

Clinical pharmacology of propafenone

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ABSTRACT We determined the efficacy, pharmacokinetics, and plasma concentration–response relationships of propafenone, a promising new antiarrhythmic drug. Thirteen patients with frequent and complex ventricular premature beats were studied after receiving four increasing doses, during drug washout and during a randomized double-blind placebo-controlled trial, to evaluate the optimal dose in each patient. A nonlinear relationship was found between propafenone dose and steady-state mean concentration with a 10-fold increase in drug concentration as dose increased threefold from 300 to 900 mg/day. There was great intersubject variability in elimination half-life (mean 6 hr, range 2.4 to 11.8), steady-state mean concentration on 900 mg/day of propafenone (mean 1008 ng/ml, range 482 to 1812), and “therapeutic” plasma concentration (mean 588 ng/ml, range 64 to 1044). The interaction of these three parameters in individual patients determined the duration of the antiarrhythmic action of propafenone during washout (mean 11.5 hr, range 4 to 22). There was a greater than 90% reduction of ventricular premature beats in 10 subjects during dose ranging and in seven during double-blind crossover. Side effects requiring discontinuation of the drug occurred in three patients and included apparent worsening of arrhythmias in two. We conclude that propafenone effectively suppresses ventricular arrhythmias and that nonlinear drug accumulation and intersubject variability in elimination of half-life, steady-state mean plasma concentration, and therapeutic concentration indicate a need for individual therapy.

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PROPAPENONE is a promising new antiarrhythmic drug. In microelectrode experiments with guinea pig atria and sheep Purkinje cells, the drug slows the rate of rise of the action potential and decreases the action potential duration.^{1,2} Propafenone also has weak β -blocking and Ca^{++} antagonist properties in isolated tissues.¹⁻³ Initial placebo-controlled trials in humans show that propafenone is effective for suppressing ventricular ectopic activity.^{4,5} Previous studies suggest that propafenone has a short half-life of 3 to 4 hr but that the duration of its antiarrhythmic effects may last longer.^{6,7} Studies with limited data have yielded conflicting information on the ability to predict antiarrhythmic effect from propafenone concentration.^{8,9}

We undertook this study to assess the pharmacokinetic and pharmacodynamic profile of propafenone with special emphasis on evaluating the relationship between drug dose and plasma concentration as well as

between plasma concentration and antiarrhythmic effect.

Methods

Protocol design. Patients with high-frequency ventricular premature beats (VPBs) were candidates for this study if they did not have disabling angina, heart failure, or unstable intercurrent illness. A complete history was obtained, physical and laboratory examinations were performed, and a baseline 48 hr ambulatory electrocardiogram (ECG) was taken to establish a minimum baseline VPB frequency of ≥ 1440 VPBs/24 hr after antiarrhythmic drugs had been discontinued for at least five half-lives. Digoxin was continued in one patient with atrial fibrillation, and propranolol was continued in one patient with angina pectoris.

All patients who met the entrance criteria and who gave informed consent were entered into an outpatient dose-ranging study in which they received progressively increasing doses of propafenone for 3 to 7 days each. The doses used were 150 mg every 12 hr, 150 mg every 8 hr, 300 mg every 12 hr, and 300 mg every 8 hr. For reasons discussed later, two patients received other doses. One patient received 150 mg every 6 hr, and one patient received 300 mg every 6 hr. After 3 to 7 days on each dose, each patient had a 24 hr ambulatory ECG taken, and blood samples were obtained for propafenone plasma concentration analysis throughout one complete dosing interval. After the final dose in each patient, a 24 hr drug washout period followed, during which a 24 hr ambulatory ECG was performed and frequent blood samples were obtained. On the final day of therapy at each dose, a 12-lead ECG and physical examination were performed, and a complete history was obtained. Blood

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samples for propafenone plasma concentration analysis were obtained at the following times after ingestion of the pill: 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hr. When a 12 hr dose interval was used, a 12 hr sample was also obtained; during washout, samples were taken at 12, 15, and 24 hr.

After the drug washout, the patients who had a $\geq 75\%$ reduction of VPBs during the dose-ranging study were entered into a randomized double-blind crossover outpatient evaluation to compare the results after the most effective dose of propafenone (not causing intolerable side effects) with those after placebo. In this phase of the study, patients received propafenone and placebo each for 2 weeks. During both propafenone and placebo periods 24 hr ambulatory ECGs were taken after 1 and 2 weeks of treatment. A 1 week washout period preceded the double-blind crossover study and also separated the propafenone and placebo periods. Control 24 hr ambulatory ECGs were taken at the end of both washout periods. Propafenone and identical placebo tablets were supplied by Knoll Pharmaceutical Co., Whippany, NJ. Patients were also evaluated weekly on the basis of history and by physical examination. Laboratory examinations were performed and trough plasma propafenone concentrations were determined after 2 weeks of both propafenone and placebo therapy. Patient compliance was assessed by pill count.

Arrhythmia monitoring and ECG analysis. All arrhythmia monitoring was performed with 24 hr ambulatory ECGs that were analyzed by the Stanford computer-assisted method, which provides accurate counts of all VPBs, paired VPBs, and runs (≥ 3 consecutive VPBs).¹⁰ When a tape was not exactly 24 hr in duration, the counts were normalized to reflect a 24 hr reading. Total counts of VPBs, pairs, and runs were also computed for each hour of each reading. We measured the ECG intervals from the 12-lead ECG performed on each study day, using the mean of three blinded readings from lead II. Change in the QT interval (QTc) was calculated by the following formula: $QTc = QT/\sqrt{RR}$, where RR is the mean beat-to-beat interval of the three beats studied.

Plasma propafenone and pharmacokinetic analysis. Propafenone plasma concentrations were measured with a high-pressure liquid chromatographic method already described.¹¹ The minimal detectable concentration of propafenone by this method is 5 ng/ml. Propafenone elimination of half-life was determined by standard methods from the negative slope of the least squares fit to the terminal portion of the log plasma concentration–time curve from the 24 hr washout in each patient. We determined the steady-state mean plasma concentration (C_{ss}) of propafenone in each patient for each dose by calculating the area under the concentration–time curve (AUC) for each complete dosing interval and dividing by the number of hours in that dose interval ($C_{ss} = AUC/\text{duration of dose interval}$).

Pharmacodynamic analysis. In each patient, percentage reduction of VPBs, pairs, and runs were calculated. During dose-ranging this was calculated as the percent reduction in the 24 hr total of each ectopic beat form as compared with the mean 24 hr total of the two baseline control recordings. During the double-blind crossover phase, percent reduction of each ectopic beat form was calculated for the propafenone period and the placebo period. This was calculated from the mean of both 24 hr total counts on both propafenone and placebo, which were compared with the mean of the two control recordings done at the end of each washout period.

The hourly counts of VPBs, pairs, and runs for each patient from the 24 hr ambulatory ECGs and the mean hourly plasma concentration for each corresponding hour calculated by interpolation on the propafenone log concentration–time curves were entered onto a Hewlett-Packard computerized graphics system, and concentration–response plots were constructed for each patient. For each patient a “therapeutic” concentration

could then be defined as the concentration at which the hourly rate of ectopic beats fell below a level equal to 10% of the mean hourly rate seen for that patient on the two baseline recordings. Therapeutic concentrations for VPBs and pairs were determined separately.

We determined the duration of antiarrhythmic action during washout in individual patients who responded. This was done by finding the hour in which the hourly rate of VPBs rose above 10% of the mean hourly rate seen on baseline recordings.

The relationship between VPB, pair, and run suppression was examined by expressing the number of VPBs, pairs, and runs for each patient as a percentage of that patient’s baseline frequency and by plotting the mean percent against the steady-state mean concentration of the group. Only the 11 patients who received all four doses were included in this analysis.

Statistical analysis. Group data are presented as the mean \pm SEM. Friedman’s analysis of variance by ranks was used to assess the stability of VPB, pair, and run counts on the 6 drug-free days of the study. Spearman’s rank correlation method was used to determine the coefficient of correlation between half-life and steady-state mean concentration and between half-life and body weight. Student’s *t* test for paired data was used to assess the significance of differences in electrocardiographic intervals between the baseline reading and that done at the highest dose. Student’s *t* test for paired data was also used to assess the significance of differences in the levels of VPBs, pairs, and runs expressed as a percent of control levels (see figure 4) at each propafenone dose.

A *p* value of .05 was required to disprove the null hypothesis unless otherwise stated.

Results

Patient characteristics. Thirteen patients, 11 men and two women, between the ages of 44 and 73 years participated in this study. Seven patients had coronary artery disease, four had no structural heart disease, one had cardiomyopathy, and one had mild aortic stenosis. Body weight ranged from 64 to 109 kg. On the two baseline control ambulatory ECG readings the average number of VPBs per 24 hr was 22,503 (range 5268 to 47,791), the average number of pairs per 24 hr was 1128 (range 2 to 7681), and the average number of runs of three or more per 24 hr was 22 (range 0 to 102). Although patients were not selected on the basis of prior antiarrhythmic drug experience, they had been treated with an average of 2.5 (range 1 to 4) other drugs with unsatisfactory results. During the course of the study, 11 patients had six drug-free 24 hr ambulatory ECGs and two patients (because they did not enter the double-blind crossover phase) had two. An analysis of variance showed that there was no significant difference among the number of VPBs, pairs, or runs recorded on any of the drug-free days, indicating that the frequency of ventricular ectopy was stable over the course of the study.

Antiarrhythmic response. During the dose-ranging phase, 11 of 13 patients received all four doses. Patient 13 developed a symptomatic increase in VPBs while taking 200 mg every 12 hr and received no further

propafenone. Patient 11 developed an asymptomatic increase of 54% in QRS duration while taking 300 mg every 12 hr. He was treated effectively with 150 mg every 6 hr, which decreased the peaks of the plasma concentrations (although his QRS was also prolonged at this dose). Patient 10 also received, in addition to the four usual doses, a dose regimen not originally in the protocol design (300 mg every 6 hr), when it became apparent that she was having a return of her arrhythmia before the end of the 8 hr dose interval while taking 300 mg every 8 hr.

The 11 patients who received 300 mg every 8 hr demonstrated an $82.0 \pm 10.2\%$ reduction in VPBs (table 1). Eight patients had greater than 90% VPB suppression while taking 300 mg every 8 hr. Ten patients (77%) had greater than 90% VPB suppression while on their highest dose. Of the remaining three patients, one had 75% suppression, one had no suppression, and one had an increase in VPBs. In the 11 patients who received 300 mg every 8 hr, pairs were reduced by $94.5 \pm 3.3\%$ and runs by $96.7 \pm 3.3\%$. When data from each patient at their highest dose were considered, pairs were abolished in eight patients and runs in 11 patients. Neither pairs nor runs increased in any patient.

Two patients were not entered into the double-blind crossover phase of the study because of lack of beneficial response during the dose-ranging phase; one patient failed to complete the double-blind crossover

study because he had a 50 sec run of symptomatic ventricular tachycardia while taking propafenone during the double-blind crossover. In the 10 patients completing the double-blind crossover phase of the study, the mean VPB suppression was $88.0 \pm 4.4\%$, which confirms the findings of the dose-ranging study. One patient had no antiarrhythmic response during the double-blind crossover in spite of greater than 99% suppression during dose-ranging — a difference which could not be explained by differences in trough propafenone plasma concentration. During the double-blind crossover phase, pairs were reduced by an average of $97.0 \pm 1.2\%$ and runs were abolished in all patients.

Pharmacokinetics. The mean elimination half-life of propafenone was 6 hr (range 2.4 to 11.8).

Figure 1 demonstrates the relationship between steady-state mean plasma concentration and daily dose at each of the four doses for all patients. There is a nonlinear relationship between dose and steady-state mean concentration over the range of doses used in this study. For a threefold increase in daily dose from 300 to 900 mg, there is a 9.9-fold increase in steady-state mean concentration. At each dose there was a wide range of steady-state concentrations among individuals. For example, at the highest dose of 900 mg/day the steady-state mean concentration ranged from 482 to 1812 ng/ml. Steady-state mean concentration did not correlate significantly with individual body weight ($r = .25$, $p > .10$). Steady-state mean concentration

TABLE 1
VPBs expressed as percentage of control

Patient	Dose	Dose-ranging phase					Randomized double-blind crossover	
		150 mg q12hr	150 mg q8hr	300 mg q12hr	300 mg q8hr	Other doses	Propafenone	Placebo
1		+17.4	-52.0	-56.1	-98.5	—	-91.7	+7.9
2		+20.6	+0.9	-3.4	-93.6	—	—	—
3		-14.4	-55.6	-91.8	-75.3	—	-90.9	+6.6
4		+14.1	-32.0	-90.1	-96.3	—	-71.6	+8.1
5		-42.3	-40.5	-72.1	-98.7	—	-99.5	-31.1
6		+281.1	+193.9	+102.7	-99.7	—	-59.6	-69.6
7		+6.2	-96.4	-100	-100	—	-100	-0.5
8		-19.6	-76.3	-97.5	-99.6	—	-98.7	-0.6
9		+75.0	+14.5	-74.8	-95.6	—	-77.3	+43.0
10		-29.7	-24.9	-40.4	-56.0	-98.5 ^A	-91.7	-39.3
11		+61.0	+114.1	-60.8	—	-91.7 ^B	-98.9	+182.1
12		-2.9	+9.7	+8.1	+11.1	—	—	—
13		-90.2	+100.9	+313.5	—	—	—	—
Mean		+21.3	+4.3	-30.2	-82.0		-88.0	+10.7
SE		24.7	23.4	31.9	10.2		4.4	21.5
n		13	13	13	11		10	10

^AReceived 300 mg q6hr. Received 300 mg orally q8hr during crossover.

^BReceived 150 mg q6hr both during dose-ranging and crossover phases.

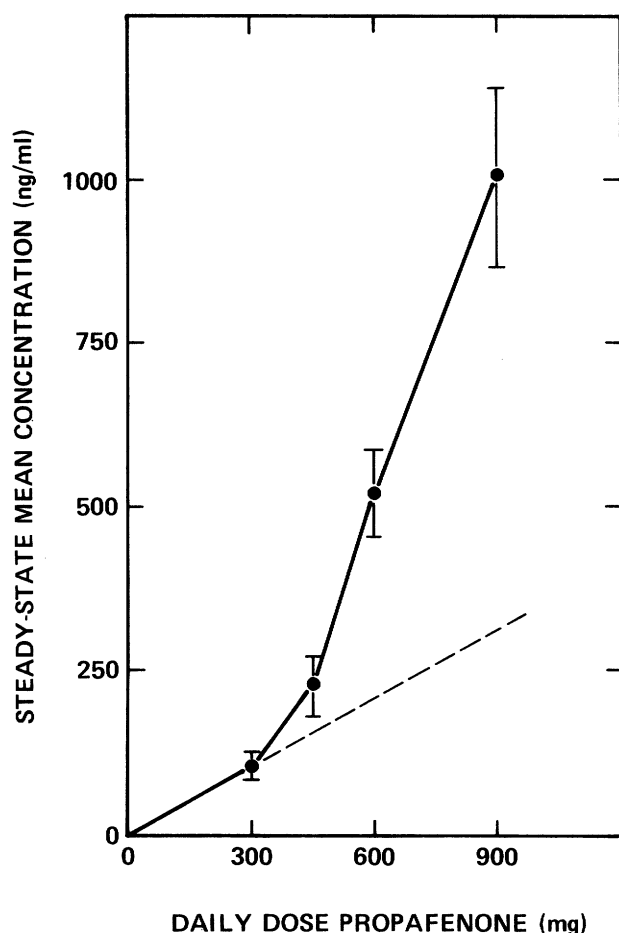


FIGURE 1. Relationship between steady-state mean plasma concentration and total daily dose. The dashed line indicates the response expected if the relationships were linear. Points and bars indicate mean and SEM.

positively correlated with individual elimination half-life ($r = .58$, $p < .05$). However, this correlation was not strong and explains only part of the variability in steady-state concentration.

Electrocardiographic intervals. The mean changes in electrocardiographic intervals for the group are shown in figure 2. There was no significant change in heart rate. The PR interval increased 20.1% from 179 ± 4.7 to 215 ± 7.0 msec ($p < .001$). The QRS duration increased 19.2% from 78 ± 7.2 to 93 ± 8.7 msec ($p < .05$). The QTc interval increased 5.1% from 430 ± 11.2 to 452 ± 15.4 msec ($p < .10$).

Concentration-response relationships. A concentration-response relationship for VPB suppression was observed in all patients (11/13) in whom an antiarrhythmic response to propafenone was demonstrated. Eight patients also had significant numbers of ventricular pairs to permit construction of concentration-response plots for the suppression of pairs. In most patients a characteristic configuration of these plots was

seen (figure 3). At lower concentrations no antiarrhythmic response is seen. In all patients a drug plasma concentration was found at and above which maximal ectopic beat suppression occurred. An approximately log-linear relationship between concentration and response occurred at intermediate concentrations in many patients. In all but one of the patients who responded to propafenone, a concentration was defined above which 100% suppression of all ventricular ectopy occurred; that one patient had only 90% VPB suppression at the highest concentrations. In most patients, less than 100% suppression was recorded over 24 hr periods because the drug plasma concentration was not maintained above this level throughout the whole day. To achieve maximal antiarrhythmic response in most patients, a more frequent dosing sched-

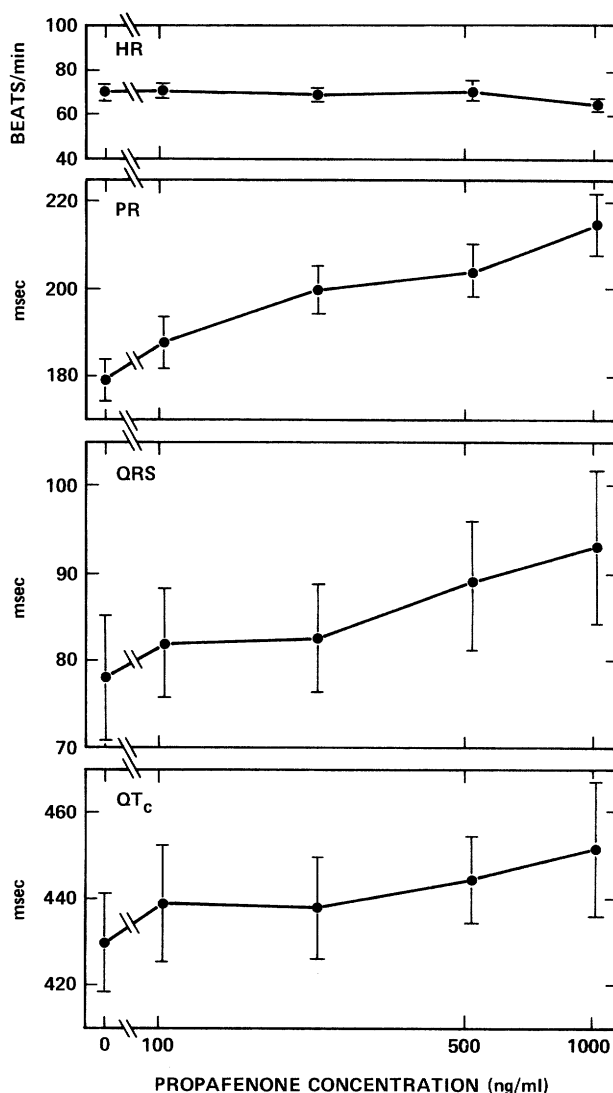


FIGURE 2. Relationship between electrocardiographic intervals and steady-state mean concentration during the dose-ranging phase. Points and bars indicate mean and SEM.

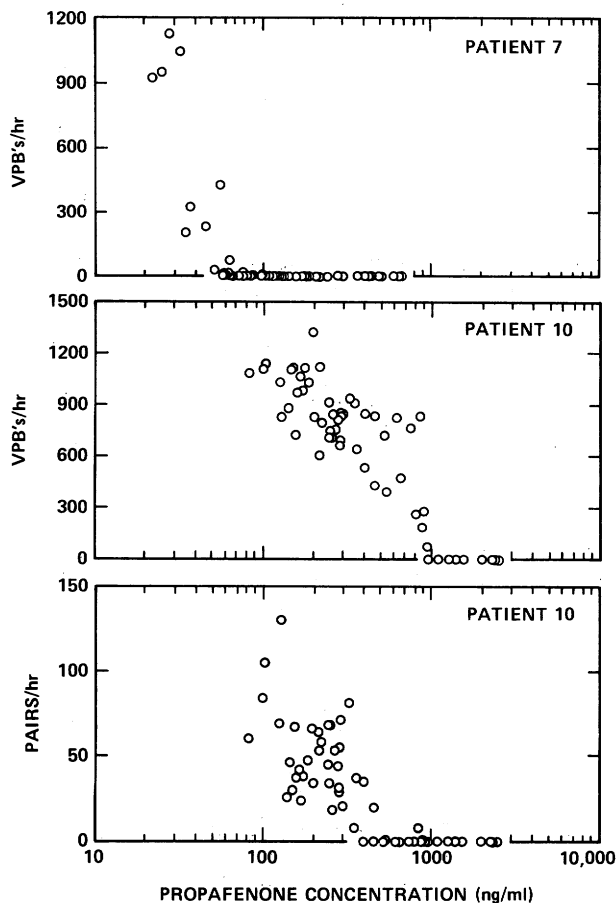


FIGURE 3. Concentration-response relationships for ectopic beat suppression for two subjects. Each point represents the hourly ectopic beat frequency and the mean plasma concentration for that hour of treatment during the dose-ranging phase. *Top*, Data for isolated VPBs for a patient with a low therapeutic concentration. *Middle*, Similar data for a patient with a high therapeutic concentration. *Bottom*, Concentration response data for ventricular pair suppression for the latter patient.

ule would be required to reduce the peaks and troughs of plasma concentration.

There was a marked intersubject variation in the therapeutic plasma concentration, which was defined as that concentration above which there was greater than 90% VPB suppression as compared with the baseline recordings. In figure 3, for example, patient 7 has virtual abolition of VPBs above a concentration of 64 ng/ml. On the other hand, patient 10 does not have complete VPB suppression below 1000 ng/ml. The mean therapeutic concentration for VPB suppression in the 11 responders was 588 ± 88 ng/ml. The range of therapeutic concentrations was from 64 to 1044 ng/ml. In the eight subjects for whom separate curves for pair suppression could also be made, the therapeutic concentration for pair suppression was 0 to 490 ng/ml less than that for VPB suppression in the same patient (figure 3). The mean concentration for suppression of pairs was 443 ± 89 ng/ml.

Figure 4 graphically depicts the mean rates of VPBs, pairs, and runs (expressed as percentages of control values) plotted against mean plasma steady-state concentration for patients who received all four doses of propafenone. At the lowest concentrations no antiarrhythmic effect is evident. At the intermediate doses, pairs and runs are significantly more suppressed than are VPBs ($p < .05$). At the highest concentration the difference between the suppression of VPBs and complex forms diminishes, since both are almost completely eliminated.

In the 10 responders who underwent washout while taking the highest dose of propafenone, the mean duration of VPB suppression was 11.5 ± 1.7 hr (range of 4 to 22) (figure 5).

Adverse effects. Two patients developed apparent worsening of their arrhythmias while on propafenone that required discontinuation of the drug. One patient who had 93% reduction of VPBs during the dose-ranging phase of the study developed unsustained symptomatic ventricular tachycardia lasting 50 sec while on propafenone. A second patient had a 314% increase in VPBs while on propafenone and noted a marked increase in palpitations. These two patients had the lowest and fourth lowest steady-state mean concentrations of the whole group, and we cannot exclude inadequate drug therapy rather than toxicity as the cause of their apparent arrhythmia increase. Neither patient had excessive QRS widening or QT prolongation. A third patient required drug discontinuation after the double-blind crossover study because of weakness and disorientation. Side effects not requiring discontinuation of therapy included metallic taste in two patients, dry mouth in three, and mild nausea in

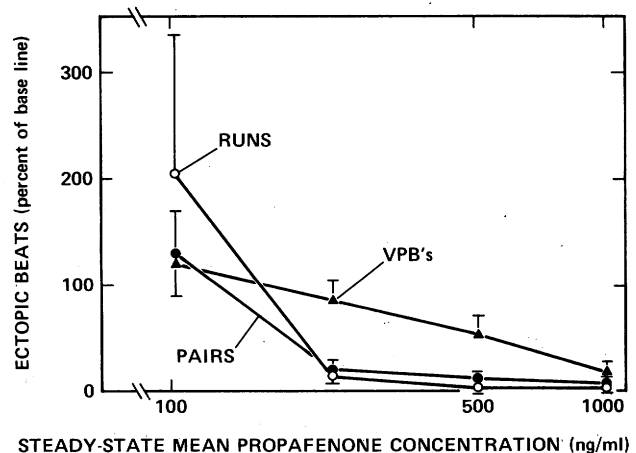


FIGURE 4. Relationship between VPBs, pairs, and runs expressed as a percentage of control levels at different steady-state mean concentrations. Each point and bar indicates the mean and SEM.

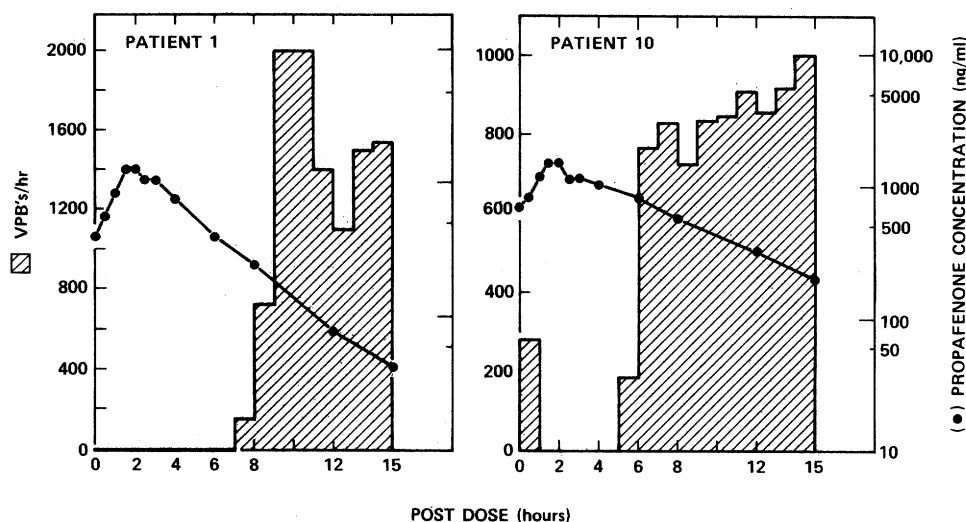


FIGURE 5. VPB frequency and plasma propafenone concentration–time curves during drug washout for two patients. The solid line represents plasma concentration (log scale) and the hatched area represents VPB frequency.

one. The patient who had a symptomatic increase in VPBs while on propafenone was also found to have an eightfold rise in serum transaminases levels, which gradually returned to normal over 4 months. He had a past history of chronic persistent hepatitis. Although all patients had some increase in PR interval (to as long as 255 msec); no patient developed second- or third-degree atrioventricular block.

Discussion

The clinical usefulness of an antiarrhythmic drug depends not only on its effectiveness in suppressing arrhythmias but also on a favorable pharmacokinetic profile. Favorable pharmacokinetic features usually include little intersubject variability in bioavailability and clearance, a predictably long half-life, and a linear relationship between dose and concentration. Ideal pharmacokinetics, however, do not guarantee an ideal therapeutic response but only that the plasma concentration will be predictable for a given dose. Concentration–response (pharmacodynamic) relationships may be complex and may vary widely among individuals. It is important in the initial investigation of a new drug to understand both its pharmacokinetics and its pharmacodynamics and their interactions. In this study we have demonstrated the antiarrhythmic effect of propafenone and also how pharmacokinetic and pharmacodynamic factors influence the clinical effectiveness of this drug.

Antiarrhythmic activity. Propafenone is a very effective drug for suppression of ventricular ectopy. Over 24 hr during the dose-ranging phase, 10 patients had a greater than 90% VPB suppression. Pairs and runs were abolished in eight and 11 patients, respectively.

The double-blind crossover phase tended to confirm the dose-ranging results, although one patient no longer appeared to respond. Previous placebo-controlled studies with propafenone have shown similar degrees of effectiveness.^{4,5} Recent reports of the effectiveness of other experimental antiarrhythmic drugs have also reported similar degrees of success.^{12–14}

Although a concentration at which 100% VPB suppression occurred could be defined in 10 of 13 patients, VPBs were less well suppressed during 24 hr monitoring. Maximal VPB suppression was not sustained because of plasma concentration fluctuations that occurred over 24 hr. Only one patient with a very low therapeutic concentration had 100% suppression over 24 hr.

Pharmacokinetics. The mean elimination half-life of propafenone in our group of patients is 6 hr, which is considerably longer than the mean half-life of 3.6 hr previously reported.⁶ We also found that there was large interindividual variability in elimination half-life (range 2.4 to 11.8 hr). This variability was not explained by clinical factors such as age, liver disease, heart failure, or the presence of concomitant medications that could interfere with the elimination of a drug that is highly metabolized. The rate of metabolism of another antiarrhythmic drug, procainamide, has been shown to be subject to interindividual differences in enzyme activity related to genetic polymorphism.¹⁵ Individual differences in the metabolism of encainide can markedly affect the rate of elimination of this drug.¹³ Individual differences in drug metabolism may cause the differences seen in propafenone elimination half-life.

Variability was also found in the steady-state mean

concentration in different patients on the same dose of propafenone. Some of this variability can be explained by differences in elimination half-life; however, the correlation between half-life and steady-state concentration was not strong ($r = .52$), suggesting that other factors are involved. A factor, not examined in this study, that may affect interindividual differences in steady-state mean concentrations is systemic bioavailability. It is possible that a highly metabolized compound that shows variability of elimination half-life may be subject to interindividual differences in first-pass hepatic metabolism. Variability in protein binding of propafenone could affect steady-state levels but was not evaluated in this study.

A nonlinear relationship between dose and steady-state concentration was seen. The practical implications of this finding are that dose increases must be made with caution. The increases in drug plasma concentration resulting from a small increase in drug dose can be quite large. This study does not provide an explanation of why concentration increases nonlinearly with dose; however, it is likely that either first-pass clearance or elimination or both are decreased at higher concentrations. Dose-related changes in bioavailability have been demonstrated with another antiarrhythmic drug, lorainide, and have been attributed to saturation of first-pass metabolism.¹⁶

Concentration-response relationships. A concentration-response relationship could be demonstrated in each patient who had an antiarrhythmic response to propafenone. In all patients a concentration could be defined at which maximal antiarrhythmic effect occurred. Below this concentration in several patients a log-linear relationship between concentration and effect was seen. There was great variation (64 to 1044 ng/ml) in the concentration at which 90% suppression of VPBs occurred (therapeutic concentration). Inter-subject variability in therapeutic concentration emphasizes the need to individualize therapy to the patient. Although the therapeutic concentration for VPB suppression can be determined relatively easily, this may be considerably more difficult in patients with sustained ventricular tachycardia or fibrillation. The use of the maximum tolerated doses and shorter dose intervals may be the best approach to therapy in these patients to avoid periods of subtherapeutic plasma concentrations. It is important to recognize that the ability to suppress VPBs does not necessarily correlate with antiarrhythmic efficacy in the treatment of more serious arrhythmias, as shown by the patient in this study whose VPBs were significantly suppressed but who had a 50 sec episode of ventricular tachycardia.

Runs and pairs were suppressed at lower propafenone plasma concentrations than were VPBs in all but two patients. Both procainamide and encainide suppress repetitive ventricular activity at plasma concentrations lower than those at which they suppress isolated VPBs.^{13, 17} These data suggest that different mechanisms may be responsible for single and repetitive forms of ventricular ectopy. Although this dissociation between suppression of VPBs and repetitive ectopy occurs, there is no controlled information as to whether suppression of repetitive ectopy alone is adequate prophylaxis for sustained ventricular tachyarrhythmias or sudden death.

Wiebringhaus et al.⁹ did not find any relationship between plasma concentration and antiarrhythmic effect, which is in contrast to our findings. Their inability to do so is likely due to the fact that they only used single samples drawn 3 to 4 hr after a dose in each patient. Blanke et al.⁸ measured plasma concentrations throughout a complete dose interval to determine mean concentration and did demonstrate a log-linear concentration-response relationship for the group. They did not assess concentration-response relationships in individual patients. The findings of our study emphasize the importance of sampling throughout complete dose intervals at multiple doses if interindividual variation in concentration-response relationships are to be appreciated.

Pharmacokinetic-pharmacodynamic interactions. The duration of antiarrhythmic response during long-term therapy after each dose is related to an interplay of both pharmacokinetic and pharmacodynamic factors, the most important of which are drug plasma concentration, elimination half-life, and therapeutic plasma concentration. In our subjects, considerable interindividual variation occurred in all three of these parameters to such an extent that a knowledge of all three is necessary to predict duration of antiarrhythmic response in an individual. Figure 5 demonstrates the interactions of these three variables in individual patients. Patient 1 had a very short elimination half-life of 2.4 hr, but because of a low therapeutic concentration for VPB suppression, he had an 8 hr duration of VPB suppression during washout. Had his therapeutic concentration been as high as 600 ng/ml (the mean therapeutic concentration for the group), the duration of antiarrhythmic action would have only been 4 hr and would have resulted in treatment failure. Patient 10, in spite of a longer elimination half-life, had a duration of VPB suppression of only 4 hr because she had a very high therapeutic threshold (figure 5). She required dosing of propafenone every 6 hr to prevent a breakthrough of

arrhythmias at the end of each dose interval. Tocainide, another antiarrhythmic drug, shows a similar degree of intersubject variability in concentration-response relationships. Although tocainide pharmacokinetics vary little between individuals, large differences in response to a given dose occur among patients because of different concentration-response relationships.¹⁸ The assessment of individual differences in concentration-response relationship is as important as and complements the assessment of the pharmacokinetics of a new drug.

Propafenone seemed to exacerbate arrhythmias in two subjects, one of whom developed unsustained ventricular tachycardia and one who had a marked increase in VPBs. It appears that all antiarrhythmic drugs have some capacity for worsening arrhythmias.¹⁹ In the case of some class I drugs such as quinidine and disopyramide, excessive QT prolongation is associated with arrhythmia aggravation. Propafenone, however, causes little change in QT interval, and our two subjects had arrhythmia exacerbation without excessive QT prolongation.

Elevation of serum transaminase levels was seen in one patient who had a history of chronic persistent hepatitis. Propafenone has previously been reported to cause cholestatic hepatitis in two patients.²⁰ The rise in serum enzyme levels occurred in our patient after 15 days of therapy. In the two reported cases as well as in our patient, serum enzyme levels gradually returned to normal levels over 2 to 3 months after propafenone was discontinued.

Although propafenone has β -blocking properties in isolated tissues,² we found that propafenone had no effect on resting heart rate in our subjects. Three of our subjects underwent graded treadmill exercise testing before and during propafenone therapy at 900 mg/day and none showed attenuation of heart rate at submaximal exercise. Thus the clinical relevance of the *in vitro* β -blocking properties of the drug remain to be elucidated.

In conclusion, we found that propafenone is an effective drug for suppressing ventricular ectopy. The drug has marked interpatient variability in elimination half-life, steady-state mean concentration, and therapeutic concentration. In spite of a relatively short elimination half-life in many patients, an 8 hr dosing interval was adequate for treatment in all but one subject. However, in some patients a shorter dose interval would have improved antiarrhythmic response. Individualization of therapy where possible is recommended to optimize therapy. Minor side effects were com-

mon and propafenone can apparently exacerbate arrhythmias in some patients.

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References

- Kohlhardt M, Seifert C: Inhibition of V_{max} of the action potential and its voltage-, time-, and pH-dependence in mammalian ventricular myocardium. *Arch Pharmacol* **315**: 55, 1980
- Ledda F, Mantelli L, Manzini S, Amerini S, Mugelli A: Electrophysiological and antiarrhythmic properties of propafenone in isolated cardiac preparations. *J Cardiovasc Pharmacol* **3**: 1162, 1981
- Harder OR, Belandinelli L: Effects of propafenone on TEA-induced action potentials in vascular smooth muscle of canine coronary arteries. *Experientia* **36**: 1082, 1980
- Schmutzler H: Beeinflussung der ventriculären extrasystolie durch propafenon. *Herz Kreislauf* **10**: 183, 1978
- Wieser H, Philippi M, Schuler CF: Die antiarrhythmische Wirkung von propafenon bei stabiler ventricularer extrasystolie. *Herz/Kreislauf* **11**: 71, 1979
- Keller K, Meyer-Estorf G, Beck OA, Hochrein H: Correlation between serum concentration and pharmacologic effect on atrioventricular conduction time of the antiarrhythmic drug propafenone. *Eur J Clin Pharmacol* **13**: 17, 1978
- Seipel L, Breithardt G: Propafenone — a new antiarrhythmic drug. *Eur Heart J* **1**: 309, 1980
- Blanke H, Aschbrenner B, Karsch KR, Kreuzer H: Plasmaspiegel — Wirkungen — Beziehung und organverteilung von propafenon. *Dtsch Med Wochenschr* **104**: 587, 1979
- Wiebringhaus E, Seipel L, Breithardt G, Loogen F: Lanzeitergebnisse mit dem neuen antiarrhythmikum propafenon unter Berücksichtigung der plasmaspiegel. *Z Kardiol* **66**: 625, 1977
- Bragg-Remschel DA, Harrison DC: A computerized two channel ambulatory arrhythmia analysis system. *In* Computers in cardiology (IEEE 80 CHI 606.3), Williamsburg, VA, October 1980, p 197
- Harapat SR, Kates RE: High pressure liquid chromatographic analysis of propafenone in human plasma samples. *J Chromatogr* **230**: 448, 1982
- Anderson JL, Stewart JR, Perry BA, Van Hamersveld DD, Johnson TA, Conard GJ, Chang SF, Kuam DC, Pitt B: Oral flecainide acetate for the treatment of ventricular arrhythmias. *N Engl J Med* **305**: 473, 1981
- Roden DM, Reece SB, Higgins SD, Mayol RF, Gammans RE, Oates JA, Woosley RL: Total suppression of ventricular arrhythmias by encainide: pharmacokinetic and electrocardiographic characteristics. *N Engl J Med* **302**: 877, 1980
- Winkle RA, Peters F, Kates RE, Tucker C, Harrison DC: Clinical pharmacology and antiarrhythmic efficacy of encainide in patients with chronic ventricular arrhythmias. *Circulation* **64**: 290, 1981
- Reidenberg MM, Drayer DE, Levy M, Warner H: Polymorphic acetylation of procainamide in man. *Clin Pharmacol Ther* **17**: 722, 1975
- Klotz U, Muller-Seydlitz P, Heimburg P: Pharmacokinetics of lorcinide in man: a new antiarrhythmic agent. *Clin Pharmacokinet* **3**: 407, 1978
- Meyerburg RJ, Kessler KM, Kiem I, Pefkhros KC, Cande CA, Cooper D, Castellanos A: Relationship between plasma levels of procainamide, suppression of premature ventricular complexes and prevention of recurrent ventricular tachycardia. *Circulation* **64**: 280, 1981
- Meffin PJ, Winkle RA, Blaschke TF, Fitzgerald J, Harrison DC: Response optimization of drug dosage: antiarrhythmic studies with tocainide. *Clin Pharmacol Ther* **22**: 42, 1977
- Velebit V, Podrid P, Lown B, Cohen BH, Graboyes TB: Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. *Circulation* **65**: 886, 1982
- Schuff-Werner P, Kaiser D: Cholestatic hepatitis nach antiarrhythmischer Therapie mit propafenon. *Dtsch Med Wochenschr* **105**: 137, 1980