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Additional Antianginal and Anti-Ischemic Efficacy of Mibefradil in Patients Concomitantly Treated with Long-Acting Nitrates for Chronic Stable Angina Pectoris

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Summary

Background: Mibefradil, a newly approved antihypertensive and antianginal drug, is the first member of a new class of calcium antagonists (CAs), the tetralol derivatives, that selectively blocks T-type Ca^{2+} channels in contrast to classical CAs which, at therapeutic concentrations, block only L-type Ca^{2+} channels. Since patients with chronic stable angina pectoris typically may be treated with the combination of a long-acting nitrate and a CA, the additive efficacy and safety of mibefradil in combination with nitrate therapy needs to be determined.

Hypothesis: This study was designed to assess the efficacy, tolerability, and safety of mibefradil when added to long-acting nitrate therapy in patients with chronic stable angina pectoris.

Methods: Following a 1-week placebo run-in period, patients were randomized to receive either mibefradil 50 mg (n = 96) or placebo (n = 93) once daily in addition to their nitrate therapy. After 2 weeks of active treatment, patients receiving the mibefradil were force titrated to 150 mg once daily for an additional 2 weeks. Exercise tolerance tests (ETTs) were performed at the end of Weeks 2 and 4; patients also maintained an anginal diary during the 4-week treatment period.

Results: After 2 weeks of treatment with 50 mg mibefradil (within the current recommended dose range), a statistically significant but modest increase in total exercise duration was observed (treatment effect 16.4 s, $p = 0.04$). Similarly, there was a significant increase in time to onset of ischemia (treatment effect 26 s, $p = 0.008$). The adverse event profile of the 50 mg dose was indistinguishable from placebo, indicating that this dose was extremely well tolerated. At Week 4, the mibefradil-treated patients were taking 150 mg, which is above the current recommended dose range. The increase in total exercise duration was larger for the mibefradil 150 mg group than for the placebo group. For the intent-to-treat population, this difference did not reach statistical significance, whereas in the standard population it did (treatment effect 21 s, $p = 0.05$). The other two ETT variables, time to onset of angina and time to onset of 1 mm ST-segment depression, demonstrated significantly greater effect with mibefradil 150 mg (treatment effects 40 s, $p = 0.002$, and 55 s, $p < 0.001$, respectively, for the intent-to-treat population). Mibefradil 150 mg was associated with more adverse events than placebo, specifically, dizziness, leg edema, and postural hypotension.

Conclusions: This study demonstrates that mibefradil 50 mg once daily in the setting of the background long-acting nitrate therapy produces additive antianginal and anti-ischemic effects and is extremely well tolerated.

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Introduction

Coronary heart disease is the leading cause of death in Western societies. Management usually includes revascularization and/or pharmacologic therapy. Nitrates have long

formed the basis of treatment for symptomatic coronary vascular disease. By dilating the peripheral vasculature, nitrates reduce the preload on the heart, thereby reducing cardiac work. By their effects on coronary arteries, nitrates can increase coronary blood flow and may improve oxygen supply to the heart.[1]

Calcium antagonists (CAs) are also widely used in the treatment of symptomatic myocardial ischemia. All CAs are able to lower arterial pressure and dilate coronary arteries, and some are associated with a potentially beneficial negative chronotropic effect.[2] By decreasing heart rate, lowering arterial blood pressure, and dilating coronary arteries to increase oxygen supply to the myocardium, CAs can favorably affect oxygen supply and demand and should complement the therapeutic effects of nitrates.[2]

Mibefradil, a newly approved antihypertensive and antianginal drug, is the first member of a new class of CAs, the tetralol derivatives, that selectively blocks T-type Ca^{2+} channels in contrast to classical CAs which, at therapeutic concentrations, block only L-type Ca^{2+} channels.[3] Mibefradil has a high bioavailability (about 80%) and long plasma half-life (17–25 h), both of which make it suitable for once-a-day dosing. Clinical studies have shown that mibefradil is effective and well tolerated in the treatment of systemic hypertension[4–7] and angina[8–12] when administered once daily at doses of 50 and 100 mg.

Since patients with chronic stable angina pectoris typically may be treated with the combination of a long-acting nitrate and a CA, the additive efficacy and safety of mibefradil in combination with nitrate therapy needs to be determined. This article reports the results of a trial assessing the efficacy, tolerability, and safety of mibefradil when added to long-acting nitrate therapy in patients with chronic stable angina pectoris.

Methods

Male and female patients, 18–70 years old, with a documented history of chronic stable angina pectoris for at least 2 months and receiving a stable dose of long-acting nitrate therapy for at least 2 weeks, were enrolled in a prospective, randomized, double-blind, placebo-controlled, parallel-design trial in 22 centers throughout the United States. Patients were excluded if they had had a myocardial infarction, coronary artery bypass graft, or coronary angioplasty within 3 months of the screening visit; congestive heart failure (CHF); second- or third-degree atrioventricular (AV) block; a clinically significant arrhythmia; uncontrolled hypertension (blood pressure >180/105 mmHg); or a history of alcohol or drug abuse. Concomitant use of antianginal medications other than nitroglycerin (NTG) and long-acting nitrates was prohibited during the study.

To qualify for study entry, patients had to demonstrate significant ST-segment change and moderate anginal pain during a symptom-limited exercise tolerance test (ETT) (Bruce protocol). Total duration of the ETT had to be between 3 and 8 min, and termination had to be because of moderate angina (ETT termination for reasons other than moderate angina disqualified patients for the study). Following a 1-week placebo run-in period, patients underwent a second ETT and, provided that the results of this ETT were within ±15% of those of the Visit 1 ETT, patients were randomized to receive either mibefradil 50 mg or placebo once daily in addition to their nitrate therapy. After 2 weeks of treatment with mibefradil 50 mg, the patients receiving mibefradil were force titrated to 150 mg once daily for an additional 2 weeks. Exercise tolerance tests were performed at the end of Weeks 2 and 4. Patients also maintained an anginal diary during the 4-week treatment period.

Tolerability of trial medication was assessed by recording adverse events at each visit. Laboratory parameters, including blood chemistry, hematology, and urinalysis, were analyzed on Days 0 (baseline) and 28, and 12-lead electrocardiograms (ECGs) were performed on Days 0, 14, and 28.

Data Analysis

Three patient populations were analyzed. The main analysis of the efficacy parameters was performed on the intent-to-treat (ITT) population, which included all randomized patients who had received at least one dose of study medication and had had at least one baseline ETT and one postrandomization ETT. The standard population comprised all patients who completed the protocol and had a valid ETT at baseline and at Week 4. Patients who withdrew prior to the end of the study because of treatment failure or worsening angina but had at least 4 days of high-dose treatment were not excluded from the standard population. The safety population was the group who received at least one dose of study medication and for whom a safety evaluation was available.

The primary efficacy parameter was the change baseline in symptom-limited ETT duration. Secondary efficacy parameters included change in time to onset of angina, time to persistent 1 mm ST-segment duration, change in number of anginal episodes per week, and change in weekly consumption of NTG. The therapeutic success rates at Weeks 2 and 4, defined as an increase in ETT duration of ≥60 s or an increase in ETT duration without the development of angina, were also calculated.

The evaluation of the changes from baseline in ETT parameters at trough (24 h ± postdose) was performed with an analysis of covariance (ANCOVA), using a model containing treatment, center, and treatment-by-center as fixed factors and the related baseline ETT parameter as a covariant. To compare the active treatment with placebo, estimated treatment effects were defined as the paired difference between both groups in the center-adjusted mean change from baseline (calculated from the ANCOVA model). For the evaluation of the changes from baseline in anginal diary variables (weekly anginal attacks and NTG consumption), analysis of variance (ANOVA) was performed.

All tests were two sided and performed at an alpha level of 0.05. Data are expressed as the mean ± standard deviation unless otherwise stated.

Results

Patient Characteristics

The demographic characteristics and cardiovascular secondary diagnoses of all randomized patients are presented in Table I. In all, 189 patients satisfied the entry criteria and were randomized: 96 to the placebo group and 93 to the mibefradil group. Four patients were excluded from the ITT population because no efficacy data were collected after randomization. Thirty-five patients were excluded from the standard population, mainly for the absence of an ETT after the start of randomized treatment. Thirteen patients withdrew prematurely: 12 patients because of adverse events or ECG changes (3 in the placebo group, 2 during treatment with mibefradil 50 mg, and 7 during treatment with mibefradil 150 mg) and 1 for administrative reasons (during mibefradil 50 mg treatment). The two groups were well matched with regard to age, gender, race, and weight.

TABLE I Patient characteristics and study populations

	Placebo (n = 96)	Mibefradil (n = 93)
Sex (M:F)	81:15	76:17
Age (years) (mean ± SD)	63.6 ± 8.6	62.9 ± 8.4
Weight (kg) (mean ± SD)	84.1 ± 17.4	83.4 ± 12.6
Race (W:B:O)	84:7:5	80:9:4
Previous MI (%)	39.6	47.3
Previous CABG (%)	36.5	28.0
Populations		
Safety[a]	96	93
ITT[b]	95	90
Standard[c]	84	70

[a] Safety population = received at least one dose of study medication, and a safety evaluation is available.
[b] ITT population = all randomized patients with at least one symptom-limited ETT. Four patients were excluded because no efficacy data were collected after randomization.
[c] Standard population = all patients who had valid baseline and 4-week ETTs. Patients who withdrew prior to end of study due to treatment failure or worsening angina but had at least 4 days of high-dose treatment were not excluded.
Abbreviations: M = male, F = female, W = white, B = black, O = other, MI = myocardial infarction, CABG = coronary artery bypass graft, ITT = intent to treat, ETT = exercise tolerance test.

Exercise Performance at Week 2 (50 mg Dose)

After 2 weeks of treatment with mibefradil 50 mg, there was statistically significant but clinically modest improvement in total ETT duration versus placebo (treatment effect 16.4 s, p = 0.04) and in time to 1 mm ST-segment depression versus placebo (treatment effect p = 26.2 s, p = 0.008) in the ITT population. Although there was a somewhat greater improvement in time to onset of angina in the mibefradil versus the placebo group, it did not reach the level of statistical significance (treatment effect 19.6 s, p = 0.063) (Table II).

After 2 weeks of mibefradil 50 mg treatment, an increase in exercise duration of at least 60 s was recorded in 18.9% of patients in the placebo (nitrate monotherapy) group and 25.6% of mibefradil-treated patients in the ITT population. This differences between the treatment groups were not statistically significant. However, the other measure of success rate, an increase in ETT duration without the development of angina, was achieved significantly more often in the mibefradil-treated group than in those given placebo (p = 0.05).

Exercise Performance at Week 4 (150 mg Dose)

Following an additional 2 weeks of treatment with mibefradil 150 mg, the increase in ETT duration compared with

TABLE II Change from baseline in ETT parameters after 2 weeks of treatment (50 mg dose) in the ITT population

	Placebo (n = 95)	Mibefradil 50 mg (n = 90)	Treatment effect (s)
Exercise duration			
Baseline (BL) (s)	344.8 ± 76.4	353.2 ± 79.1	
Change from BL	15.6 ± 48.3	30.3 ± 60.9	16.4
Change (%)	4.5	8.6	p = 0.035
Time to onset of angina			
Baseline (BL) (s)	260.8 ± 85.6	258.8 ± 94.1	
Change from BL	23.4 ± 61.9	42.4 ± 84.5	19.6
Change (%)	9.0	16.4	p = 0.063
Time to onset of ischemia[a]			
Baseline (BL) (s)	279.2 ± 83.2	292.3 ± 84.8	
Change from BL	14.4 ± 62.7	38.7 ± 76.2	26.6
Change (%)	5.2	13.2	p = 0.008

[a] Ischemia is defined as ≥ 1 mm ST-segment depression.
Abbreviations: ETT = exercise tolerance test, ITT = intent to treat, BL = baseline.

TABLE III Change from baseline in ETT parameters after 4 weeks of treatment (150 mg dose) in ITT and standard populations

	ITT population			Standard population		
	Placebo (n=95)	Mibefradil 150 mg (n=90)	Treatment effect	Placebo (n=84)	Mibefradil 150 mg (n=70)	Treatment effect
Exercise duration						
Baseline (BL) (s)	344.8 ± 76.4	353.2 ± 79.1		343.9 ± 74.5	354.2 ± 77.2	
Change from BL (s)	37.8 ± 59.8	51.7 ± 77.9	15.4	35.9 ± 54.3	54.2. ± 7.5	20.6
Change (%)	11	14.6	p = 0.129	10.4	15.3	p = 0.05
Time to onset angina						
Baseline (BL) (s)	260.8 ± 85.6	258.8 ± 94.1		259.9 ± 85.1	258.8 ± 94.1	
Change from BL (s)	39.2 ± 72.7	78.0 ± 97.5	39.7	40.5 ± 69.0	76.1 ± 98	35.1
Change (%)	15	30.1	p = 0.002	15.5	29.5	p = 0.009
Time to onset ischemia[a]						
Baseline (BL) (s)	279.2 ± 83.2	292.3 ± 84.8		279.6 ± 85.8	299.4 ± 77.3	
Change from BL (s)	28.3 ± 68.9	80.7 ± 93.9	55.3	31.9 ± 69.4	81.6 ± 90.9	51.2
Change (%)	10.1	27.6	p < 0.001	11.4	27.3	p < 0.001

[a] Ischemia is defined as ≥ 1 mm ST-segment depression.
Abbreviations as in Table II.

placebo was statistically significant (treatment effect 20.6 s, p = 0.05) for the standard population, but did not reach statistical significance for the ITT population (treatment effect 15.4 s, p = 0.13). The increases in time to onset of angina were statistically significant for both the ITT population (treatment effect: 39.7 s, p = 0.002) and the standard population (treatment effect: 35.1 s, p = 0.009). Similarly, the increase in time to onset of ischemia was statistically significant for the ITT population (treatment effect: 55.3 s, p < 0.001) and for the standard population (treatment effect 51.2 s, p = 0.001) (Table III).

At Week 4, 28.4% of the placebo-treated patients and 41.1% of the mibefradil-treated patients were able to increase total ETT duration by at least 60 s. As was the case at Week 2, the difference between the treatment groups was not statistically significant. However, the percentage of patients who were able to increase their ETT duration without the development of angina was significantly greater in those treated with mibefradil than in those receiving placebo (p < 0.001).

Hemodynamic Effects

Table IV summarizes the changes in blood pressure (BP), heart rate (HR), and rate–pressure product (HR × systolic BP) at rest and at ETT termination in the ITT population. After 4 weeks of treatment with mibefradil 50/150 mg, there were highly significant (p < 0.001) decreases compared with placebo for all hemodynamic parameters with the exception of systolic BP at exercise termination.

Anginal Symptoms and Nitroglycerin Consumption

Compared with placebo, treatment with mibefradil 50 mg was associated with a significantly larger reduction in the number of weekly anginal attacks (−28 vs. −46%, p = 0.05) and use of NTG (−33 vs. −62%, p = 0.04) in the ITT population. Similar findings were observed at Week 4 after an additional 2 weeks of therapy with mibefradil 150 mg. Compared with placebo, there were significantly greater reductions in both diary parameters: weekly anginal attacks (−36 vs. −54%, p = 0.03) and NTG consumption (−33 vs. −52%, p = 0.02).

Tolerability and Safety

The combination of mibefradil 50 mg and long-acting nitrates was well tolerated, with similar incidences of patients with at least one potentially treatment-related adverse event

TABLE IV Changes from baseline in hemodynamic parameters during ETT in the ITT population after 4 weeks of treatment (150 mg dose)

	Placebo (n = 95)	Mibefradil (n = 90)	Treatment effect
At rest			
DBP (mmHg)	−1.3 ± 8.2	−8.0 ± 9.5	−6.3[a]
SBP (mmHg)	−1.7 ± 15.2	−9.3 ± 16.1	−7.2[a]
HR (beats/min)	−1.9 ± 9.7	−9.6 ± 9.9	−8.2[a]
Rate–pressure product	−335 ± 1507	−1816 ± 144	−1519[a]
At termination of ETT			
DBP (mmHg)	−0.9 ± 9.0	−8.2 ± 10.6	−6.9[a]
SBP (mmHg)	−1.7 ± 18.5	−1.0 ± 19.9	0.6
HR (beats/min)	0.9 ± 10.4	−14.2 ± 12.1	−15.4[a]
Rate–pressure product	38.2 ± 3363	−2499 ± 3413	−2605[a]

[a] p < 0.001.
Abbreviations: ETT = exercise tolerance test, ITT = intent-to-treat, DBP = diastolic blood pressure, SBP = systolic blood pressure, HR = heart rate.

(AE) observed in the placebo group (11.8%) and the combination therapy group (9.4%). Comparing mibefradil 150 mg with placebo, more AEs were reported by patients receiving mibefradil than by those on placebo (37.6 vs. 21.9%, respectively). The most frequent AEs with mibefradil 150 mg compared with placebo are summarized in Table V. Twelve patients withdrew prematurely from the study as a consequence of AEs and treatment-emergent ECG changes: 3 (3%) in the placebo-treated group (including two cases of myocardial infarction); 2 (2%) at the mibefradil 50 mg dose; and 7 (8%) at the mibefradil 150 mg dose (including one death as a consequence of limb embolism).

The main treatment-emergent ECG changes were dose-related asymptomatic sinus bradycardia and first-degree AV block (Table VI). During the 2 weeks of treatment with mibefradil 50 mg, the incidence of these ECG changes was similar in the mibefradil- and placebo- treated groups [sinus bradycardia: mibefradil (50 mg) 3.2% vs. placebo 2.1%; first-degree AV block: mibefradil (50 mg) 2.2% vs. placebo 5.2%]. However, over the course of the whole study including 2 weeks of treatment with mibefradil 150 mg, the proportion of patients experiencing such changes was higher [sinus bradycardia: mibefradil (150 mg) 12.9% vs. placebo 2.1%; first-degree AV block: mibefradil (150 mg) 10.7% vs. placebo 6.3%].

There were no clinically relevant findings with any of the clinical laboratory tests in either treatment group.

Discussion

This trial was initiated before the final recommended mibefradil dosages (50 and 100 mg) were determined. As a result, a supratherapeutic dosage (150 mg) was incorporated in the design of this trial. Adding mibefradil 50 mg to long-acting nitrate therapy produced significant but minimal improvements in both objective and subjective ETT parameters, including ETT duration and time to onset of ischemia. At Week 4, therapy with mibefradil 150 mg also resulted in significant improvements in both objective and subjective ETT parameters (i.e., time to onset of angina and time to onset of ischemia). The improvement in the clinical status of the mibefradil-treated patients compared with those receiving placebo was also reflected in the significantly larger proportion of mibefradil-treated patients, at both the 50 and 150 mg doses, who could increase total exercise duration without developing angina. Treatment with both the 50 and 150 mg doses of mibefradil was associated with significantly larger reductions in weekly anginal attacks and NTG use compared with placebo.

Including the present study, the efficacy of mibefradil in the treatment of chronic stable angina pectoris was assessed in five placebo-controlled trials involving a total of 865 patients randomized to one of four mibefradil dosages (25, 50, 100, or 150 mg once daily, n = 565) or to placebo (n = 300).[8–12] In two trials, mibefradil was administered as mono-

TABLE V Most frequent adverse events (excluding those unrelated to treatment)

	Week 2		Week 4	
	Placebo (n=96)	Mibefradil 50 mg (n=93)	Placebo (n=96)	Mibefradil 150 mg (n=93)
Fatigue (%)	2 (2.1)	3 (3.2)	3 (3.1)	5 (5.4)
Angina pectoris (%)	2 (2.1)	—	2 (2.1)	—
Dizziness (%)	—	2 (2.2)	0 (0)	10 (10.8)
Nausea (%)	—	2 (2.2)	3 (3.1)	3 (3.2)
Postural hypotension (%)	—	—	—	1 (1.1)
Headache (%)	—	—	3 (3.1)	5 (5.4)
Leg edema (%)	—	—	1 (1.0)	5 (5.4)
Total patients with at least one adverse event	9 (9.4)	11 (11.8)	21 (21.9)	35 (37.6)

TABLE VI Most frequent treatment emergent ECG changes

	Week 2		Week 4	
	Placebo (n=96)	Mibefradil 50 mg (n=93)	Placebo (n=96)	Mibefradil 150 mg (n=93)
ST-T changes (%)	9 (9.4)	2 (2.2)	10 (10.1)	3 (5.4)
First-degree AV block (%)	5 (5.2)	2 (2.2)	6 (6.3)	10 (10.7)
Sinus bradycardia (%)[a]	2 (2.1)	3 (3.2)	2 (2.1)	12 (12.9)
Total patients with at least one ECG change (%)	22 (22.9)	10 (10.7)	25 (26)	33 (35.5)

[a] Heart rate< 55 beats/min with a change from baseline of > 10 beats/min or heart rate < 45 beats/min with any decrease from baseline.
Abbreviations: ECG = electrocardiogram, AV = atrioventricular.

therapy and in three trials it was given to patients who continued their background therapy with either beta blockers or, as in the case of the present study, long-acting nitrates. In all five studies, mibefradil 50 mg once daily improved ETT duration compared with placebo. The placebo-corrected treatment effect reached statistical significance in those studies (including the present one) when mibefradil 50 mg was given in addition to background antianginal therapy. Time to onset of ischemia was significantly delayed in all five studies (including the present one) with mibefradil 50 mg. The significant reduction in anginal symptoms and NTG consumption observed with mibefradil 50 mg in the present study contributed to the significant dose-related decrease both in the number of anginal attacks and in the intake of NTG ($p < 0.01$ for both variables) observed in a pooled analysis of all five placebo-controlled studies.[13]

A possible explanation for the lack of significant improvement in ETT duration with mibefradil 150 mg in the ITT population is that some patients could not tolerate that dose, which led them to terminate the ETT for other symptoms prior to reaching moderate angina. Support for this hypothesis is the markedly higher proportion of patients on the 150 mg dose of mibefradil stopping ETT for symptoms other than angina compared with those on the 50 mg dose (34.4 vs. 13.3%, respectively). By contrast, in the analysis of the standard population, which accounts for the impact of protocol violations and premature withdrawals on study results, a statistically significant difference between 150 mg mibefradil treatment and placebo was observed.

In the present study, there was little difference in the incidence of AEs or treatment-emergent ECG changes between patients treated with mibefradil 50 mg and those receiving placebo (nitrate therapy). During the additional 2 weeks of treatment with mibefradil 150 mg, there was a noticeable increase in the incidence of AEs relative to the placebo group. Three AEs were clearly more frequent in the mibefradil 150 mg group: dizziness, leg edema, and postural hypotension. The overall incidence of ECG changes was also greater with mibefradil 150 mg, mainly because of more frequent instances of sinus bradycardia and first-degree AV block.

Consistent with the findings of the present study were the observations of the placebo-controlled, dose-finding studies with mibefradil monotherapy.[9, 10, 12] These demonstrated that the incremental gain in efficacy obtained with the 150 mg dose compared with the 100 mg dose is small and that the increase in the incidence of AEs and ECG changes is relatively high indicating that mibefradil 100 mg should be regarded as the highest dose with the best balance of efficacy and tolerability.

Although mibefradil 100 mg once daily added to long-acting nitrates was not evaluated in the present study, the 100-mg dose, as monotherapy and in combination with beta blockers, has been shown to be effective and well tolerated in the treatment of chronic stable angina pectoris. In fact, in all of the placebo-controlled studies where mibefradil 100 mg was evaluated, a significant placebo-corrected treatment effect for all three ETT variables was observed that was larger than that noted for the 50 mg dose. One can speculate that mibefradil 100 mg in addition to long-acting nitrate therapy would, likewise, result in improvements in antianginal and anti-ischemic efficacy.

Perspective on the safety of the highest recommended dosage of mibefradil, 100 mg once daily, is provided by data from Tzivoni *et al.*[12] They evaluated mibefradil 50 and 100 mg as monotherapy in a placebo-controlled study in patients with chronic stable angina. The overall incidence of AEs was similar for the placebo and mibefradil 50 mg groups (Table VII), while the frequency of AEs was higher in patients treated with mibefradil 100 mg. Treatment emergent ECG changes for placebo and the mibefradil 50 and 100 mg groups are summarized in Table VIII.

Another important aspect concerning the safety of mibefradil relates to the pharmacokinetics of the drug. Mibefradil is eliminated by dual metabolic pathways: cytochrome P450 (CYP)3A4 mediated oxidation and by esterase hydrolysis. At steady state, mibefradil is not only a substrate for but also an inhibitor of CYP3A4. Furthermore, there is evidence that mibefradil and its major metabolite (RO 40-5967) also inhibit CYP2D6. Thus, in routine clinical practice, the metabolism of mibefradil is shunted almost entirely to the high capacity esterase system. This mechanism is responsible for several phar-

TABLE VII Adverse events occurring in ≥25 of patients excluding unrelated events[12]

	Placebo (n=62)	Mibefradil 50 mg (n=61)	Mibefradil 100 mg (n=60)
Dyspepsia (%)	1 (1.6)	2 (3.3)[a]	4 (6.7)[a]
Headache (%)	4 (6.5)	2 (3.3)	2 (3.3)
Leg edema (%)	2 (3.2)	1 (1.6)	—
Dizziness (%)	1 (1.6)	2 (3.3)	1 (1.7)
Abdominal pain (%)	—	2 (3.3)	3 (5.0)
Other (%)	8 (12.9)	7 (11.5)	8 (13.3)
Total patients with ≥1 adverse event (%)	12 (19.4)	12 (19.7)	17 (28.3)

Adverse events with overall incidence < 2% are pooled under "other."

[a] Believed to be secondary to noncommercial large gelatin capsules used in this study.

TABLE VIII Relevant treatment—emergent ECG changes[12]

	Placebo (n = 62)	Mibefradil 50 mg (n = 61)	Mibefradil 100 mg (n = 60)
First degree AV block (%)	—	1 (2)	4 (7)
Sinus bradycardia (%)	—	—	2 (3)
ST-T changes (%)	2 (3)	1 (2)	1 (2)
Total patients with ≥1 ECG change (%)	5 (8)	6 (10)	12 (20)

Sinus bradycardia: heart rate < 55 beats/min with a drop from baseline >10 beats/min, or heart rate < 45 beats/min with any decrease from baseline (as in Table VI).

Abbreviations: ECG = electrocardiogram, AV = atrioventricular.

macologic features of mibefradil, including high bioavailability, low clearance, prolonged half-life, and the absence of effect on mibefradil pharmacokinetics of physiologic factors (i.e., disease state, hepatic blood flow, and age) or coadministration of other drugs. However, the inhibition by mibefradil of CYP3A4 and CYP2D6 does reduce the metabolism of drugs biotransformed by these CYP isoenzymes. When considering the coadministration of mibefradil with other drugs metabolized by CYP3A4 and 2D6, the clinician should proceed cautiously, appropriately adjusting the doses of some drugs and avoiding others.

In the more than 200,000 patients exposed to mibefradil 50 mg and 100 mg (postmarketing surveillance), some cases of slow junctional rhythm have been reported mainly in elderly patients on concomitant beta blockers. Because there is an age-related increase in susceptibility to sinus node depression,[14, 15] caution should be exercised when prescribing mibefradil to elderly patients with a sinus rate below 55 beats/min. The combination of mibefradil and a beta blocker should be avoided when the pretreatment sinus rate is below 55 beats/min, as such a combination can unmask underlying sick sinus syndrome.

Unlike established CAs (e.g. verapamil, diltiazem, the dihydropyridines) that block L-type calcium channels, mibefradil blocks both L- and T-type calcium channels with a higher selectivity for T-type calcium channels.[16, 17] As mibefradil is the first available compound with this mechanism of action, the complex relationships between the blockade of T-type calcium channels and the resultant clinical effects have not yet been fully elucidated. However, it is known that within cardiovascular tissues, T-type channels are mainly found on arterial vascular walls, along the myocardial conduction system (primarily in the sinus node), and at neurohormonal release sites.[18] It is hypothesized that many of the features of mibefradil might be related to the compound's effect on T-type channels at these locations. Mibefradil's characteristics include a slight heart rate-lowering effect,[4] no clinically relevant negative inotropism[19] (presumably because normal ventricular myocardial cells contain mainly L-type calcium channels), coronary and peripheral vasodilation,[20] and the absence of reflex increases in neurohormones and sympathetic activity.[21] Lack of a negative inotropic effect coupled with the heart rate-lowering effect distinguishes mibefradil from L-type CAs.

Conclusion

Mibefradil 150 mg once daily added to long-acting nitrates for patients with chronic stable angina resulted in an increase in the frequency of adverse events and treatment-emergent ECG changes, which was consistent with the findings of other studies and supports the recommendation that mibefradil 100 mg once daily is the highest dosage offering a balance of efficacy and tolerability. Adding mibefradil 50 mg to long-acting nitrate therapy modestly improved patients' exercise performance and clinical status. The additive effects of the two drugs were not achieved at the expense of safety or tolerability, as the combination of mibefradil 50 mg and long-acting nitrates was as well-tolerated as long-acting nitrate monotherapy. Thus, this study demonstrates that mibefradil 50 mg once daily produces additive antianginal and anti-ischemic effects when added to background long-acting nitrate therapy and is extremely well tolerated.

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