The Effectiveness of Antiarrhythmic Agents on Early-cycle Premature Ventricular Complexes

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SUMMARY Twelve patients completed a double-blind, crossover antiarrhythmic drug trial in which 300 mg of quinidine, 500 mg of procainamide, 100 mg of phenytoin, or placebo was given four times daily on subsequent weeks. Analysis of 24-hour Holter tapes with a computerized analysis system (Argus/H) permitted accurate counting of premature ventricular complexes (PVCs) subclassified according to coupling interval. No antiarrhythmic agent demonstrated a significant overall reduction in the number of PVCs, but both quinidine and procainamide showed a statistically significant (p < 0.05) reduction of PVCs with coupling intervals less than 400 msec. This effect was noted both in isolated PVCs (quinidine only) and in PVCs that were part of a couplet or run (both drugs). These findings demonstrate that clinically important effects of procainamide and quinidine can occur in the absence of an overall reduction in the number of PVCs.

Most studies of the prognostic significance of premature ventricular complexes (PVCs) have emphasized the importance of the "complex" features and frequency of the PVCs in determining prognosis.¹⁻⁴ Complex features include multifocality, presence of two (couplets) or more (runs) consecutive PVCs and the R-on-T phenomenon. Elimination of the specific "malignant forms" with or without reduction of overall PVC rates may be a reasonable goal of therapy designed to protect against symptomatic ventricular tachycardia or sudden death.⁵ However, previous evaluations of the effectiveness of antiarrhythmic agents have usually focused simply on the total number of PVCs. An accurate measurement of the effects of antiarrhythmic agents on specific forms of ventricular ectopic beats could not be performed because of limitations of standard Holter analysis techniques.

The Argus/H computerized Holter analysis system allows enumeration of PVCs, couplets and runs subgrouped by coupling intervals.⁶⁻⁷ In this study, we used this analytic capability to evaluate the therapeutic activity of phenytoin, quinidine and procainamide against these complex PVCs.

Methods

Thirteen patients (11 men and two women) who had multifocal PVCs, couplets or runs and who had an average PVC rate of over 50/hour on each of two qualifying 10-hour ambulatory Holter recordings were enrolled in this study. All patients had coronary heart disease, and all had survived one or more myocardial infarctions 3–35 months before the study. Two patients had undergone coronary bypass surgery 6 and 11 months previously. The patients ranged in age from 50–70 years. No patient had hepatic or renal disease, uncompensated heart failure or atrioventricular block. Seven patients continued taking digoxin; serum levels were measured and dosage was initially adjusted to maintain a level of 1–2 ng/ml. Serum potassium was measured weekly and maintained at greater than 3.5 mEq/l. Patient 1 had been taking 20 mg of propranolol four times a day for control of angina before the study, and continued this regimen through-
out the study. All patients and their personal physicians were informed of the purpose of the study and each patient gave written informed consent. Relevant patient characteristics are presented in table 1.

The drugs and dosages used in this study reflect current medical practice. To simplify the double-blind format, no attempt was made to regulate dosage according to measured drug levels. Quinidine was administered four times a day at 300 mg, procaainamide at 500 mg four times a day, phenytoin at 100 mg four times a day and placebo four times a day. All drugs and placebo were packaged in identical-appearing capsules and were administered for 7 days, with the order of drug administration randomized within groups of four. A loading dose of 500 mg was given at the start of the phenytoin trial. No other loading doses were used, but patients received a standard dose with four identical placebo capsules at the start of the other drug trials to maintain the blinding.

A 24-hour, single-channel Holter recording was obtained on the seventh day of drug administration and a serum drug level was obtained when the recording was begun. No attempt was made to standardize the time the serum level was obtained. Each patient kept a diary for the complete 7 days of drug administration. They also completed a questionnaire about side effects at the time of the Holter recording. All unused capsules were collected and counted to monitor compliance. If reported side effects required, the particular drug was discontinued and the next drug initiated at the originally scheduled time. Patient 3 had only one 10-hour recording during the placebo period, so only 10-hour results were tabulated for him. Patient 4 had only one 10-hour recording during the quinidine drug trial, so the results for quinidine were compared with the first 10 hours of the placebo tape.

The Holter tapes were processed and analyzed by the Argus/H computer system. In brief, the analog tape was digitized and processed by a cascading series of data-reduction algorithms. Each computer-identified PVC was then presented to a trained editor, who examined it within 16 seconds of context and confirmed or denied the computer label. Representative strips documenting the editing decisions were produced and subsequently reviewed by a cardiologist. The annotated ECG in the form of a machine-readable beat-by-beat data stream was then passed as input to a program that reduced that data stream to 150 variables of interest. Subsequent data management and statistical analyses were performed using the SAS system.

The following variables were chosen for analysis. Average heart rate was based on the average coupling interval between consecutive normal beats. A couplet was defined as two consecutive PVCs and a run as three or more consecutive PVCs. An isolated PVC was a PVC preceded and followed by a non-PVC beat. The coupling interval of the PVC was the time in milliseconds from the onset of the QRS preceding the PVC to the onset of the PVC. Coupling intervals of PVCs within couplets or runs included only PVC-to-PVC intervals within the couplets or runs. The rate of runs was calculated from the average PVC-to-PVC coupling interval within the run. The PVC rates per hour were calculated and corrected for data loss when the signal was unanalyzable. Because the range of PVC rates was wide and not normally distributed, a log transform was used for all statistical analyses. This resulted in more nearly normal distributions and served to control severe heterogeneity of the variance. For clarity of presentation, the mean PVC rates were converted back to natural units as PVCs/hour. Comparison between placebo and drug was performed using a paired t test. A p value < 0.05 was considered significant.

Results

Twelve patients satisfactorily completed the study. Patient 13, who was in compensated congestive heart failure at the onset of the trial, developed pulmonary edema during the trial and was excluded from the analysis. Patients 5 and 10 had fewer than three PVCs/hour during the placebo period and were excluded from further analysis. The other 10 patients successfully completed the trials of quinidine and procaainamide. Patients 7, 9 and 11 discontinued phenytoin because of severe side effects — allergic rash and pruritis in two and severe weakness and muscle aches in the other. All of the symptoms resolved rapidly after discontinuation of the phenytoin and the patients continued the study at the end of the week with the next drug. Side effects not severe enough to

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>Age (years)</th>
<th>CHF</th>
<th>CM</th>
<th>MI</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>56</td>
<td>+</td>
<td>+</td>
<td>35</td>
<td>D, P</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>52</td>
<td>+</td>
<td>+</td>
<td>21</td>
<td>D, Me</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>69</td>
<td>+</td>
<td>+</td>
<td>15</td>
<td>D, K</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>61</td>
<td></td>
<td></td>
<td>21</td>
<td>V</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>57</td>
<td></td>
<td></td>
<td>8</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>50</td>
<td>+</td>
<td></td>
<td>10†</td>
<td>D</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>63</td>
<td></td>
<td></td>
<td>22</td>
<td>A, H, Me</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>69</td>
<td>+</td>
<td></td>
<td>28</td>
<td>T</td>
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<tr>
<td>9</td>
<td>M</td>
<td>61</td>
<td>+</td>
<td></td>
<td>72†</td>
<td>D, Fu, Dy</td>
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<tr>
<td>10</td>
<td>M</td>
<td>69</td>
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<td></td>
<td>33</td>
<td>H, K</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>67</td>
<td>+</td>
<td></td>
<td>3</td>
<td>D, H</td>
</tr>
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<td>51</td>
<td>+</td>
<td></td>
<td>34</td>
<td>A, H, V, K</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>70</td>
<td>+</td>
<td></td>
<td>7</td>
<td>V, D, H, N</td>
</tr>
</tbody>
</table>

*Number of months since last myocardial infarction.
†The patient underwent coronary bypass 6 months before entering the study.
‡The patient underwent coronary bypass 11 months before entering the study.

Abbreviations: + = present; A = methylodopa; CHF = congestive heart failure; CM = cardiomegaly on chest x-ray; D = digoxin; Dy = dyreum; Fu = furosemide; H = hydrochlorothiazide; K = potassium supplement; Me = mepropramide; N = nitroglycerin; P = propranolol; T = tolbutamide; V = diazepam.
TABLE 2. Number of Patients Experiencing Side Effects

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Placebo</th>
<th>Quinidine</th>
<th>Phenytoin</th>
<th>Procainamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staggering</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Stomach distress</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>15</td>
<td>18</td>
<td>16</td>
</tr>
</tbody>
</table>

exclude patients from the study are described in table 2. The responses of average PVC rates in individual patients are listed in table 3.

Effect of Phenytoin

Seven patients completed the trial with phenytoin and all seven had serum levels at or near the therapeutic range of 10–18 μg/ml. Three discontinued the drug because of intolerable side effects. Patient 1, who took 20 mg of propranolol four times daily throughout the study for control of angina, had more than 99% reduction in PVCs. There were no statistically significant differences in any of the PVC categories (table 4) or in the rate of coupllets or runs in the entire group that took phenytoin (table 5).

Effect of Procainamide

All 10 patients completed the study without serious side effects, although seven noted insomnia, a potential side effect of procainamide not usually noted. Three patients had serum level less than 2 μg/ml, but all patients were included in the statistical analysis. Patient 1 had a greater than 90% reduction in PVC rates while on procainamide; he also was taking 20 mg of propranolol four times daily for control of angina. The overall PVC rate decreased, but this did not reach statistical significance (table 4).

Procainamide reduced the numbers of PVCs in coupllets and runs with PVC-to-PVC coupling intervals (V–V) of less than 400 msec, (p < 0.02) and also reduced coupllets with V–V of 400–500 msec (p < 0.05, table 5). Figure 1 shows the relative reduction of PVCs with shorter V–V coupling intervals. Patients who took procainamide had fewer runs than those who took placebo, but this difference did not reach statistical significance. Coupllets with a rate faster than 100/minute (V–V < 600 msec), however, were significantly reduced (p < 0.02). Coupllets with a longer coupling interval were also reduced but the reduction was not statistically significant.

Effect of Quinidine

All 10 patients completed the study, although one complained of severe diarrhea and another of gastric distress, which ultimately might have caused discontinuation of the drug. Two patients had serum levels lower than 2 μg/ml, but statistical analysis was carried out on all 10 patients. Four patients had a greater than 90% reduction in PVCs. Overall, patients who took quinidine had fewer PVCs than those who took placebo, but the results did not reach statistical significance (p > 0.09). The number of coupllets with V–V intervals less than 600 msec was reduced (p < 0.05) and the number of runs with V–V intervals less than 600 msec was also reduced slightly, but the numbers are smaller and not significant (table 4).

Table 3. Summary of Response*

<table>
<thead>
<tr>
<th>Pt</th>
<th>Placebo PVC rate</th>
<th>Quinidine PVC rate</th>
<th>%Δ</th>
<th>Procainamide PVC rate</th>
<th>%Δ</th>
<th>Phenytoin PVC rate</th>
<th>%Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>363</td>
<td>191†</td>
<td>-47%</td>
<td>25</td>
<td>-93%</td>
<td>0.5</td>
<td>-99.9%</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>0.2</td>
<td>-98%</td>
<td>14</td>
<td>+75%</td>
<td>9</td>
<td>+12%</td>
</tr>
<tr>
<td>3</td>
<td>50‡</td>
<td>4</td>
<td>-92%</td>
<td>39</td>
<td>-22%</td>
<td>27</td>
<td>-46%</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
<td>490§</td>
<td>+590%</td>
<td>380</td>
<td>+435%</td>
<td>186</td>
<td>+162%</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>3.4</td>
<td>-90%</td>
<td>7</td>
<td>-79%</td>
<td>30</td>
<td>-12%</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
<td>120</td>
<td>-22%</td>
<td>186</td>
<td>+21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>21</td>
<td>105</td>
<td>+400%</td>
<td>26</td>
<td>+24%</td>
<td>245</td>
<td>+106%</td>
</tr>
<tr>
<td>9</td>
<td>128</td>
<td>60</td>
<td>-53%</td>
<td>89</td>
<td>-30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>263</td>
<td>21</td>
<td>-92%</td>
<td>95</td>
<td>-64%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>72</td>
<td>53</td>
<td>-26%</td>
<td>35</td>
<td>-52%</td>
<td>190</td>
<td>+164%</td>
</tr>
</tbody>
</table>

*Data on patients 5 and 10 not reported, as they had < 3 PVCs/hour during the placebo period.
†PVC rates are given in terms of PVCs/hour.
‡The analysis for this patient was based on the first 10-hour period only.
§Only one 10-hour tape was available on quinidine, which was compared against comparable 10-hour placebo period.

Abbreviations: %Δ = percentage change calculated as 100 – (100 × PVC rate for drug/PVC rate placebo) for negative changes and (100 × PVC rate for drug/PVC rate for placebo) – 100 for positive changes; PVC = premature ventricular complex.
There was a slight increase in the number of couplets and runs with average V-V coupling intervals longer than 600 msec when the patients were taking quinidine.

Quinidine had a marked effect on PVCs with coupling intervals less than 400 msec ($p < 0.02$). The cumulative distribution of PVCs according to coupling interval (fig. 2A) shows the reduction in the percentage of PVCs with shorter coupling intervals. Quinidine also reduced the number of PVCs in couplets and runs with V-V coupling intervals of less than 400 msec ($p < 0.02$, table 5, fig. 2B). In addition, isolated PVCs with coupling intervals of 400–500 msec and PVCs in couplets and runs with coupling intervals of 400–500 msec were less frequent ($p < 0.05$).

**Discussion**

PVCs in any one person may demonstrate different morphologies, coupling intervals and patterns of presentation, such as bigeminy, trigeminy, couplets or runs, presumably reflecting different mechanisms or sites of origin. It would be reasonable to expect that a given antiarrhythmic agent might be very effective in eliminating one or more of the different subgroups but not necessarily all. If the proportion of PVCs comprising these subsets were small relative to the total population of PVCs, an overall effect of the agent might not be seen, even though it might be extremely effective in one subset (see Appendix).

In these patients with coronary artery disease and asymptomatic arrhythmias, quinidine and procainamide preferentially reduced PVCs with short (< 400 msec) coupling intervals either after a normal beat (N-V) (quinidine alone) or another PVC (V-V) (both drugs). This effect could be demonstrated, although an overall reduction in PVC rate did not reach statistical significance in this small patient population. Studies using programmed ventricular stimulation have also demonstrated a prolonged refractory period of the right ventricle in patients given quinidine or procainamide, which prevented ventricular response to
a measurable reduction in total PVCs in only a minority of patients. However, the very beats that these agents are most effective against, i.e., early beats, and especially the PVCs with shorter coupling intervals within salvos (short V-V intervals), may be associated with the highest risk of sudden death in patients with heart disease. Both ventricular tachycardia and early PVCs deteriorate into ventricular fibrillation in the setting of acute myocardial ischemia or infarction, so eliminating or reducing these PVCs through the use of antiarrhythmics might be expected to reduce the risk of sudden death, even though other PVCs are not affected.

Several reports have indirectly supported this hypothesis. Winkle et al. used intensive and carefully individualized antiarrhythmic therapy and eliminated recurrent symptomatic ventricular tachycardia in eight of 11 patients. Therapy that eliminated symptoms, however, did not eliminate all PVCs. Some patients actually had more frequent asymptomatic PVCs, even though the symptomatic ventricular tachycardia was controlled. Jones et al. found a reduction in episodes of ventricular tachycardia using quinidine after a myocardial infarction but no change in PVC frequencies. Lown and Graboys, adjusting antiarrhythmic medications to eliminate or reduce all repetitive beats and early (R-on-T) beats during 24-hour Holter recordings and during exercise provocation, reported a markedly improved 1-year survival in 26 patients who had survived ventricular fibrillation or tachycardia, even though they continued to have frequent multifocal and unifocal PVCs.

The effectiveness of procainamide at the dosage level administered in our trial is somewhat surprising. At the time of the trial, 2 g/day was the standard therapeutic dose. More recently, investigators have suggested that serum levels of 4–8 µg/ml are required for therapeutic effect, so doses of 3–6 g/day are now commonly administered. However, Giardina and Bigger demonstrated prolongation of the PVC coupling interval when serum procainamide levels were 2–4 µg/ml. These levels were attained in most of the patients in our study. Ogunkelu et al. also reported effects on the refractoriness of the His-Purkinje system at "subtherapeutic" levels of procainamide, an effect that could also be related to suppression of some ventricular arrhythmias.

Studies like this, which use the double-blind crossover design, permit evaluation of the effect of antiarrhythmic agents on the total population of PVCs in the entire group of patients, but evaluation of the response of an individual patient is not possible. Only one patient who took phenytoin or procainamide showed more than 90% reduction in PVC rates, whereas only four showed such a reduction while taking quinidine. Because of the wide day-to-day variation in PVC rates that may occur, less complete reduction in PVC rates cannot be ascribed to drug with the number of recordings used in this study. Similarly, in view of the lack of data on daily variation of coupling-interval-specific PVC rates, no statements regarding response of an individual patient's early PVCs to drugs can be made.

Figure 1. Cumulative percentage of premature ventricular complexes (PVCs) by coupling interval; effect of procainamide. N-V = coupling interval, normal beat to PVC; V-V = coupling interval, PVC to PVC. Coupling intervals are in milliseconds. The graph demonstrates the relative effectiveness of procainamide on the PVCs with the shorter coupling intervals in salvos. The statistical significance of the effect on specific coupling intervals is described in the text and in table 5.

Figure 2. Cumulative percentage of premature ventricular complexes (PVCs) by coupling interval; effect of quinidine. Abbreviations as in figure 1. The graph demonstrates the relatively greater effectiveness of quinidine on PVCs with shorter coupling intervals. The statistical significance of the effect at specific coupling intervals is described in the text and in table 5.
The goal of treatment of the patient with asymptomatic ventricular arrhythmia is the prevention of sudden death. We have shown that antiarrhythmic agents may act preferentially against forms of ectopy that may be more likely to deteriorate into ventricular fibrillation. Further investigation will be required to determine whether elimination or reduction in the numbers of these more "dangerous" PVCs alone will be associated with prevention of sudden death.

References


Appendix

In the present patient group, the subset of PVCs with a coupling interval of < 10 msec constituted less than 10% of the total number of PVCs. If all these beats were eliminated, the PVC rate would be reduced only 10%. From our data, at least 2000 patients would be required to have a 75% chance of demonstrating a 10% reduction in PVCs. On the other hand, with an analysis system like the Argus/H, which can detect and count subsets of PVCs, only 13 patients would be required to give a 75% chance of establishing a 75% reduction in a subset comprising 10% of the number of PVCs.

For sample size calculations, four questions are of interest: the significance level, the power (the difference), the sample size, and the true difference in means (usually specified in standard deviation units). Given any of these, the fourth can be computed using straightforward calculations using the noncentral t distribution (e.g., Johnson NL, Kotz S: Continuous Univariate Distributions-2, Houghton Mifflin, New York, 1970).

Comparisons in this report were based on the use of a paired test on the log 10 of PVC rates. The standard deviation of the difference in PVC rates averaged 0.57 for the procainamide comparisons, 0.87 for the quinidine comparisons and 1.18 for the phenytoin comparisons. Using the value for quinidine, a 10% reduction in PVC rate corresponds to a difference of 0.053 standard deviation units: 20%, 0.111; 30%, 0.178; 50%, 0.346; and 75% reduction 0.692. With a one-tail significance level of 0.05 and a power of 90%, a sample size of 3092 is required for a 10% reduction in PVC rate; for a 50% power, 978; 67%, 1556; 75%, 1943; and 95%, 3907. Using a power of 90%, a reduction requires a sample of 692; 30%, 272; 50%, 73; and 75%, 20.
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