Cibenzoline for Treatment of Ventricular Arrhythmias: A Double-Blind Placebo-Controlled Study

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Cibenzoline, a new class I antiarrhythmic drug, was administered to 24 patients with frequent (> 30/h) premature ventricular complexes. Three patients discontinued the medication because of epigastric distress before repeat ambulatory electrocardiography. Of the remaining 21 patients, 13 responded to 130 mg twice daily by more than 75% suppression of premature ventricular complex frequency and 6 additional patients responded to 160 mg twice daily during an open-label titration phase. Events of ventricular tachycardia (≥ 3 beats) were totally suppressed in 9 of 10 patients and markedly diminished in the 1 remaining patient. During a double-blind placebo-controlled crossover phase in 16 patients (21 patients minus 2 nonresponders and 3 who developed side effects), cibenzoline suppressed the number of premature ventricular complexes per 24 hours (4,075 ± 868 to 1,758 ± 1,089, p = 0.02), the number of events of ventricular tachycardia (31 ± 30 to 2 ± 0, p = 0.01) and the number of premature ventricular complex pairs (61 ± 28 to 25 ± 21, p = 0.01). Cibenzoline plasma concentration was 59 to 421 ng/ml in responders and higher (387, 758 and 852 ng/ml, respectively) in the three subjects with side effects (right bundle branch block in one, hypotension in one, gastrointestinal upset and central nervous system complaints in one). Cibenzoline plasma concentration correlated with PR interval (r = 0.55, p = 0.0106) and corrected QT interval (r = 0.58, p = 0.0054). Further clinical investigation of this new antiarrhythmic agent is needed.

Frequent and complex ventricular ectopic activity is associated with increased risk of future mortality, especially when structural cardiac disease is present (1–8). Although definite evidence that suppression of these asymptomatic arrhythmias decreases mortality is lacking, efforts to develop better antiarrhythmic drugs are in progress (9). Cibenzoline, a new class I antiarrhythmic agent with a chemical structure unrelated to that of other antiarrhythmic agents ([4,5 dihydro-2-(2,2-diphenyl cyclopropyl)-1H-imidazole butanedioate]), is effective in suppressing experimentally induced ventricular arrhythmias in the rat, cat and dog (10–13). In open-label or single-blind studies performed on human subjects, it has been found effective in suppressing symptomatic ventricular tachycardia unresponsive to conventional drugs, preventing ventricular tachycardia induced by programmed electrical stimulation and decreasing the frequency of premature ventricular complexes (14–19). We

performed a double-blind, placebo-controlled crossover trial of cibenzoline in 24 patients with frequent asymptomatic premature ventricular complexes.

Methods

Patients. With the permission of the Committee for the Protection of Human Subjects in Research we enrolled 24 consenting patients (18 men and 6 women, mean age [± SD] 57 ± 11 years, range 31 to 75); 18 had coronary artery disease, 3 had valvular disease and 3 had idiopathic premature ventricular complexes. These patients had a minimum of 30 premature ventricular complexes per hour averaged over two consecutive 24 hour periods. Patients with severe angina or congestive heart failure (New York Heart Association functional class III or IV), conduction defects, Wolff-Parkinson-White syndrome, severe bradycardia (< 50 beats/min) or recent (< 3 months) myocardial infarction were excluded. Antiarrhythmic agents were discontinued at least five half-lives before entry into the study (> 6 days in 15 patients and 4 days in 2 patients). Seventeen patients had unacceptable side effects or had not responded to the following drug regimens: quinidine, four patients; procainamide, four patients; both quinidine and procainamide, seven

patients and quinidine, procainamide and disopyramide, two patients.

Treatment protocol. After this run-in or wash-out period, the patients underwent a titration period and then a double-blind placebo-controlled period (Fig. 1). During the titration period, all patients were given 130 mg cibenzoline twice daily for 1 week. Patients who showed at least 75% suppression of premature ventricular complexes compared with the initial 48 hour recording were considered responders. Patients who did not show adequate (> 75%) premature ventricular complex suppression while taking 130 mg cibenzoline twice daily were then given 160 mg twice daily for 1 week. Responders to either dose were entered into the double-blind crossover phase of the study. During this phase, patients were given either cibenzoline at the dose found effective during the titration period or matching placebo in a double-blind randomized fashion for 1 week followed by a second week when the patients were crossed over from cibenzoline to placebo treatment and vice versa.

Ambulatory electrocardiography and statistical analysis. Twenty-four hour ambulatory (Holter) electrocardi-

ography, 12 lead electrocardiography and blood sampling for the measurement of cibenzoline plasma concentration were performed at the end of each week. Analysis of the Holter tapes was performed by Cardio Data (Haddonfield, New Jersey) in a blind fashion to quantitate the number of premature ventricular complexes, couplets, events of ventricular tachycardia ($\geq$ 3 premature ventricular complexes in a row) and total number of ventricular tachycardia beats per 24 hours. This system has an acceptable sensitivity and specificity in detecting premature ventricular complexes with adequate accuracy and precision (20). RR, PR, QRS and QT intervals were measured on the 12 lead electrocardiogram recorded at a speed of 25 mm/s. Corrected QT (QT_c) interval was computed using Bazett's formula ($QT_c = QT/\sqrt{RR}$) (21). Cibenzoline plasma concentration was measured using high pressure liquid chromatography (22).

Statistical analysis. This was performed using the Statistical Analysis System program using nonparametric (premature ventricular complex-related variables) or parametric (premature ventricular complexes/heart rate) techniques as appropriate (23). Descriptive statistics, Spearman or Pearson correlation, two-way analysis of variance and Wilcoxon test for paired data were employed (24). Analysis using log (premature ventricular complex frequency + 1), log (pair frequency + 1), log (ventricular tachycardia beats + 1) and log (ventricular tachycardia events + 1) to obtain a more normal distribution of these variables and allow the use of parametric techniques yielded similar statistical inferences and did not result in modification of the conclusions (Fig. 2) (25).

Figure 1. Study protocol and flow of patients. BC = double-blind cibenzoline (dose as in open-label cibenzoline), 16 patients; BID = twice daily; BP = double-blind placebo (16 patients); ↓ B.P. = decrease in blood pressure; EKG = electrocardiogram; GI = gastrointestinal; HC = open-label cibenzoline, either 130 mg twice daily (13 patients) or 160 mg twice daily (8 patients); LC = open-label cibenzoline, 130 mg twice daily; R = run-in; RBBB = right bundle branch block.
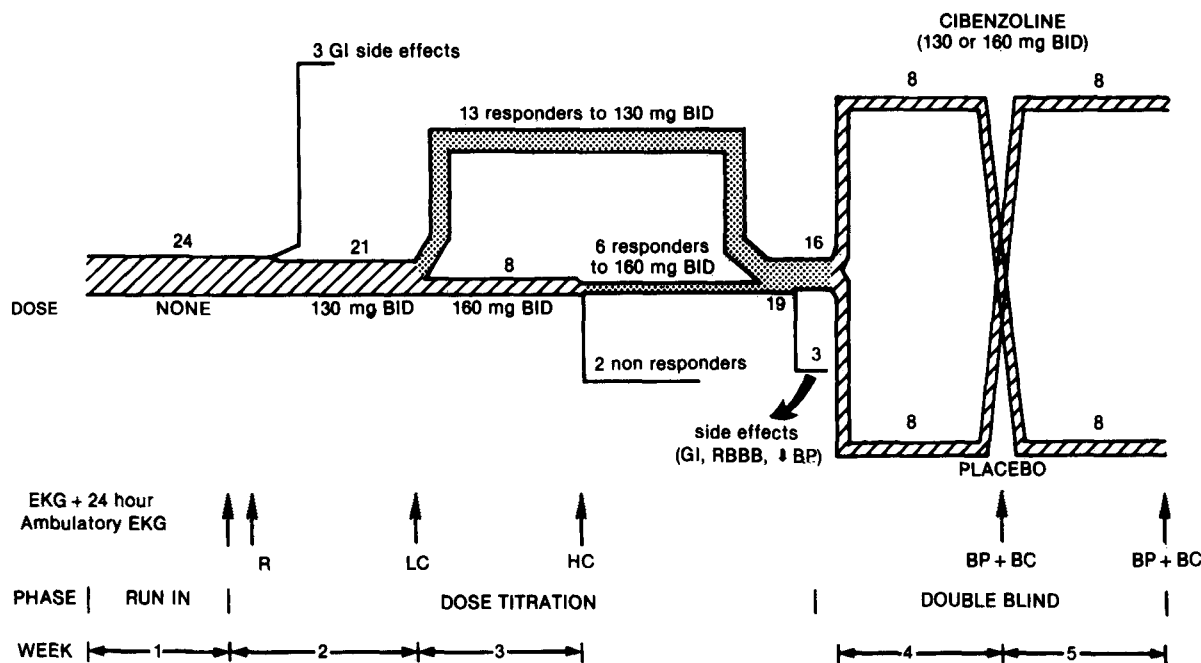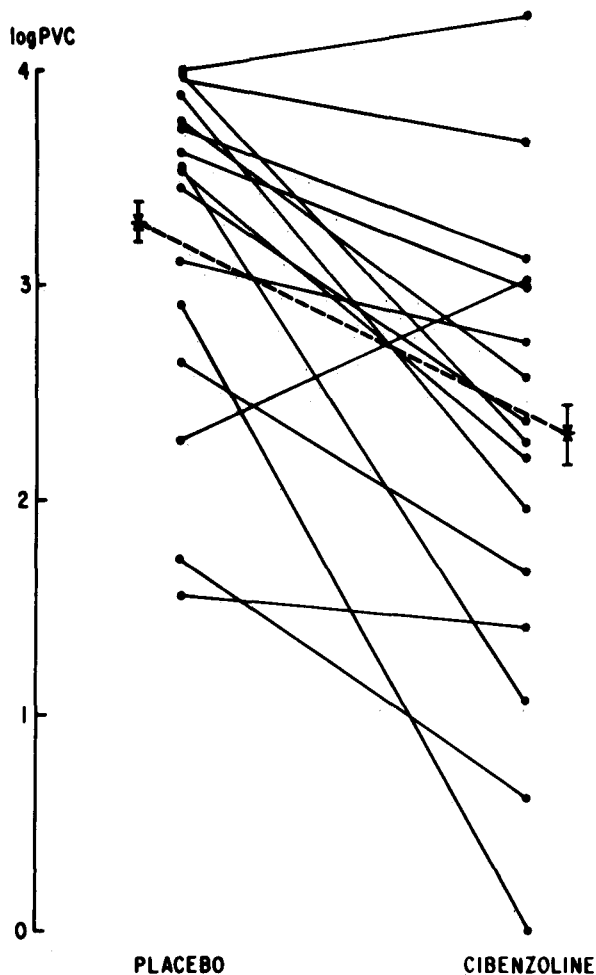
Figure 2. Effect of cibenzoline on the frequency of premature ventricular complexes during the double-blind phase. logPVC = logarithm (number of premature ventricular complexes per 24 hours + 1).

Results

Titration phase (Table 1). Of the 24 patients enrolled in the study, 3 did not complete the low dose (130 mg twice daily) phase of the titration period because of epigastric distress (Fig. 1). Since ambulatory electrocardiography, used to obtain efficacy data, was not performed while these three patients were taking cibenzoline, they are not included in further analysis. Of the remaining 21 subjects, 13 responded with more than 75% suppression of the total number of premature ventricular complexes per 24 hours. The remaining eight subjects were given 160 mg twice daily. Six of these eight patients responded to this higher dose by more than 75% suppression of the total number of premature ventricular complexes. Thus, 19 of the 21 patients responded to either 130 or 160 mg cibenzoline twice daily. Of the 19 responders, only 16 completed the double-blind placebo-controlled phase (Fig. 1). The remaining three pa-

tients were unable to complete it because of side effects (hypotension in one, right bundle branch block in one and upper gastrointestinal complaints, tremor and "dazed feeling" in one).

Ninety percent (19 of 21) of the patients responded to either 130 or 160 mg twice daily. However, if one considers only the patients who were able to tolerate and respond to the medication, 66.7% (16 of 24) of the patients showed a satisfactory response. The side effect threshold for discontinuation of cibenzoline in this study was low because of the availability of other marketed and investigational agents. Thus, four or five patients who were instructed to discontinue taking cibenzoline (excluding the patient who developed hypotension and probably the patient who developed right bundle branch block) could probably be maintained on this drug if other agents were not effective. Premature ventricular complex suppression was seen in all subjects (range 21 to 100%, median 93.4). Aggravation of premature ventricular complexes was not seen in any patient during the titration period. Although the total number of premature ventricular complexes was lower in the second of the two 24 hour recordings performed at baseline (8,116 ± 1,753 versus 7,496 ± 1,526), this difference was not statistically significant by paired Wilcoxon test. The second recording was used for statistical comparison with the recording obtained at the end of the titration phase (130 or 160 mg twice daily).

Significant correlations of cibenzoline plasma concentration with QT_c (r = 0.58, p = 0.0054) and with PR interval (r = 0.55, p = 0.0106), but not with antiarrhythmic effect, were noted. There were no significant correlations of the corrected QT interval (or of the change of corrected QT interval induced by cibenzoline) with premature ventricular complex suppression. There were no significant differences in average, maximal and minimal heart rates or QRS duration (when the patient with right bundle branch block was excluded).

Double-blind phase (Table 1). The effects of cibenzoline observed during the titration period were reproduced in the double-blind period. The average number of premature ventricular complexes per 24 hours, premature ventricular complexes per 1,000 beats, number of pairs, events of ventricular tachycardia, ventricular tachycardia beats per 24 hours and the percent of subjects with multiform beats were lower during the placebo phase of the double-blind period than at baseline. These differences were due, in part, to the fact that patients who did not enter the double-blind phase (because of lack of response or side effects) tended to have more pronounced ventricular ectopic activity than those who entered the double-blind phase.

Compared with placebo, (Fig. 2 and 3) cibenzoline caused a decrease in the total number of premature ventricular complexes per 24 hours, premature ventricular complexes per

Table 1. Effect of Cibenzoline on Premature Ventricular Complexes and Electrocardiographic Time Intervals

	Titration Phase				Double-Blind Phase			
	No.	Run-in	Cibenzoline	p Value	No.	Placebo	Cibenzoline	p Value
PVC/24 h	21	7,496 ± 1,526	1,723 ± 669	0.003	16	4,075 ± 868	1,758 ± 1,089	0.02
PVC/1,000 beats	21	66 ± 13	11 ± 4	0.003	16	43 ± 9	16 ± 10	0.02
PVC pairs/24 h	21	133 ± 44	22 ± 13	0.008	16	61 ± 28	25 ± 21	0.02
VT events/24 h	21	65 ± 61	1 ± 0	0.008	16	31 ± 30	2 ± 0	0.01
VT beats/24 h	21	371 ± 355	3 ± 0	0.001	16	241 ± 239	8 ± 0	0.01
Plasma cibenzoline (ng/ml)	21	—	293 ± 46	—	16	0	196 ± 24	—
PR (ms)	21	16 ± 5	177 ± 11	NS	16	160 ± 5	168 ± 6	NS
QTc (ms)	21	430 ± 10	435 ± 11	NS	16	415 ± 9	427 ± 8	NS

No. = number of; NS = not significant; PVC = premature ventricular complex; QTc = corrected QT interval; VT = ventricular tachycardia (≥ 3 beats).
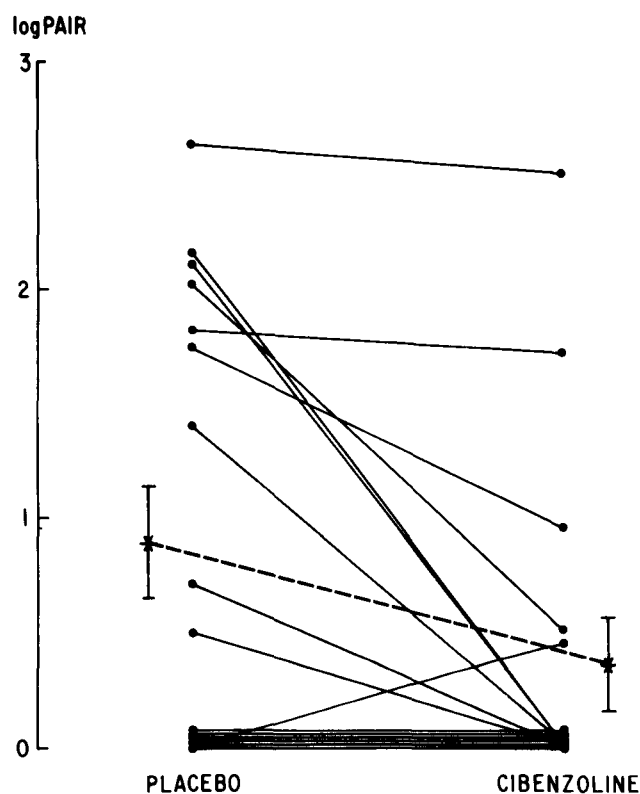
1,000 beats, pairs per 24 hours, number of events of ventricular tachycardia, number of ventricular tachycardia beats per 24 hours (241 ± 239 versus 8 ± 0, p = 0.01) and of the percent of subjects with multiform premature ventricular beats (81 [13 of 16 subjects] to 50% [8 of 16 subjects]).

Compared with the blinded placebo-controlled phase, the number of premature ventricular complexes per 24 hours decreased in 14 subjects (29 to 100% suppression) and increased in 2 subjects (9,658 to 17,517 and 194 to 1,068,

Figure 3. Effect of cibenzoline on the number of pairs of ventricular premature complexes per 24 hours during the double-blind phase. logPAIR = logarithm (number of pairs per 24 hours + 1).

respectively; that is, 81 and 451% increase, respectively). When all 16 patients were included, median suppression was 89%. In these 16 subjects, premature ventricular complex pairs were present in 9 subjects (56%) during placebo administration and in 5 subjects (31%) during cibenzoline administration. Ventricular tachycardia was present in 6 (38%) of the 16 subjects during placebo administration and in 1 subject (0.6%) during cibenzoline treatment.

Cibenzoline trough plasma concentration was zero during the placebo period and 186 ± 101 ng/ml (range 40 to 421) during cibenzoline administration 300 to 990 minutes (range 729 ± 169) after the dose. The plasma concentration was positively correlated with PR interval (r = 0.67, p = 0.0067) and corrected QT interval (r = 0.44, p = 0.0984). The plasma concentration in the two subjects who showed an increase in the total number of premature ventricular complexes per 24 hours was 133 ng/ml, 300 and 645 minutes, respectively, after the dose. The patient with a plasma concentration of 40 ng/ml (855 minutes after the dose) showed 93% suppression of premature ventricular complexes (from 5,919 to 338 premature ventricular complexes per 24 hours). A weak positive correlation of the percent change of the corrected QT interval to the percent premature ventricular complex suppression was noted (r = 0.46, p = 0.0948).

Discussion

Efficacy. This double-blind placebo-controlled study demonstrates the effectiveness of cibenzoline treatment in suppressing premature ventricular complexes. Seventy-five percent or more suppression was obtained in 19 (90.5%) of 21 patients during the dose titration period. This high rate of suppression was maintained in the double-blind placebo-controlled period in which a decrease in premature ventricular complex frequency was seen in 14 (87.5%) of 16 subjects. Average (median) suppression of premature ventricular complexes was 93.4% in the titration period and 89% in the double-blind period. This high degree of suppression by cibenzoline verifies previous, mostly uncontrolled studies

performed with this antiarrhythmic agent (15–17) and is higher than that reported for quinidine (26–29), the reference class I antiarrhythmic agent.

Although studies comparing cibenzoline with other antiarrhythmic agents are not yet available, the degree of suppression found here appears at least as pronounced as that of disopyramide, procainamide and tocainide based on previous studies (28,30,31) with these agents. In contrast (again based on previous reports), the degree of premature ventricular complex suppression induced by cibenzoline administration appears less pronounced than that reported for encainide (32) and flecainide (25,26). Despite this, and especially in the absence of comparative studies, it appears that cibenzoline may still obtain a place in antiarrhythmic therapy because of its twice daily dosing and its reported effectiveness in suppressing symptomatic ventricular tachyarrhythmias resistant to conventional antiarrhythmic agents (18,19). In addition, complete suppression of ventricular tachycardia and pairs and more than 75% decrease in premature ventricular complex frequency were observed in 12 (63.2%) of the 19 subjects in the titration period, as were a decrease in premature ventricular complex frequency and total elimination of ventricular tachycardia and pairs in 50% of the patients during the double-blind placebo period; these findings are less impressive but similar to those reported for flecainide (68 and 70%) (25,26).

Plasma levels. The efficacy of the twice daily dosing schedule of cibenzoline reported here is in agreement with the long (10 to 15 hours) elimination half-life of this agent. At steady state with twice daily dosing, using 130 mg (13 patients) or 160 mg (8 patients), average cibenzoline concentration (obtained approximately 11 hours, 705 ± 210 minutes after the dose) was 293.62 ± 210.11 ng/ml (range 59 to 852). With 130 mg twice daily, the level was higher (336 ± 238 ng/ml) in the 13 patients who showed more than 75% suppression than in the 8 who did not respond to that dose (195 ± 94 ng/ml). In these eight nonresponders, the level increased to 220 ± 111 ng/ml when they were given cibenzoline, 160 mg twice daily. Thus, the need for a higher dose in these patients may be due, in part, to lower absorption, faster elimination or greater distribution of cibenzoline. Since oral bioavailability of cibenzoline appears to approach 100%, these differences are more likely to be caused, in part, by differences in renal clearance. The range of the therapeutic trough plasma concentration was wide, with one patient showing premature ventricular complex suppression with a concentration as low as 59 ng/ml (720 minutes after ingestion of the twice daily dose), while the two nonresponders in the run-in period had a concentration of 191 and 377 ng/ml (740 and 930 minutes after the doses), respectively. Nine responders in the titration phase and six in the double-blind phase had a trough concentration below 190 ng/ml.

The three responders who did not complete the double-

blind period because of side effects (right bundle branch block, hypotension, gastrointestinal and central nervous system complaints) had high cibenzoline plasma concentrations (387, 758, 852 ng/ml at 750, 900 and 770 minutes, respectively) although they were all receiving 130 mg twice daily. The blood urea nitrogen in one of these subjects had increased from 31 mg/dl at run-in to 61 mg/dl when the side effect (hypotension) occurred. Blood urea nitrogen was normal in the other two subjects. Thus, on the basis of this study, the therapeutic plasma concentration (approximately 11 hours after the twice daily dose) for premature ventricular complex suppression appears to be between 150 and 700 ng/ml or between 150 and 400 ng/ml, depending on whether one considers the right bundle branch block that occurred in a patient with calcific aortic stenosis and a history of aortic valve replacement and aortocoronary bypass surgery. Similar findings (cibenzoline concentrations corresponding to 90% premature ventricular complex suppression between 215 and 405 ng/ml in six of eight patients) were recently reported in a dose-ranging study (33).

Side effects. Although the incidence of gastrointestinal complications was high, serious adverse reactions due to cibenzoline were not observed. One patient with a history of congestive heart failure and cardiomegaly caused by severe coronary artery disease developed clinically significant hypotension requiring a short hospitalization. This isolated case suggests that cibenzoline treatment may adversely affect the hemodynamics of patients with borderline cardiac compensation because of its negative inotropic effect observed in the laboratory (10,11,17). A common side effect was gastrointestinal upset. Although this was not severe and did not result in vomiting in any patient, it prompted discontinuation of the participation of the affected patients because of the easy availability of other agents.

The prolongation of PR and corrected QT intervals and their positive correlation with cibenzoline plasma concentration are explained by the effects of this class I antiarrhythmic agent on the AH interval and action potential duration (10,12,19). Although one patient developed right bundle branch block, a significant prolongation of the QRS duration was not noted when this patient was excluded from the analysis. However, QRS duration was measured on tracings recorded at a speed too slow (25 mm/s) to allow detection of small changes. A consistent association of electrocardiographic changes induced by cibenzoline with antiarrhythmic efficacy that could serve as markers for effectiveness was not observed in this study (34). However, in the double-blind phase, a weak positive correlation (r = 0.46, p = 0.0948) of the percent change of the corrected QT interval to the percent premature ventricular complex suppression was noted.

Aggravation of ventricular arrhythmias by antiarrhythmic drugs has been observed with most agents and may occur in approximately 10% of patients (35). Increase

in premature ventricular complex frequency did not occur in any patient during the titration phase, but a 4.5-fold increase occurred in a patient taking cibenzoline during the double-blind phase (194 premature ventricular complexes, zero cibenzoline plasma concentration with placebo; 1,068 premature ventricular complexes, plasma concentration 133 ng/ml with cibenzoline 160 mg twice daily).

The efficacy, twice daily dosing schedule and mild side effects of cibenzoline suggest that further clinical investigation of this new antiarrhythmic drug is desirable.

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