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Addition of Zatebradine, a Direct Sinus Node Inhibitor, Provides No Greater Exercise Tolerance Benefit in Patients With Angina Taking Extended-Release Nifedipine: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

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Objectives. **We examined the antianginal and anti-ischemic effects of oral zatebradine, a direct sinus node inhibitor that has no blood pressure-lowering or negative inotropic effects in patients with chronic stable angina pectoris taking extended-release nifedipine.**

Background. **Heart rate reduction is considered an important pharmacologic mechanism for providing anginal pain relief and anti-ischemic action in patients with chronic stable angina, suggesting a benefit for sinus node-inhibiting drugs.**

Methods. **In a single-blind placebo run-in, randomized double-blind, placebo-controlled, multicenter study, patients already receiving extended-release nifedipine (30 to 90 mg once a day) were randomized to receive zatebradine (5 mg twice a day [n = 64]) or placebo (n = 60). All subjects had reproducible treadmill exercise-induced angina at baseline, and after randomization they performed a serial exercise test 3 h after each dose for 4 weeks.**

Results. **Zatebradine reduced rest heart rate both at 4 weeks ([mean ± SEM] 12.9 ± 1.23 vs. 2.3 ± 1.6 [placebo] beats/min, $p < 0.0001$) and at the end of comparable stages of Bruce exercise (16.7 ± 1.2 vs. 3.4 ± 1.2 [placebo] beats/min, $p < 0.0001$). Despite the significant effects on heart rate at rest and exercise, there were no additional benefits of zatebradine from placebo baseline in measurements of total exercise duration, time to 1-mm ST segment depression or time to onset of angina. Subjects taking zatebradine also had more visual disturbances as adverse reactions.**

Conclusions. **Zatebradine seems to provide no additional antianginal benefit to patients already receiving nifedipine, and it raises questions regarding the benefit of heart rate reduction alone as an antianginal approach to patients with chronic stable angina.**

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Heart rate reduction at rest and during exercise has been considered an important mechanism for the antianginal and anti-ischemic effects of beta-adrenergic blocking agents and the rate-lowering calcium channel blocking agents diltiazem and verapamil (1–3). A new class of drugs—the direct sinus node inhibitors—has been developed. These drugs have bradycardic actions without effects on myocardial contractility, blood pressure or peripheral and coronary vascular resistances (4–7).

Zatebradine (Fig. 1), a prototype agent of this class, has been shown (8,9) to reduce heart rate at rest and during exercise in humans. We report the results of a multicenter, randomized, double-blind, placebo-controlled trial designed to investigate whether exercise tolerance could be favorably affected by the addition of zatebradine in patients with angina pectoris whose exercise tolerance is limited despite treatment with 30 to 90 mg of extended-release nifedipine (Procardia XL). A secondary objective was to assess the safety profile of concomitant zatebradine and nifedipine administration.

Methods

Patients with stable exertional angina who were already receiving 30 to 90 mg/day of extended-release nifedipine were enrolled in this double-blind, randomized, placebo-controlled trial at 17 separate centers (see Appendix). The trial was approved by the appropriate institutional review board at each participating center. All subjects signed a written consent form that fully explained the purposes and potential risks and benefits of participation in the study.

Study patients. Patients (150 men, 25 women; age range 30 to 82 years) had a ≥3-month history of chronic stable angina triggered by physical activity and relieved by rest or nitroglycerin. Study inclusion required electrocardiographic (ECG)

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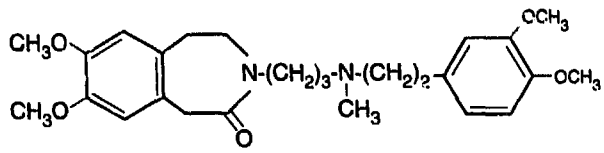


Figure 1. Chemical structure of zatebradine.

evidence of exercise-induced myocardial ischemia (ST segment depression ≥1 mm from baseline) or documented angiographic evidence of coronary artery disease, or both. Patients with conditions that would hinder or confuse follow-up evaluations and those unable to undergo the protocol requirements for the study were excluded.

Study design. This was a multicenter, double-blind, randomized, parallel-group comparison of 5 mg of zatebradine and placebo administered orally twice a day in patients with chronic stable angina pectoris whose exercise tolerance was limited despite treatment with 30, 60 or 90 mg of extended-release nifedipine administered once a day. With the exception of nifedipine and sublingual nitroglycerin, as needed for the relief of attacks of angina, no other antianginal therapy was allowed at any time during the study.

The study design is described in Figure 2. Qualifying patients were enrolled in a run-in phase consisting of 3 to 4 visits over a 2- to 3-week period, during which they received placebo twice a day. Patients performed two consecutive treadmill exercise tests according to the standard Bruce protocol. To qualify the patient for randomization, both exercise tests had to be between 4 and 9 min long, be limited by moderate angina and show ST segment depression of at least 0.1 mV in at least one ECG lead. In addition, the duration of the shorter of the two tests had to be within 15% of the duration of the longer test. If these criteria were not met on the first two tests, a third exercise test could be scheduled 1 week after the second test.

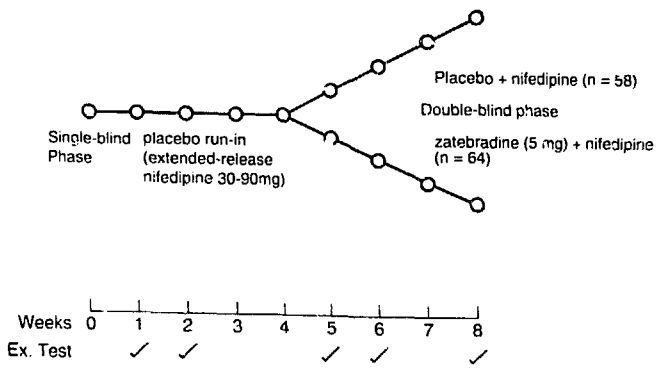
After randomization, patients received a single dose of double-blind study medication in the clinic, and heart rate and blood pressure were monitored for 3 h after dosing. No patients were excluded from participation in the study because of excessively low blood pressure (≤80/60 mm Hg) or excessive bradycardia (≤40 beats/min) after the first dose. Visits were scheduled after 1, 2 and 4 weeks of double-blind treatment. During these visits, exercise tests were performed 3 h (±30 min) after the morning dose of extended-release nifedipine and double-blind study medication.

Throughout the trial, patients kept a diary documenting the number of anginal attacks experienced and number of nitroglycerin tablets taken. During the follow-up exercise tests, time to angina was recorded both at onset of angina and at moderate exercise angina (the degree of angina at which the patient would normally stop exercising and take nitroglycerin). This was done uniformly throughout the study centers. Electrocardiographic strips for determining ST segment depression were recorded while the patients were standing on the treadmill, before exercise, at the end of each minute of exercise, at the onset of angina and at the end of exercise.

A 48-h ambulatory ECG was recorded, and an ophthalmologic examination was performed during the placebo run-in period and at the end of the study.

Statistical considerations. Data are presented as mean value ± SEM. The basic statistical model for the present study was an analysis of the change from baseline of a given variable using ordinary least squares (SAS Type II). Zatebradine was compared with placebo by a one-way analysis of covariance model that included treatment group, trial center and baseline exercise duration. Other baseline covariates that were found to be prognostic of change in exercise duration in the blinded data and therefore included in the model were age, gender, weight and current smoking status. All efficacy analyses were based on the so-called last observation carried forward data set, in which the last available values after randomization were carried forward for patients who failed to complete an exercise test at week 2 or 4. Only two patients, one in each group, had data carried forward to the week 4 time point. Exercise duration was substituted for time to ST segment depression or time to onset of angina when these end points did not occur after randomization. The planned sample size of 60 patients/treatment group was chosen to detect a 60-s difference in total exercise duration with 90% power at the 5% two-sided significance level, assuming a standard deviation of 100 s.

Figure 2. Study design. Ex. = exercise.



Results

Patient disposition and demography. A total of 124 patients completed screening and qualified for randomization. Four patients who were assigned to receive placebo were not able to complete the study because of adverse events (worsening angina, congestive heart failure). The demographics of the placebo and zatebradine treatment groups are described in Table 1. Of those patients randomized, 80% were men; 68% had Canadian Cardiovascular Society class II and 32% class II or III angina pectoris. The mean (±SEM) duration of angina pectoris was 7 years (range 0.3 to 25). All patients had objective evidence of coronary artery disease (previously documented myocardial infarction or positive findings on coronary angiography, scintigraphy or stress echocardiography). Coronary angiography had been performed in 96 patients, 93% of

Table 1. Pertinent Patient Characteristics at Baseline

	Placebo (n = 60)	Zatebradine (5.0 mg bid) (n = 64)
Gender		
Male	51 (85)	48 (75)
Female	9 (15)	16 (25)
Age (yr)		
Mean (SD)	62.3 (8.3)	63 (9.6)
Range	37–80	30–82
Race		
White	53 (88)	56 (88)
Black	2 (3)	5 (8)
Other	5 (9)	3 (4)
Height (in.)		
Mean (SD)	68.6 (3.9)	66.9 (3.6)
Range	60–76	59–74
Weight (lb)		
Mean (SD)	181.8 (35.3)	181.7 (34.8)
Range	119–328	104–306
Evidence of CHD		
Myocardial infarction	26 (43)	30 (47)
Imaging	33 (55)	28 (44)
Echocardiogram	7 (12)	11 (17)
Coronary angiography	47 (78)	49 (77)
At least one of these factors	60 (100)	64 (100)
Risk factors		
Hypertension	29 (48)	30 (47)
Hyperlipidemia	43 (72)	47 (73)
Hyperuricemia	5 (8)	0 (0)
Diabetes mellitus	9 (15)	17 (27)
Previous smoker	39 (65)	39 (61)
Current smoker	8 (13)	5 (8)
Oral contraceptive use	1 (2)	3 (5)
At least one of these factors	56 (93)	58 (91)
Duration of angina (yr)		
Mean (SD)	8.2 (5.8)	6.7 (5.6)
Range	0.3–25	0.3–23
Canadian Cardiovascular Society class		
II	41 (68)	43 (67)
II or III	19 (32)	21 (33)
Baseline nifedipine, total daily dose (mg)		
30	40 (67)	35 (55)
60	18 (30)	21 (33)
90	2 (3)	8 (13)

Data presented are number (%) of patients, unless otherwise indicated. bid = twice daily; CHD = coronary heart disease.

whom showed at least 60% diameter narrowing in at least one major coronary artery. None of the differences observed in demographics of clinically important baseline characteristics between the two treatment groups reached statistical significance.

The treatment groups were well balanced at baseline with respect to age, dose of nifedipine, Canadian Cardiovascular Society classification of severity of angina and total exercise duration (Table 1). Slight baseline imbalances in the number of anginal attacks, number of women and time to 0.1-mV ST segment depression were taken into account in the analysis.

The dose distribution of extended-release nifedipine throughout the study was as follows: 75 patients received 30 mg, 39 received 60 mg, and 10 received 90 mg.

One patient did not reach the primary end point of moderate exercise-induced angina pectoris at either qualifying exercise test. This patient also did not reach ST segment depression of at least 0.1 mV. The data for this patient were excluded from all efficacy analyses but were included in all safety analyses.

Efficacy response variables. *Exercise duration.* Data summarizing the exercise test findings for both treatment groups at weeks 1, 2 and 4 appear in Table 2. The data proved less variable, with the residual standard deviation ranging from 57 s at week 1 to 74 s at week 4. With 64 evaluable patients receiving zatebradine and 58 placebo, the detectable difference at week 4 was 44 s with 90% power, 38 s with 80% power and 26 s with 50% power. The difference between the zatebradine and placebo treatment groups in mean exercise duration after 4 weeks of treatment was only 3 s. Similar results were observed for time to onset of 1-mm ST segment depression and time to onset of angina (Fig. 3).

At 4 weeks, exercise times were similar in both placebo and zatebradine treatment groups because ~20% of patients in both treatment groups had improved their exercise duration ≥20% from baseline.

Heart rate and blood pressure data. The effects of zatebradine and placebo on heart rate at rest and during exercise are shown in Table 3. Heart rate at rest and during exercise was significantly lower in the zatebradine group than in the placebo group ($p < 0.0001$). Heart rate was reduced by 11 to 13 beats/min at rest and by 13 to 14 beats/min at the end of the last comparable exercise stage. There were no significant changes in rest and exercise blood pressure variables with either placebo or zatebradine (Table 4).

Anginal attack rate and nitroglycerin consumption. At baseline, patients in the zatebradine group had 1.59 ± 0.32 anginal attacks/week and were taking 0.73 ± 0.17 nitroglycerin tablets/week. Subjects in the placebo group had 2.53 ± 0.42 anginal attacks/week and were taking 1.48 ± 0.73 nitroglycerin tablets/week. After 4 weeks of treatment, there was a small but significant reduction in anginal attacks and nitroglycerin consumption in the zatebradine group compared with the placebo group (Table 5).

Adverse effects. Clinically significant adverse events occurred in two patients during the course of the study. Four patients (3.2%), including the two with serious adverse events, were dropped from the trial due to adverse events. All four were in the placebo run-in treatment group. There were no deaths in the study.

The most frequent adverse effect in the zatebradine treatment group was visual phenomena, reported by 19 patients (29.7%); only two patients (3.3%) reported visual phenomena in the placebo group. In eight patients receiving zatebradine, these visual phenomena persisted from 2 to 9 days after

Table 2. Least-Squares Analysis of Exercise Tolerance Test Variables: Placebo (n = 58) Versus Zatebradine (5 mg, n = 64) Treatment

	Baseline		Change From Baseline				
	Mean	SE	Mean	SE	Adj Mean*	Tx Effect*	p Value†
Total Exercise Duration (s)							
Week 1							
Placebo	395	9.7	9	7.8	17		
Zatebradine	390	11.4	29	7.5	36	19	0.089
Week 2							
Placebo	395	9.7	19	9.5	25		
Zatebradine	390	11.4	34	7.0	36	12	0.31
Week 4							
Placebo	395	9.7	27	11.8	37		
Zatebradine	390	11.4	35	8.0	40	3	0.85
Time to 0.1-mV ST Segment Depression (s)							
Week 1							
Placebo	329	10.9	8	9.4	14		
Zatebradine	301	12.7	48	10.0	47	33	0.017
Week 2							
Placebo	329	10.9	22	9.6	24		
Zatebradine	301	12.7	46	9.7	40	16	0.20
Week 4							
Placebo	329	10.9	25	11.9	37		
Zatebradine	301	12.7	40	10.2	46	9	0.57
Time to Onset of Angina (s)							
Week 1							
Placebo	313	10.6	16	9.2	23		
Zatebradine	298	11.0	35	9.9	35	12	0.38
Week 2							
Placebo	313	10.6	14	10.9	20		
Zatebradine	298	11.0	42	10.2	40	20	0.16
Week 4							
Placebo	313	10.6	32	13.4	47		
Zatebradine	298	11.0	43	13.0	46	−1	0.97

*Adjusted (Adj) for trial center and baseline. †Zatebradine versus placebo. Tx = treatment.

discontinuation of the drug in six patients and much longer in two.

The most frequent side effect in the placebo group was dizziness, reported by four patients (6.7%); only one patient (1.6%) reported dizziness in the zatebradine group.

Ophthalmologic examinations revealed clinically significant changes from baseline in only two patients; one patient in the placebo group had blepharitis, and one patient in the zatebradine group had increased intraocular pressure (glaucoma).

Data from 48-h ambulatory ECG monitoring showed no significant increase in arrhythmia in either treatment group, and zatebradine did not demonstrate a proarrhythmic effect according to the predefined criteria.

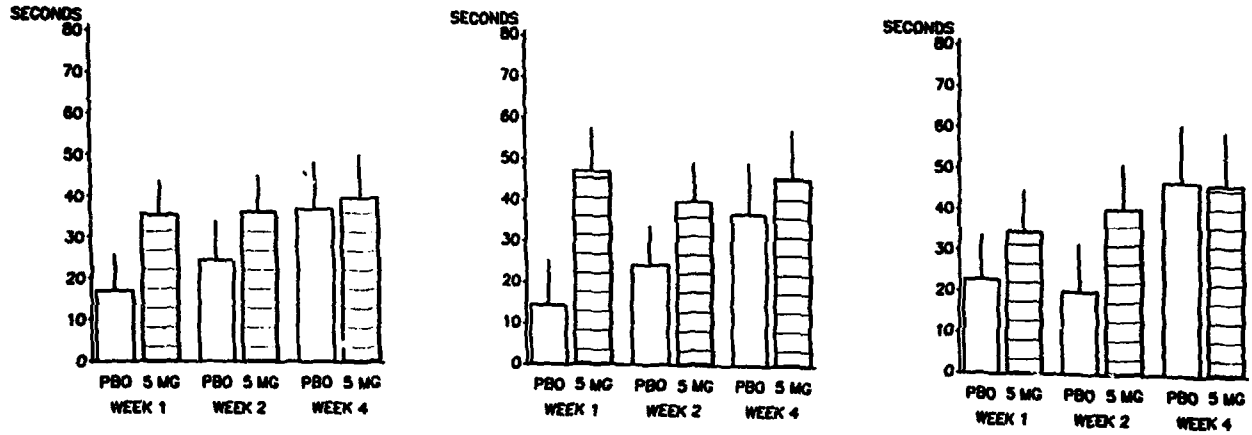
There were no clinically significant changes in PR, QRS or QT intervals in either treatment group, although the mean changes from baseline were in some cases statistically significantly different from placebo. The increased QT intervals in the zatebradine group were consistent with the bradycardic effect of the drug.

There were no clinically relevant mean changes from baseline in any of the laboratory variables measured.

Discussion

The patients in our study had mild to moderate angina, and despite some modest reductions in episodes of angina pectoris with the use of zatebradine, there were no effects of treatment on any of the exercise response variables. At the same time there were significant effects of zatebradine on rest and exercise heart rate, consistent with the pharmacologic activity of the drug.

The lack of an effect on exercise tolerance in the present study with zatebradine conflicts with previous animal and clinical studies performed in Europe (8–10). In the largest European placebo-controlled efficacy and dose-finding trial (162 patients), 5 mg twice a day of zatebradine was shown to be effective in relieving angina pectoris episodes and improving exercise tolerance compared with placebo (9). The drug's



effect on heart rate was similar to that found in our study. However, there was a much less impressive placebo treatment effect shown in the European study (9), and its active treatment phase was only 2 weeks (9). In two recent double-blind studies

Figure 3. Adjusted mean changes from baseline in exercise duration (**left**); time to 0.1-mV ST segment depression (**center**); and time to onset of angina (**right**). At 4 weeks there were significant differences in the treatment groups. PBO = placebo plus nifedipine; 5 MG = zatebradine plus placebo.

Table 3. Effect of Placebo and Zatebradine (5 mg) on Heart Rate

	Baseline		Change From Baseline				
	Mean	SE	Mean	SE	Adj Mean*	Tx Effect*	p Value†
Rest Heart Rate (beats/min): Placebo Group, n = 58; Zatebradine Group, n = 64							
Week 1							
Placebo	83.9	1.40	−1.4	1.04	−0.5		
Zatebradine	80.0	1.94	−11.5	1.20	−12.1	−11.7	<0.0001
Week 2							
Placebo	83.9	1.40	−2.7	1.20	−1.3		
Zatebradine	80.0	1.94	−14.6	1.25	−14.3	−13.0	<0.0001
Week 4							
Placebo	83.9	1.40	−2.3	1.60	−1.6		
Zatebradine	80.0	1.94	−12.9	1.23	−13.0	−11.4	<0.0001
Heart Rate (beats/min) at End of Last Comparable Stage of Exercise: Placebo Group, n = 57; Zatebradine Group, n = 64							
Week 1							
Placebo	120.3	2.40	−1.8	1.06	−1.5		
Zatebradine	120.6	1.98	−15.9	1.02	−15.6	−14.1	<0.0001
Week 2							
Placebo	120.1	2.22	−3.1	1.20	−2.5		
Zatebradine	120.5	1.87	−16.4	0.98	−15.5	−13.0	<0.0001
Week 4							
Placebo	119.4	2.39	−3.4	1.21	−4.0		
Zatebradine	120.1	1.89	−16.7	1.16	−16.8	−12.8	<0.0001
Heart Rate (beats/min) at End of Exercise: Placebo Group, n = 58; Zatebradine Group, n = 64							
Week 1							
Placebo	133.2	2.09	−1.0	1.28	0.6		
Zatebradine	131.8	1.87	−13.0	1.24	−12.0	−12.6	<0.0001
Week 2							
Placebo	133.2	2.09	−1.8	1.41	0.2		
Zatebradine	131.8	1.87	−11.9	1.37	−10.8	−10.9	<0.0001
Week 4							
Placebo	133.2	2.09	−0.6	1.54	0.8		
Zatebradine	131.8	1.87	−12.5	1.43	−12.8	−12.8	<0.0001

*Adjusted (Adj) for center and baseline. †Zatebradine versus placebo. Tx = treatment.

Table 4. Effect of Placebo and Zatebradine (5 mg) on Systolic Blood Pressure

		Baseline		Change From Baseline				
	No. of Pts	Mean	SE	Mean	SE	Adj Mean*	Tx Effect*	p Value†
Rest Blood Pressure (mm Hg)								
Week 1								
Placebo	59	126.2	2.04	−0.4	1.70	−0.7		
Zatebradine	64	127.2	2.22	1.9	1.93	1.2	1.9	0.45
Week 2								
Placebo	58	126.4	2.08	0.2	1.81	0.4		
Zatebradine	63	127.1	2.25	1.4	1.65	1.3	0.9	0.71
Week 4								
Placebo	57	126.8	2.08	0.9	1.71	−0.9		
Zatebradine	64	127.2	2.22	0.9	1.89	−0.9	0.0	1.00
Blood Pressure (mm Hg) at End of Last Comparable Stage of Exercise								
Week 1								
Placebo	57	157.7	3.09	−0.9	2.10	−1.3		
Zatebradine	64	159.9	2.99	2.5	2.22	1.7	3.0	0.32
Week 2								
Placebo	57	157.6	3.16	−2.9	2.25	−4.7		
Zatebradine	63	159.6	2.97	−1.8	1.84	−3.8	0.9	0.74
Week 4								
Placebo	55	158.0	3.18	−3.3	2.41	−7.2		
Zatebradine	64	159.6	2.96	0.3	1.93	−2.2	5.0	0.085
Blood Pressure (mm Hg) at End of Exercise								
Week 1								
Placebo	58	167.3	3.19	0.6	2.30	0.8		
Zatebradine	63	168.5	2.80	5.5	1.79	5.2	4.4	0.12
Week 2								
Placebo	57	167.4	3.24	−0.5	2.38	−2.5		
Zatebradine	62	168 3	2.84	2.8	2.29	−0.1	2.4	0.48
Week 4								
Placebo	55	166.7	3.23	−0.4	2.62	−3.3		
Zatebradine	63	168.5	2.80	2.0	1.88	−0.3	3.0	0.33

*Adjusted (Adj) for trial center and baseline. †Zatebradine versus placebo. Pts = patients; Tx = treatment.

that compared zatebradine with either diltiazem (11) or placebo (12) in patients with angina pectoris, only diltiazem improved total exercise time over placebo baseline values.

Potential biases. There are at least two possible explanations for our findings: 1) The primary response variable (e.g., exercise duration) using the Bruce protocol might not be sufficiently sensitive to the reduction in cardiac ischemia expected to result from a decrease in heart rate of 12 to 14 beats/min. We previously reported (13) the limitations of this protocol for evaluating anti-ischemic treatments. 2) The reduction in heart rate might offset by an increase in other determinants of maximal oxygen consumption. Although systolic blood pressure was the only other index measured and rate pressure product declined, it is possible that ventricular preload or contractility increased.

Clinical implications. Despite the theoretic benefit of using bradycardic agents in the treatment of angina, especially those that lack negative inotropic effects and cardiac conduction depressant actions, perhaps heart rate reduction alone is not enough to provide a long-acting antianginal benefit.

Beta-blockers (2) and the calcium channel blockers verapamil and diltiazem (3) are bradycardic drugs which manifest an antianginal benefit. In addition to their bradycardic actions, each of these agents has negative inotropic activity that may produce a more important anti-ischemic action than previously thought in patients with chronic angina.

In contrast to our study, when nifedipine is combined with a beta-blocker, there are additive effects on exercise tolerance greater than with either treatment alone (14). In addition, the combination of dihydropyridine amlodipine with a beta-blocker in patients with chronic angina pectoris also provides added antianginal and anti-ischemic efficacy compared with either drug used alone (15).

In a clinical comparison of propranolol with other beta-blockers having less negative inotropic action but similar bradycardic activity, Pepine and Walker (16) demonstrated that propranolol had a greater antianginal effect. In patients with refractory angina pectoris and medication-induced bradycardia, Moss et al. (17) were able to demonstrate the effec-

Table 5. Effect of Placebo and Zatebradine (5 mg) on Anginal Attacks and Nitroglycerin Consumed

		Baseline		Change From Baseline		
	No. of Pts	Mean	SE	Mean	SE	p Value*
No. of Anginal Attacks/Week						
Week 2						
Placebo	58	2.53	0.42	0.33	0.35	
Zatebradine	64	1.59	0.32	−0.55	0.29	0.016
Week 4						
Placebo	58	2.53	0.42	−0.22	0.35	
Zatebradine	64	1.59	0.32	−0.80	0.27	0.0058
No. of Nitroglycerin Tablets Consumed/Week						
Week 2						
Placebo	58	1.48	0.35	0.45	0 38	
Zatebradine	64	0.73	0.17	−0.27	0.19	0.035
Week 4						
Placebo	58	1.48	0.35	0.14	0.37	
Zatebradine	64	0.73	0.17	−0.23	0.22	0.086

*Zatebradine versus placebo. Pts = patients.

tiveness of a transvenous pacemaker to prevent severe bradycardia combined with augmented antianginal therapy. In their study, the rate of the implanted demand pacer was set at 60 to 72 beats/min, which allowed increases in doses of beta- and calcium channel blockers. A long-term remission in symptoms was observed and no patient developed heart failure. It would be interesting to examine whether a nonvasodilating treatment intervention with negative inotropic activity only (e.g., a sodium channel blocking agent, left bundle branch block from right ventricular pacing) and no effect on heart rate could have antianginal efficacy.

Conclusions. Our results indicate that pure sinus node inhibition with the bradycardic agent zatebradine probably does not provide sufficient antianginal and anti-ischemic effects to be useful for long-term treatment in patients with chronic stable angina who are taking nifedipine. However, investigators are exploring the utility of zatebradine and other sinus node blocking agents as short-term treatments in both oral and intravenous forms in a number of other settings, such as acute myocardial infarction and perioperative tachycardia (18–20). Furthermore, these agents may prove useful in controlling the untoward tachycardia induced by anesthetic and inotropic agents, which is especially important in the treatment of patients with acutely decompensated congestive heart failure (18).

Appendix

Study Investigators and Participating Institutions

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