Long-term efficacy of oral pirmenol in suppressing ventricular premature depolarizations

Pirmenol is an investigational type 1A antiarrhythmic drug the long-term efficacy of which has not been fully determined. Therefore the long-term efficacy of oral pirmenol in suppressing ventricular premature depolarizations (VPDs) was assessed in an open-label, dose-titration study. Twelve patients (eight men and four women; mean age 57 ± 12 years) were treated for 24 to 36 months (mean 33 ± 4). Seven had structural heart disease (three valvular heart disease, two ischemic heart disease, and two hypertensive heart disease) and five did not. The mean left ventricular ejection fraction was 0.63 ± 0.13. Exclusion criteria included <30 VPDs/hr, >15 beats of ventricular tachycardia (VT), or prior failure of more than two antiarrhythmic drugs. Drug efficacy was assessed by 24-hour ambulatory ECG monitoring performed every 3 months during the first year, every 4 months during the second year, and at 6-month intervals during the third year. The mean hourly frequency of VPDs during the placebo phase was 732 ± 608. Seven patients (58%) were treated successfully with effective (>75%) long-term suppression of VPDs. Two patients (17%) had a partial response with effective suppression of VPDs for the first 16 months and 5 months of treatment, respectively. Three patients failed to show consistent suppression of VPDs while receiving pirmenol. The daily dose of pirmenol ranged from 200 to 500 mg (mean 317 ± 94 mg at the beginning of the study and 375 ± 97 mg at the end). No proarrhythmic effects were identified during long-term treatment, and none of the patients withdrew from the study prematurely. Mild side effects included dry mouth, bad taste, and urinary hesitancy. We conclude that oral pirmenol maintains effective long-term suppression of VPDs in approximately 60% of patients and is well tolerated during chronic administration. No proarrhythmic effects occurred during long-term treatment. (Am Heart J 1988;116:379.)

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Pirmenol is an investigational type 1A antiarrhythmic drug that has been shown in short-term studies to be effective in suppressing ventricular premature depolarizations (VPDs).[1-10] To date only two studies have examined in detail the long-term efficacy of oral pirmenol in suppressing VPDs. Hampton et al.[11] treated 11 patients for 1 to 24 months, but only six patients continued treatment for more than 12 months. Farnham[9] reported data on 28 patients who were treated for 25 months. In the present report we describe the efficacy of oral pirmenol in suppressing VPDs over a follow-up period of 24 to 36 months.

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METHODS

Patients. Men and postmenopausal women, aged 21 to 79 years, were suitable for inclusion in this study if they had >30 VPDs/hr on a 24-hour ambulatory ECG recording during the prestudy screening period. Patients with multiform or repetitive VPDs or nonsustained VT were included, whereas patients with sustained VT were excluded. Nonsustained VT was defined as VT 3 to 15 beats in duration. All patients were either asymptomatic or had palpitations as the only symptom of arrhythmia. Only patients with a left ventricular ejection fraction >0.30, determined by radionuclide ventriculography or echocardiography, were considered for inclusion in the study. Exclusion criteria included congestive heart failure, severe valvular heart disease, significantly impaired renal or hepatic function, second- or third-degree atrioventricular block, atrial flutter or fibrillation, severe obstructive airways disease, prolonged QT syndrome, and myocardial

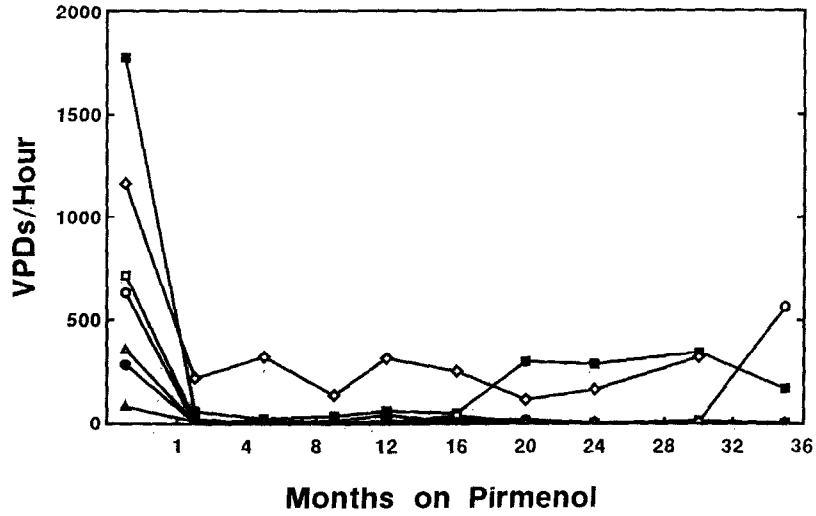

Fig. 1. VPDs/hour during treatment with placebo and pirmenol in seven patients (Nos. 1, 3, 4, 5, 8, 9, and 12) who displayed >75% long-term suppression of VPDs.

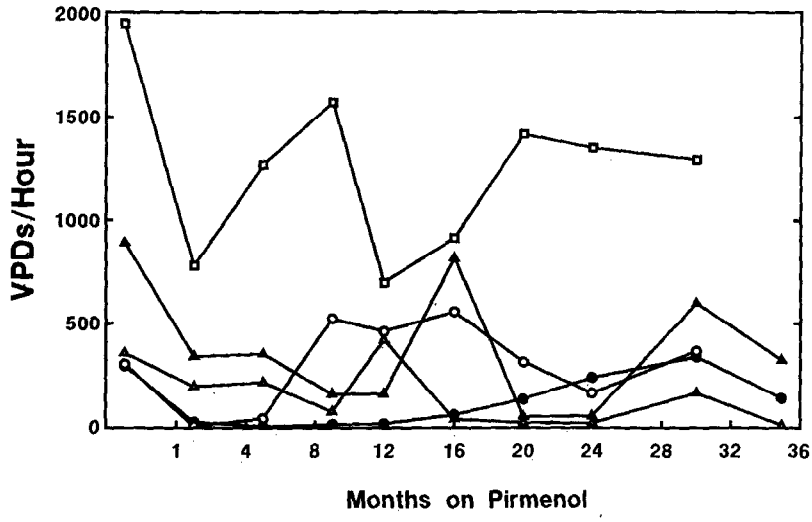

Fig. 2. VPDs/hour during treatment with placebo and pirmenol in five patients (Nos. 2, 6, 7, 10, and 11) who failed to achieve long-term suppression of VPDs.

infarction or cardiac surgery within the previous 3 months.

Twelve patients (eight men and four women; mean age 57 ± 12 years [± standard deviation]) were recruited into the study. Three patients had valvular heart disease, two had ischemic heart disease, two had hypertensive heart disease, and the remaining five patients had no structural heart disease. Mean left ventricular ejection fraction was 0.63 ± 0.13. The mean number of antiarrhythmic drugs that patients had been treated with before entry into the study was 2.5 ± 1.4 (range 0 to 4); these had been discontinued because of either inefficacy or intolerable side effects.

Study design. The study was open label in design and included dose titration as necessary to achieve efficacy. The study protocol was approved by the institutional review board of the University of Michigan Medical Center, and all patients gave written informed consent. The study was a continuation of a short-term, double-blind, randomized, placebo-controlled evaluation of oral pirmenol reported previously.[1] The study included patients who had been successfully treated with pirmenol (>75% reduction in 24-hour VPD counts) in the short-term study and also those who had received placebo. Another patient was also included, despite a reduction in VPDs of only 47% during the short-term study, because of a decrease in symptoms and episodes of nonsustained VT. The previous short-term study[1] consisted of 19 consecutive patients, of whom 14 received pirmenol and five received placebo. Thus the present group of 12 patients was selected from an original population of 19 patients.

Patients who had been successfully treated during the

Table I. Long-term efficacy of pirmenol

Patient No.	Age	Sex	Placebo phase	Mean VPDs/hr by months on treatment									Mean % change vs placebo
				1	*5*	*9*	*12*	*16*	*20*	*24*	*30*	*36*	
1	51	M	717	19	2	1	3	2	9	1	12	2	−99
				(−99)	(−99)	(−99)	(−99)	(−99)	(−99)	(−99)	(−99)	(−99)	
2	55	F	355	194	214	72	420	35	19	17	163	6	−64
				(−45)	(−40)	(−80)	(+18)	(−90)	(−95)	(−95)	(−54)	(−98)	
3	61	M	281	5	2	2	10	17	16	3	1	3	−97
				(−98)	(−99)	(−99)	(−96)	(−94)	(−94)	(−99)	(−99)	(−99)	
4	79	F	79	8	3	11	40	4	3	1	0	1	−90
				(−90)	(−96)	(−86)	(−49)	(−95)	(−96)	(−99)	(−100)	(−99)	
5	70	M	1776	57	21	35	59	48	296	284	342	166	−92
				(−97)	(−99)	(−98)	(−97)	(−97)	(−83)	(−84)	(−81)	(−91)	
6	55	M	294	23	0	10	14	57	133	237	337	138	−64
				(−92)	(−100)	(−97)	(−95)	(−81)	(−55)	(−19)	(+15)	(−53)	
7	45	F	891	339	351	157	158	816	49	51	597	322	−65
				(−62)	(−61)	(−82)	(−82)	(−8)	(−95)	(−94)	(−33)	(−64)	
8	35	F	631	1	2	1	0	37	2	3	562	—	−88
				(−99)	(−99)	(−99)	(−100)	(−94)	(−99)	(−99)	(−11)	—	
9	58	M	1161	216	320	134	313	249	113	161	317	—	−80
				(−81)	(−72)	(−88)	(−73)	(−79)	(−90)	(−86)	(−73)	—	
10	68	M	302	2	39	522	461	556	313	162	365	—	0
				(−99)	(−87)	(+73)	(+53)	(+84)	(+4)	(−46)	(+21)	—	
11	48	M	1951	779	1269	1572	698	914	1415	1349	1293	—	−40
				(−60)	(−35)	(−19)	(−64)	(−53)	(−27)	(−31)	(−36)	—	
12	55	M	354	6	14	6	1	1	6	4	—	—	−98
				(−98)	(−96)	(−98)	(−99)	(−99)	(−98)	(−99)	—	—	

Numbers in parentheses represent percentage change versus placebo.

short-term study initially continued to receive the same dose of pirmenol with upward titration as necessary to maintain efficacy. Other patients were given an initial daily dose of 200 or 300 mg of pirmenol given in two equally divided doses. If the next 24-hour ambulatory ECG showed <75% suppression of VPDs, the daily dose was increased by 100 mg. Subsequent 100 mg increments in daily dose were made in a similar fashion, to a maximum of 500 mg, provided the drug was well tolerated.

Patient evaluation. The study was conducted on an outpatient basis, and patients were seen at monthly intervals during the first year, at 2-month intervals during the second year, and at 3-month intervals during the third year of treatment. On each visit patients underwent a complete clinical examination and were questioned about the occurrence of side effects. General biochemical indexes and ECGs were checked during alternate clinic visits. Patients had an annual chest x-ray examination and an ophthalmologic examination at the end of the first year.

Ambulatory ECG recordings. Twenty-four–hour ambulatory ECG recordings were obtained every 3 months during the first year, every 4 months during the second year, and every 6 months during the third year. A Cardio Data Systems two-channel (leads 2 and V_1) Avionics recorder was used. All tapes were read by Cardio Data Systems (Haddonfield, NJ) with computerized analysis. Pirmenol was considered to be clinically effective if there was more than 75% reduction in the daily frequency of VPDs on each 24-hour recording compared to the screening period. This criterion for efficacy was used because prior studies have demonstrated its validity.[12]

The screening period took place before patients entered the short-term study,[1] and was not repeated before the long-term trial. It was 1 week in duration at the end of which frequency of VPDs was measured by a single 24-hour ambulatory ECG recording after all antiarrhythmic drugs had been discontinued for at least five half-lives.

Plasma pirmenol concentration. A venous blood sample was drawn for determination of trough plasma pirmenol concentration on each clinic visit. Analysis of plasma pirmenol concentrations was performed by Warner Lambert/Parke Davis Research Division by means of a high-pressure liquid chromatographic technique.[13]

Patients were permitted to continue taking pirmenol after 3 years on a compassionate basis. During this time they were evaluated every 4 months, but no 24-hour ambulatory ECG recordings were performed.

Statistics. Statistical comparisons were performed by means of repeated-measures analysis of variance to determine time effects. Fisher's least significant difference multiple-comparisons procedure was used to determine significant differences between individual time points. A mixed-model analysis of variance was used to compare plasma pirmenol concentrations in responders and nonresponders. An unpaired t test was used where appropriate. A p value of less than 0.05 was considered significant, and

all variables were expressed as mean ± one standard deviation.

RESULTS

Efficacy of pirmenol (Table I; Figs. 1 and 2). Seven patients (58%) showed effective long-term suppression of VPDs (92% compared with placebo) during a mean follow-up period of 33 ± 4 months (range 24 to 36) (Fig. 1). In four of these seven patients (Nos. 1, 3, 5, and 12) suppression of VPDs exceeded 80% on each of the 24-hour ambulatory ECGs. In two of the seven patients (Nos. 4 and 8), suppression of VPDs decreased to 49% and 11%, respectively, on a single 24-hour recording but exceeded 85% on all others. The final patient (No. 9) had a mean overall 80% suppression of VPDs, but on three individual ambulatory ECG recordings suppression of VPDs fell slightly below 75%.

Of the remaining five patients (Fig. 2), two (Nos. 6 and 10) had a partial response, with effective suppression of VPDs for the first 16 months and 5 months of treatment, respectively. However, patient No. 10 and a 4% to 84% increase in VPDs on five of six subsequent 24-hour ambulatory ECG recordings. This increase in the frequency of VPDs did not meet standard criteria for proarrhythmia.[14] Three patients (25%) failed to show consistent suppression of VPDs while receiving pirmenol. Mean suppression of VPDs among the three nonresponders was 50%. These patients have continued to receive treatment because of symptomatic improvement.

Six of the 12 patients have completed the 36-month study protocol and have entered a compassionate-use phase. Five patients have completed 30 months of treatment, and the final patient has completed 24 months of treatment. Of the seven patients who displayed effective suppression of VPDs during the short-term study, four maintained long-term suppression of VPDs.

The mean daily dose of pirmenol at the beginning of the study was 317 ± 94 mg and at the last visit it was 375 ± 97 mg. Five patients continued to receive the same dose throughout the study, whereas in six patients the dose was increased. In one patient the onset of side effects necessitated a reduction in dose from 400 to 300 mg/day. The mean daily dose of pirmenol among the seven long-term responders was 343 ± 113 mg and among the three nonresponders, 433 ± 58 mg; the difference was not statistically significant. There was no significant difference in left ventricular ejection fraction between responders (0.65 ± 0.12) and nonresponders (0.60 ± 0.16), and there was no significant difference in underlying heart disease between the two groups.

Adverse effects. Pirmenol was well tolerated and caused only mild side effects during chronic administration. None of the patients withdrew from the study because of side effects. In one patient it was necessary to reduce the dose of pirmenol from 400 mg to 300 mg/day because of nausea, dizziness, fatigue, and a sensation of bad taste. Reduction in the dose resulted in resolution of the side effects. Overall, eight patients complained of dry mouth, five reported urinary hesitancy and occasional palpitations, four noted occasional dizziness or lightheadedness, two complained of a metallic or bad taste and constipation, and nausea and blurring of vision occurred in one patient each.

ECG findings. There was a statistically significant lengthening of the QT interval with active treatment from a mean of 0.38 ± 0.03 second with placebo to 0.42 ± 0.03 second after 1 month of pirmenol (11% increase; $p < 0.001$). QT prolongation was maintained during continuous treatment with pirmenol but never exceeded 0.42 ± 0.05 second. There was no correlation between the degree of QT prolongation and suppression of VPDs. There was no significant change in the PR interval or QRS duration during treatment with pirmenol.

Biochemistry and hematology. There were no significant changes in serum potassium, creatinine, blood urea nitrogen, or plasma glucose levels or in liver function during the study. Of 10 patients who had serum antinuclear antibody detectable intermittently during the study, seven had received prior treatment with procainamide. In 5 of the 10 patients serum antinuclear antibody had not been detectable before they entered the study. However, lupus-like syndrome did not develop in any of the patients. Eight patients had been treated with procainamide before beginning treatment with pirmenol and of these, seven had serum antinuclear antibody detectable during the study. The white cell count or platelet count did not change significantly in any patient during the study. There were no drug-related changes on serial chest x-ray or ophthalmologic examinations during the study.

Plasma pirmenol concentrations. Only plasma pirmenol levels drawn between 10 and 14 hours of the dosing interval were included in the analysis. The mean trough plasma pirmenol concentration among the seven responders was 0.91 ± 0.44 μg/ml, and among the three nonresponders it was 1.12 ± 0.54 μg/ml. There were no significant differences between the two values. Within-patient variability in trough plasma pirmenol levels was almost as large as that between patients.

Of the two patients who displayed partial sup-

pression of VPDs patient No. 6 had a plasma pirmenol concentration of 0.86 ± 0.41 μg/ml during suppression and 0.68 ± 0.03 μg/ml during relapse. In patient No. 10, plasma pirmenol levels were similar during the effective suppression (1.22 ± 0.11 μg/ml) and relapse phases (1.10 ± 0.15 μg/ml.

DISCUSSION

The results of this study show that oral pirmenol maintains effective long-term suppression of VPDs in a significant proportion of patients (58%) in whom it is used. In an additional small number of patients, pirmenol shows initial efficacy for a period of months with subsequent recurrence of VPDs.

Pirmenol is well tolerated during long-term administration, and mild side effects are related mainly to its known anticholinergic properties. In our investigation, all patients who entered the study are still receiving pirmenol, and in only one patient was a reduction in dose necessary because of side effects. No proarrhythmic effects were noted during long-term administration, which contrasts with a possible 14% incidence of proarrhythmia during our short-term study.[1] Therefore, as is the case with other type 1A antiarrhythmic drugs, proarrhythmic events may be more likely to occur during the early weeks of treatment.

In the present study there was no significant difference in the trough plasma pirmenol concentration between responders and nonresponders. These data suggest that plasma pirmenol concentrations are unlikely to be of much value in guiding antiarrhythmic therapy. In contrast to our findings, Hampton et al.[11] found that nonresponders had a lower steady-state plasma pirmenol level than responders (1.08 ± 0.52 vs 1.72 ± 0.74 μg/ml), despite receiving a larger daily dose (447 ± 102 mg vs 315 ± 94 mg). Farnham[9] found that effective suppression of VPDs was more frequent when the trough plasma pirmenol concentration was ≥1.6 μg/ml.

Two patients in our study (Nos. 6 and 10) displayed initial effective suppression of VPDs with subsequent recurrence of VPDs despite continuing treatment. In patient No. 6, mean trough plasma pirmenol concentration during effective suppression of VPDs was slightly higher than that during recurrence. The patient received the same dose of pirmenol during both phases. Although the difference in plasma levels was not statistically significant, it is possible that a higher plasma pirmenol concentration during the later part of the study would have achieved greater suppression of VPDs. In patient No. 10, plasma pirmenol levels were similar during the effective suppression and relapse phases despite an increase in dose. Treatment for chronic obstructive pulmonary disease may have increased this patient's frequency of VPDs.

The finding of an intermittently positive antinuclear antibody titer in 10 of 12 patients is of interest. Seven of the 10 patients had been treated with procainamide before pirmenol. These data suggest that pirmenol is similar to procainamide, but notably all patients remained asymptomatic with no evidence of a lupus-type reaction. Thus it appears that a lupus-type syndrome, if it occurs at all, may be rare during treatment with pirmenol.

ECG changes consisted of a significant prolongation (11%) of the QT interval. In this regard, pirmenol is typical of other type 1A antiarrhythmic drugs. It is noteworthy that we found no correlation between suppression of VPDs and degree of QT prolongation.

The present study is the first to report follow-up data up to 3 years for patients receiving oral pirmenol for suppression of VPDs. The majority of previous studies have been short-term, but two have reported long-term results. In one study,[11] 5 of 11 patients (45%) had effective long-term suppression of VPDs during a mean follow-up period of 21 ± 3 months. One early responder had a later recurrence of VPDs, probably related to a low plasma pirmenol concentration. Two patients had increased frequency of VPDs during treatment with pirmenol (124% and 168% compared to the placebo phase). As in our study, adverse effects were mild and 9 of 10 patients had at least one positive antinuclear antibody titer. However, none of the patients had any signs or symptoms of a lupus-type reaction. Farnham[9] found that 87% of 75 patients treated for 17 months had effective suppression of VPDs (>70%). The most common side effect was unusual taste, but dry mouth, headache, dizziness, and fatigue occurred also. A possible proarrhythmic effect was noted in three patients (2%).

Pirmenol compares very favorably with other type 1A antiarrrhythmic drugs in suppressing VPDs. In two short-term studies quinidine was effective in 57% of patients in one (>80% suppression of VPDs)[15] and in 70% of patients in the other (>70% suppression of VPDs).[16] However, quinidine had to be discontinued in 15% of patients in one study because of side effects.[15] Procainamide is effective in suppressing VPDs in 65% to 76% of patients but is also poorly tolerated over the long term.[17]

In conclusion, pirmenol is an effective drug for long-term suppression of VPDs and is well tolerated. An effective dosing regimen consists of an initial

daily dose of 200 mg with subsequent upward titration guided by suppression of VPDs as determined by 24-hour ambulatory ECG recordings.

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