstrated to be effective for symptomatic ischemia, studies evaluating their efficacy in the suppression of asymptomatic ischemic episodes on continuous ECG recordings have had mixed results. Bala Subramanian et al. (24) demonstrated a significant reduction in the number of asymptomatic episodes with verapamil, but not with short-acting nifedipine. Frishman et al. (25) performed a crossover study with diltiazem and nifedipine. Although both drugs had a similar effect on exercise tolerance, only diltiazem suppressed asymptomatic ischemic episodes. Deedwania et al. (26) compared the anti-ischemic efficacy of nifedipine and atenolol and found that both agents

Table 2. Effect of Mibefradil on the Number and Duration of Silent Ischemic Episodes

Silent Ischemic Episodes	Placebo (n = 10)	Mibefradil 25 mg (n = 8)	Mibefradil 50 mg (n = 9)	Mibefradil 100 mg (n = 11)	Mibefradil 150 mg (n = 7)	p Value (by linear trend test)
No.						
Baseline	5.3 ± 4.7	2.7 ± 2.1	5.5 ± 6.5	5.1 ± 5.1	10.9 ± 10.6	—
Change from baseline	1.5 ± 5.0	0.2 ± 2.5	−1.5 ± 4.1	−3.2 ± 3.8	−8.0 ± 8.7	—
Placebo corrected	—	−1.9	−4.1	−5.7*	−9.6†	< 0.001
Duration (min)						
Baseline	7.9 ± 116	21 ± 22	98 ± 165	43 ± 52	116 ± 115	—
Change from baseline	27 ± 63	−3 ± 6	−43 ± 85	−25 ± 49	−91 ± 98	—
Placebo corrected	—	−27	−91*	−76†	−127*	< 0.001

*$p < 0.01$. †$p < 0.02$. Data are expressed as mean value or mean value ± SD.

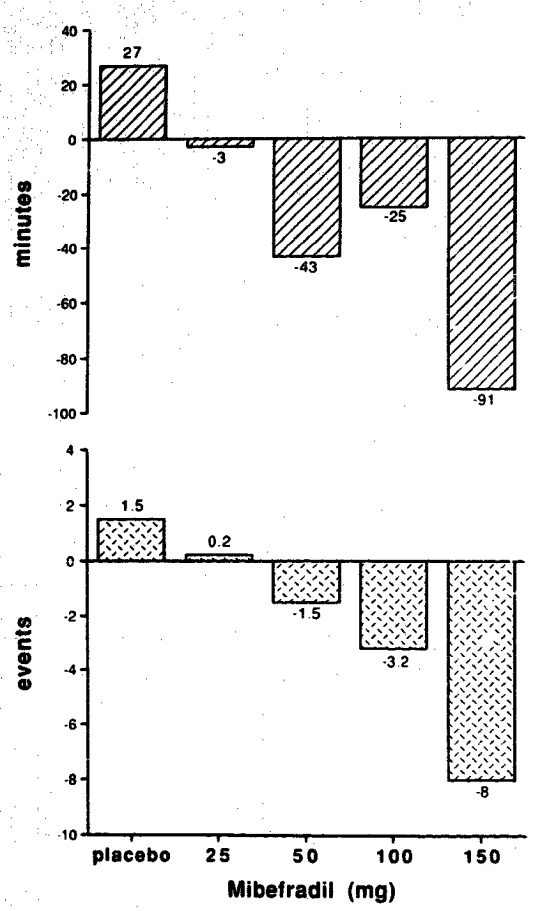

Figure 2. Bar graph showing changes in the number and duration of silent ischemic events with mibefradil treatment. A significant linear dose-response relation is shown across all treatment groups for ischemic events and ischemia duration ($p < 0.001$).

had a significant suppressive effect on asymptomatic ischemia, but the magnitude of the suppression by the beta-blocker was significantly larger than that of the calcium channel antagonist. In a placebo-controlled study, Theroux et al. (27) demonstrated a 67% reduction in the number of asymptomatic ischemic episodes with diltiazem. In their large scale placebo-controlled study, Stone et al. (28) found that neither nifedipine nor diltiazem demonstrated a significant effect on the number of asymptomatic episodes of ischemia. In comparison, propranolol exhibited a profound effect, reducing both the number and the duration of asymptomatic ischemic episodes.

The less potent anti-ischemic effects reported with calcium channel antagonists in comparison with beta-blockers may be due in part to the less potent reduction by the former agents of indexes of myocardial oxygen demand. In addition, many of the dihydropyridine calcium antagonists tested are short-acting preparations, causing significant peaks and troughs in serum levels and thereby exposing the patients to the risk of reflex tachycardia associated with a transient reduction of blood pressure.

Anti-ischemic mechanisms of mibefradil. The profound effect of mibefradil on reducing asymptomatic ischemic episodes may be explained by the unique properties of this agent compared with those of other calcium antagonists. Preclinical studies have suggested that mibefradil has combined pharmacodynamic and pharmacokinetic characteristics that are lacking in other calcium antagonists. The significant effect on silent ischemia was associated with a slight but significant dose-related decrease in heart rate and blood pressure; no reflex tachycardia was observed. The effects of mibefradil on heart rate are probably related to a direct effect on the sinus and AV nodes, probably through the inhibition of calcium ion influx (16–19). This effect could be mediated through the blockade of the L-type or T-type, or both, calcium channels that exist at the level of the sinus and AV nodes. A selective inhibition of the T-type channels by mibefradil was recently demonstrated (29).

It was suggested (30) that the better anti-ischemic effect of slow release nifedipine on silent ischemia compared with that of the short-acting form may be related to its mode and duration of administration; the long-acting preparation is less likely to produce proischemic reflex tachycardia and thereby allows a greater anti-ischemic effect. Mibefradil has a duration of action of >24 h, which is longer than that of the first-generation calcium antagonists. It has a high bioavailability and a long half-life, and the plasma concentrations achieved with chronic dosing are linearly correlated with dose. These properties ensure small interpatient variability and high con-

Table 3. Overview of Clinically Relevant Electrocardiographic Abnormalities Related to Treatment

		Mibefradil				
	Placebo (n = 27)	25 mg (n = 25)	50 mg (n = 25)	100 mg (n = 26)	150 mg (n = 23)	All Mibefradil Groups (n = 99)
PQ interval > 200 ms	1 (4%)	1 (4%)	1 (4%)	1 (4%)	5 (22%)	8 (8%)
Sinus bradycardia	—	—	1 (4%)	2 (8%)	2 (8%)	5 (5%)
Wenckebach conduction*	—	—	1 (4%)	—	4 (17%)	5 (5%)
Patients with ECG abnormalities	1 (4%)	1 (4%)	3 (12%)	3 (12%)	9 (39%)	16 (16%)

*As assessed by Holter ambulatory electrocardiographic (ECG) monitoring at night. Data are expressed as number (%) of patients.

sistency, in contrast to the conditions associated with verapamil and nifedipine in the regular galenic formulation (i.e., not the slow release formulation).

A reduction of coronary blood flow is another mechanism hypothesized to induce silent ischemia. Normal variation in the tone of the coronary arteries causes reductions of 10% to 25% in the outer diameter of the arteries (31,32). In an artery with intimal thickening, even a small increase in vasomotor tone can result in either subtotal or total occlusion of the lumen. Brown et al. (33) demonstrated a reduction of up to 33% in coronary artery lumen during handgrip exercise in patients with stable angina pectoris. Gage et al. (34) showed both a 71% reduction in coronary stenosis area with dynamic exercise and its prevention by pretreatment with nitroglycerin. Mibefradil induces a selective vasodilation in the coronary vascular bed. In two models mimicking the consequences of coronary atherosclerosis (11,12), experiments with radioactive microspheres have shown that Mibefradil is a strong vasodilator in the subendocardium and therefore does not produce a steal phenomenon. These properties may explain its efficacy in reducing silent ischemia in patients with stable angina pectoris.

Conclusions. Mibefradil is a potent novel calcium antagonist with a dose-dependent high response rate for silent ischemic episodes. Its excellent efficacy and safety profile, combined with its high bioavailability in a once-a-day regimen, and the absence of reflex tachycardia and edema make it a very promising new compound for treatment of patients with angina pectoris and silent ischemia. The combination of this unique compound with other anti-ischemic drugs (having different anti-ischemic mechanisms) might even enhance the anti-ischemic effect. Further clinical trials are needed to assess the efficacy and safety of mibefradil in combination with other calcium antagonists and beta-blocking agents and in patients with impaired left ventricular function.

Appendix

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