Oral Propafenone in the Suppression of Chronic Stable Ventricular Arrhythmias*

L. Schamroth, M.D., F.C.C.P.; D. P. Myburgh, M.B., Ch.B.; C. L. Schamroth, M.B., Ch.B.; M. E. Scholtz, M.B., Ch.B.; D. R. Pincus, M.B., Ch.B.; and D. L. Kawalsky, M.B., Ch.B.

The efficacy of propafenone hydrochloride, a new antiarrhythmic agent, was evaluated in the treatment of chronic stable ventricular arrhythmias. Twenty-five patients who had suffered a myocardial infarction three months or longer before the trial were studied. All exhibited a minimum mean frequency of 30 ventricular ectopic beats per hour over at least two 24-hour Holter monitoring periods with the last recorded tape serving as a control. The mean decrease in ventricular ectopic activity with propafenone was 65.62 percent (p < 0.001). Side effects were infrequent, minimal, and of no clinical consequence. Oral propafenone was found to be an effective drug for reducing the level of chronic ventricular ectopy, as reflected by a short-term trial.

Propafenone is a class I antiarrhythmic agent having a local anesthetic action and membrane stabilizing effect on the myocardial cell. It may be administered intravenously as well as orally. Clinical studies have indicated its effectiveness in the suppression of chronic recurrent supraventricular and ventricular tachyarrhythmias and ectopic beats. The mean plasma half-life of propafenone is approximately six hours.

The following study evaluates the short-term (48 hour) effect of intermediate dosage oral propafenone in the suppression of chronic stable ectopic ventricular rhythms in ambulatory patients with chronic ischemic heart disease.

**Materials and Methods**

Twenty-five individuals were selected from a group of working postmyocardial infarction patients who were examined at three-month intervals at the Institute of Aviation Medicine, and on whom the 24-hour Holter tape showed frequent ventricular ectopic beats (ie, 30 per hour). All had sustained a myocardial infarction three months or longer before the trial. To qualify for entry into the trial, all had to exhibit a minimum mean frequency of 30 ectopic ventricular beats per hour over at least two, 24-hour Holter monitoring periods with the last recorded tape serving as a control. The patients' ages ranged from 47 to 69 years with a mean of 61.9 years, and a median of 60 years. There were two women and 23 men.

Patients with the following manifestations were excluded from the trial: intake of other antiarrhythmic agents within the preceding two weeks; intake of beta-adrenergic blocking agents and calcium ion antagonists; evidence of renal or hepatic disease; manifest heart failure; severe bradycardia: a heart rate of less than 50 beats per minute; sinoatrial, atrioventricular, and intraventricular disorders of impulse conduction; sick sinus syndrome (bradycardia-tachycardia syndrome); electrolyte imbalance; severe obstructive pulmonary disease; and marked hypotension.

The trial on each patient was conducted over five days. On day 1, informed consent and a detailed history were obtained. Each had a complete clinical examination. On day 2, a 24-hour Holter monitor was recorded to establish a baseline for ectopic ventricular activity. This was the second or last of two or more such Holter monitorings. On days 3 and 4, 150 mg of propafenone was orally administered four times daily. On day 4, a 24-hour Holter monitor was again recorded. On days 4 and 5, the patients were carefully questioned both directly and indirectly for side effects. The Holter equipment used was the Oxford Medical Systems, and all tapes were read both visually by the authors and electronically.

**Definition of Electrocardiographic Terms**

**Ventricular bigeminy:** ventricular extrasystoles after every alternate sinus impulse, i.e., an arrhythmical pattern of a conducted sinus beat followed by a ventricular extrasystole.

**Ventricular trigeminy:** an arrhythmical pattern of two conducted sinus beats followed by a ventricular extrasystole.

**Couplet:** two consecutive uniform or multiformal ventricular extrasystoles.

**Ventricular tachycardia:** three or more consecutive unifocal or multifocal ventricular extrasystoles.

**Statistical Methods**

Statistical analysis was performed using the Student's t-test for dependent samples on ratio data, and the nonparametric sign test for matched groups where the data were ordinal.

The change in ectopic activity from the control recording to the recording while on propafenone is expressed both as: a percentage change in the number of ventricular ectopic beats per hour, and a percentage change in terms of the total number of beats. This analysis was performed to eliminate any possible drug effect on heart rate, and consequently, a possible indirect change in ventricular ectopic activity.

**Results**

Table 1 reflects the basic data obtained on each patient showing the total number of beats per hour, and the percentage changes in ventricular ectopic activity per hour, as well as the total number of beats from the control to the propafenone periods.

Column A of Table 1 shows the total number of beats per hour during control and propafenone periods. This
Table 1—Parameters During the Control and Propafenone Periods*

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<th>Patient</th>
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* A, number of beats per hour; B, number of ventricular ectopic beats per hour; and C, number of ventricular ectopic beats per total number of beats.

ranged from 3071.12 beats per hour to 6343.15 beats per hour during the control period (mean 4806.05 beats per hour, median 4610.95 beats per hour); and from 2148.69 beats per hour to 6407.96 beats per hour (mean 4682.48 beats per hour, median 4989.75 beats per hour) during the propafenone period. The difference between the two periods was not statistically significant ($p = 0.425$).

Column B of Table 1 reflects the percentage change in ventricular ectopic activity per hour. Twenty-three of the 25 patients showed a reduction in ventricular ectopic activity per hour ranging from 8.29 percent to 98.23 percent. The mean change was 65.62 percent (median change 80.96 percent, $p = 0.001$). Eighteen of the 25 patients (72 percent) had a reduction greater than 65 percent. When the results are analyzed in terms of a change per total number of beats (column C, Table 1), 24 of the 25 patients showed a decrease in ectopic ventricular activity. This decrease ranged from 7.79 percent to 98.4 percent (mean 65.66 percent, median 72.34 percent, $p = 0.0001$).

Sixteen of the 25 patients (64 percent) had a decrease of ectopic activity greater than 65 percent. Thus, when patient 13, with an increase of 10.89 percent (analyzed in terms of percentage ventricular ectopic beats per hour), was analyzed in terms of ventricular ectopic beats per total number of beats, this reflected a decrease in ectopic activity of 7.79 percent.

Six patients had ventricular tachycardia with a total of 28 paroxysms. All were abolished by propafenone ($p = 0.0001$). One patient (patient 5) had 18 attacks of paroxysmal ventricular tachycardia during the control period, all of which were abolished by propafenone.

Ventricular couplets were present in 18 of the cases, were abolished in 12 cases, reduced in four, and remained unchanged in two ($p = 0.0001$). Thirteen patients had couplets as well as bigeminal or trigeminal rhythm. Of these, seven patients had abolition of the couplets, as well as the bigeminal or trigeminal rhythm. One patient (patient 25) had a reduction in the bigeminal and/or trigeminal rhythm without a change in the couplets. One patient (patient 7) had an abolition of the couplets with a reduction of the bigeminal or trigeminal rhythm. The remaining four had a reduction of the couplets as well as a reduction of the bigeminal or trigeminal rhythm.

Fifteen cases showed the presence of ectopic ventricular bigeminy or trigeminy during the control recording. This was abolished in nine cases and reduced in six ($p = 0.0001$).

The P-R intervals during the control period ranged from 0.13 sec to 0.22 sec (mean 0.167 sec, median 0.162 sec, SD, 0.023 sec). The P-R intervals during the propafenone period ranged from 0.13 sec to 0.24 sec.

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(mean 0.186 sec, median 0.184 sec, SD, 0.027 sec). The P-R interval was increased in 18 of 25 patients. The mean P-R interval change was an increase of 0.078 sec (SD, 0.02 sec, p = <0.0001). The QRS duration during the control period ranged from 0.07 sec to 0.14 sec (mean 0.10 sec, median 0.10 sec, SD, 0.017 sec). The QRS complexes during the propafenone period ranged from 0.08 sec to 0.15 sec (mean 0.111 sec, median 0.111 sec, SD, 0.018 sec). The QRS duration increased in 19 of the 25 cases. The mean QRS duration change was an increase of 0.0112 sec (SD, 0.0008 sec, p = <0.0001). The Q-Tc intervals during the control period ranged from 0.39 sec to 0.526 sec (mean 0.461 sec, median 0.458 sec, SD, 0.034 sec). The Q-Tc interval during the propafenone period ranged from 0.401 sec to 0.577 sec (mean 0.464 sec, median 0.457 sec, SD, 0.039 sec). The Q-Tc intervals were increased in 12 of the 25 cases. The mean change was an increase of 0.0036 sec (SD, 0.021 sec, p = 0.404).

### Symptoms

Fifteen of the 25 patients related a history of side effects which were either volunteered or elicited by direct questioning. All symptoms were mild and transient. The side effects noted were nausea, flushing or sweating, mild headache, insomnia, anorexia, tiredness, dizziness, lassitude, constipation, dyspnea, abnormal taste. Fifteen instances occurred on the first day of drug administration, i.e., on day 3, and 22 instances on the second day of drug administration, i.e., on day 4. The side effect was volunteered in 18 instances and elicited by direct questioning in 19 instances.

### Discussion

Appraisal of the antiarrhythmic efficacy of a drug is complex and difficult, especially in the context of chronic ectopic ventricular rhythms. The problem has been subject to increasing study during recent years and several classic papers have been published.5,15

Appraisal is difficult because of the spontaneous variability of ectopic ventricular activity. To minimize this, appraisal should be as follows: (a) objective, i.e., electrocardiographic, rather than subjective, i.e., based on clinical symptoms; and (b) carried out over many continuous hours. Holter monitoring is ideal for this purpose. At least two, 24-hour Holter monitor recordings, each having a minimum mean frequency of 30 ectopic ventricular beats per hour, should be established as a baseline.13 Holter studies have ranged from one to 48 hours. There is no doubt that the longer the duration of monitoring, the greater the accuracy in detecting the degree of ectopic ventricular activity. Thus, most studies have shown that monitoring beyond six hours is desirable.6,13,14 Monitoring for 24 hours, for example, will detect 67 percent to 85 percent of ectopic ventricular activity.13 Winkle14 indicates that: "Even recording beyond 24 hours appears to result in a moderate increase in the yield of coronary patients with frequent and complex ventricular arrhythmias." For practical purposes, however, 24 hours of monitoring would seem to be most suitable.7 This takes into account the convenience for patient routine as well as the very high cost of monitoring for longer periods.

Furthermore, a minimum lapse of three months postmyocardial infarction before conducting such a trial was considered necessary to avoid the instability of ectopic ventricular activity which is particularly marked during the first two months after an infarction.

The percentage reduction of ventricular ectopic beats required to establish drug efficacy has also been the subject of discussion. Morganroth et al state that a reduction of 83 percent in ventricular ectopic frequency per hour during 24 hours of ambulatory monitoring is necessary to establish antiarrhythmic drug efficacy with a confidence level of p = <0.05 when testing individual patients. Sami et al,11 using a different method of statistical analysis, however, found the confidence level to be a reduction of ventricular ectopic activity by 65 percent. Re-analysis of Morganroth's data by Sami et al using this method also yielded the figure of 65 percent.11 Shapiro et al,15 updating the differences in the Morganroth and Sami papers, suggest a reduction of ectopic activity by at least 75 percent.

It is also of importance to note that studies which use each patient as his own control can overcome the effect of spontaneous variability by studying the group of patients as a whole. Thus, Winkle14 emphasized that: "Evaluating antiarrhythmic drugs by examining group response rather than individual response minimizes the effect of the spontaneous variability."

Applying the aforementioned principles to the present study, 18 of the 25 patients (72 percent) had a reduction in ventricular ectopic activity greater than 65 percent (p = <0.001) when expressed as a percentage reduction per hour. Of the remaining seven cases, five still showed suppression but in the range of 8.29 percent to 44.22 percent, and two showed a small increase in ventricular activity of 10.89 percent and 21.94 percent. When expressed as a percentage per total number of beats, 16 patients showed a reduction of greater than 65 percent (p = <0.0001). Ten of the 25 patients (40 percent) had a reduction in ectopic activity greater than 83 percent when expressed as a percentage reduction per hour, and 11 of the 25 patients (44 percent) when expressed as a percentage reduction per total number of beats.

Winkle et al14 have further shown that spontaneous declines in ventricular ectopic activity exceeding 90 percent were uncommon. Thus, almost complete suppression of the arrhythmia (as reflected by a reduc-
tion exceeding 90 percent) can usually separate drug response from spontaneous variation. In this study, seven of the 25 patients (28 percent) had suppression of ectopic ventricular arrhythmia greater than 90 percent irrespective of the method of analysis.

In the context of the aforementioned data, it is also important to note that the median frequency in the reduction of ventricular ectopic activity per hour was 80.96 percent. Propafenone was even more effective in cases of high grade or complex ventricular ectopic activity. Thus, all of the 28 paroxysms of ventricular tachycardia in six patients were abolished. Couplets were abolished in 12 of 18 cases (66.67 percent) and reduced in 4 of the 18 cases (22.22 percent). A beneficial therapeutic effect was thus observed in 16 of the 18 cases (88.89 percent). In the 15 cases with trigeminy and bigeminy, the arrhythmia was abolished in nine (60 percent) and reduced in six (40 percent), reflecting a beneficial therapeutic effect in 15 of the 25 cases. These results were statistically significant (p = <0.0001).

A pro arrhythmogenic effect was seen in only two patients (patient study numbers 13 and 23) when expressed as ventricular ectopic beats, and in only one of these patients (patient study No. 23) when expressed as ventricular ectopic beats per total number of beats. These patients showed an increase in the QRS duration of 22.22 percent and 16.67 percent, respectively, during the propafenone period when compared with the control period. The Q-Tc interval in patient study 13 showed no change between the two periods, while the Q-Tc interval in patient study 23 showed a shortening of 0.01 sec during the propafenone period.

Propafenone induced a prolongation of the P-R interval in 18 of the 25 patients. Although this change was statistically significant (p = <0.0001), the clinical relevance is uncertain. There is a direct correlation between serum levels of propafenone and an increase in the A-V conduction time.9 Thus, the prolongation of the P-R interval may allow an inference of patient compliance with therapy.

The QRS duration increased in 19 of the 25 patients with no change in the remaining six patients. In only three patients did the increase exceed 20 percent. No clinical significance was attached to these increases. The average increase was 11.24 percent (p = <0.0001). Group 1 drugs tend to prolong the QRS duration. In monitoring therapy, an increase in QRS duration in the range of 20 percent to 25 percent should alert the physician to observe the patient for toxicity. This has always been the case with drugs such as quinidine and procainamide. No toxicity was observed in patients receiving propafenone, even with a QRS increase of up to 30 percent.

The Q-Tc intervals during propafenone therapy were increased in 12 of the 25 patients, no change in three, and a decrease in ten. The changes were not statistically significant (p = 0.404) and were considered to be of no clinical relevance.

Although this was not a double-blind, randomized investigation, the objective nature of the analysis should not detract from the significance of the study.

CONCLUSIONS

Short-term oral administration of propafenone is effective for the suppression of ectopic ventricular activity, particularly ventricular tachycardia. Side effects were minimal, transient, and appeared to be of no immediate clinical consequence.

REFERENCES