Antiarrhythmic Drug Therapy for Sporadic Ventricular Ectopic Arrhythmias

By Michael V. Jelinek, M.D., Leif Lohrbaumer, M.D., and Bernard Lown, M.D.

SUMMARY
Exercise stress testing and 24-hour ambulatory monitoring have been employed to evaluate antiarrhythmic drug efficacy in patients with sporadic ventricular ectopic arrhythmias (VEA). Twenty-three patients with often recurring VEA were exercised 123 times and subjected to 66 ambulatory monitoring sessions during control periods and while receiving either procaine amide or quinidine. Two dose schedules were employed; procaine amide, 3.0 and 6.0 g daily and quinidine, 1.2 and 1.8 g daily. Though adequate and even high drug blood levels were reached, an effective antiarrhythmic response was observed in only eight patients receiving procaine amide and in seven of those taking quinidine. These modest successful results were associated with a high incidence of troublesome adverse effects which were noted in 11 patients receiving procaine amide and six of those receiving quinidine. It is concluded that these antiarrhythmic drugs should not be employed in the patient with episodic VEA unless the arrhythmias are symptomatic and are clearly life-threatening.

Additional Indexing Words:
Procaine amide  Quinidine  Ventricular premature beats  Ventricular tachycardia
Monitoring  Exercise testing

Sudden death in patients with ischemic heart disease is due to ventricular fibrillation. Prevention will probably depend on the use of antiarrhythmic drugs. An immediate question, therefore, relates to recognizing the subject who is in need of prophylactic measures. In patients with acute myocardial infarction, suppression of ventricular premature beats (VPBs) reduces materially the incidence of primary ventricular fibrillation. It has been argued that the presence of VPBs may also help identify patients with coronary heart disease (CHD) who are susceptible to sudden death. Indeed, there is increasing epidemiologic evidence associating the occurrence of VPBs with an enhanced risk of sudden death.

It has been suggested that only certain grades of arrhythmia, characterized by frequency, repetitive pattern or T wave interruption, have prognostic significance. To expose these advanced grades of arrhythmia requires prolonged periods of monitoring or exercise stress testing. Once a patient is known to be at risk, the problem still remains of determining which antiarrhythmic drug is to be employed and in what dose schedule. When the arrhythmia recurs often or is continuous, or when the rhythm disorder provokes symptoms, effectiveness of an antiarrhythmic drug is easy to establish. However, when the arrhythmia is episodic and asymptomatic, how is drug efficacy to be ascertained? This report presents a methodologic approach for assessing the effectiveness of antiarrhythmic drugs in suppressing sporadic ventricular ectopic arrhythmias (VEA) in the ambulatory patient.

Material and Methods
The population consisted of 23 patients, 19 of whom were males. All were referred for management of ventricular tachyarrhythmias. To qualify for this study, patients had to show either repetitive or frequent isolated VPBs on exercise testing and/or upon ambulatory monitoring. Sixteen had repetitive ventricular arrhythmias, namely, couplets of ventricular tachycardia. Details of the patient population are shown in table 1. Fifteen patients were asymptomatic; five, the arrhythmias had provoked symptoms; three others had been resuscitated from cardiac arrest, in one documented as ventricular fibrillation. Twelve of the patients had CHD defined by a history of well-documented
myocardial infarction, angina pectoris, or both. Seven had evidence of other disease such as hypertensive cardiovascular disease, alcoholic cardiomyopathy, or other cardiomyopathies; and four were free of evidence of heart disease. The average age of the population was 52 years.

Exercise Testing

Patients had a clinical examination and a standard ECG prior to the performance of every exercise test in order to establish the absence of recent myocardial infarction or unstable angina. Electrodes were applied firmly to carefully prepared integument in the following five locations: The anterior chest wall just medial to the right and left anterior axillary lines in the second intercostal space, a standard V lead position, the right subscapular region posteriorly, and over the left iliac crest. The V5 lead was used for recording unless Q5 complexes, left ventricular hypertrophy, bundle branch block, or digitalis therapy precluded interpretation of the ST segment. Under these circumstances, a more lateral V lead was used. In selected cases, V1 was recorded to help define ectopic activity as well as assist in differentiating atrial from ventricular prematurity. ECGs were displayed on an oscilloscopic monitor and printed on a chart recorder with speeds of 1 and 25 mm/sec. The tests were also transcribed on magnetic tape from which could be obtained multiple permanent records. A special delay circuit permitted display or recording of events after a lapse of six seconds. This arrangement facilitated differentiation of premature beats from artifact due to movement.

After the electrodes were placed, the ECG was recorded for three minutes with the patient resting in the supine position. Right and then left carotid sinus massage was followed by 30 sec of hyperventilation. Exercise was carried out on a motorized treadmill according to the protocol of Doan and Bruce. The initial setting was at 1.7 mph at 10% grade elevation. Every three minutes, there was an automatic increase in speed and grade according to the following sequence: 2.5 mph at 12% elevation; 3.4 mph at 14% elevation; 4.2 mph at 16% elevation; 5.0 mph at 18% elevation; 5.5 mph at 20% elevation; and 6.0 mph at 22% elevation. The end point of the test was the development of moderate angina pectoris, symptoms of fatigue, or at least three successive VPBs defined here as ventricular tachycardia.

All tests were performed by an experienced physician. The exercise laboratory was fully equipped to respond to cardiac emergencies. It contained a cardioverter, Ambu-bag, oxygen tanks, equipment for trachial intubation, intravenous fluids, a frequently checked supply of emergency drugs, as well as an alarm system to summon additional medical help.

Ambulatory Monitoring

Continuous electrocardiographic recordings were obtained by means of a portable cassette tape unit.* The

*American Optical Company, Framingham, Massachusetts.

Table 1

Clinical Features of 23 Patients in Antiarrhythmic Study

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Age</th>
<th>Sex</th>
<th>VPB grade</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CHD, old MI</td>
<td>46</td>
<td>M</td>
<td>2</td>
<td>none</td>
</tr>
<tr>
<td>2. CHD, old MI</td>
<td>63</td>
<td>M</td>
<td>4b</td>
<td>none</td>
</tr>
<tr>
<td>3. CHD, old MI</td>
<td>49</td>
<td>M</td>
<td>2</td>
<td>none</td>
</tr>
<tr>
<td>4. CHD, old MI</td>
<td>63</td>
<td>M</td>
<td>4a, 4b</td>
<td>none</td>
</tr>
<tr>
<td>5. CHD, old MI</td>
<td>46</td>
<td>M</td>
<td>VF</td>
<td>cardiac arrest</td>
</tr>
<tr>
<td>6. CHD, old MI, AP</td>
<td>50</td>
<td>M</td>
<td>2</td>
<td>none</td>
</tr>
<tr>
<td>7. CHD, old MI, AP</td>
<td>54</td>
<td>M</td>
<td>4b</td>
<td>none</td>
</tr>
<tr>
<td>8. CHD, old MI, AP</td>
<td>71</td>
<td>M</td>
<td>4b</td>
<td>cardiac arrest</td>
</tr>
<tr>
<td>9. CHD, old MI, AP</td>
<td>59</td>
<td>M</td>
<td>2</td>
<td>none</td>
</tr>
<tr>
<td>10. CHD, old MI</td>
<td>49</td>
<td>M</td>
<td>4a, 4b</td>
<td>palpitation</td>
</tr>
<tr>
<td>11. CHD, old MI</td>
<td>44</td>
<td>M</td>
<td>4a</td>
<td>palpitation</td>
</tr>
<tr>
<td>12. CHD, old MI</td>
<td>58</td>
<td>M</td>
<td>4b</td>
<td>none</td>
</tr>
<tr>
<td>13. Cardiomyopathy, alcoholic</td>
<td>69</td>
<td>M</td>
<td>4b</td>
<td>palpitation</td>
</tr>
<tr>
<td>14. Cardiomyopathy</td>
<td>42</td>
<td>F</td>
<td>4a</td>
<td>cardiac arrest</td>
</tr>
<tr>
<td>15. Cardiomyopathy</td>
<td>45</td>
<td>M</td>
<td>4b</td>
<td>dizziness</td>
</tr>
<tr>
<td>16. Cardiomyopathy</td>
<td>34</td>
<td>F</td>
<td>2</td>
<td>none</td>
</tr>
<tr>
<td>17. Rheumatic HD</td>
<td>58</td>
<td>M</td>
<td>4a, 4b</td>
<td>none</td>
</tr>
<tr>
<td>18. Hypertensive HD</td>
<td>60</td>
<td>M</td>
<td>4a</td>
<td>none</td>
</tr>
<tr>
<td>19. Unknown form of HD</td>
<td>57</td>
<td>M</td>
<td>4a, 4b</td>
<td>syncope</td>
</tr>
<tr>
<td>20. Normal</td>
<td>42</td>
<td>M</td>
<td>4b</td>
<td>none</td>
</tr>
<tr>
<td>21. Normal</td>
<td>39</td>
<td>M</td>
<td>2</td>
<td>none</td>
</tr>
<tr>
<td>22. Normal</td>
<td>43</td>
<td>F</td>
<td>2</td>
<td>none</td>
</tr>
<tr>
<td>23. Normal</td>
<td>58</td>
<td>M</td>
<td>4a</td>
<td>none</td>
</tr>
</tbody>
</table>

Abbreviations: MI = myocardial infarction; AP = angina pectoris; HD = heart disease; VF = ventricular fibrillation. For grading of VPBs see table 3.
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Table 2

Exercise Stress Testing and 24 Hour Ambulatory Monitoring Sessions in 23 Patients

<table>
<thead>
<tr>
<th></th>
<th>Control tests (no.)</th>
<th>Quinidine g/day</th>
<th>Procaine amide g/day</th>
<th>Total tests (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise stress tests (no.)</td>
<td>42</td>
<td>22</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>Ambulatory monitoring sessions (no.)</td>
<td>22</td>
<td>13</td>
<td>7</td>
<td>16</td>
</tr>
</tbody>
</table>

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is shown in table 3. A therapeutic effect was defined as the reproducible abolition of ventricular ectopic activity (VEA) (grades 4a or 4b), or when these grades were absent, reduction in the frequency of isolated VPBs (grade 2) by at least 75% from the peak VPB frequency observed in the control session. Whenever possible, the therapeutic effect observed on exercise had to be confirmed by monitoring. In several patients, the apparent therapeutic effect observed on exercise was not supported by monitoring; in these circumstances, repeat exercise testing confirmed that a therapeutic effect had not, in fact, been obtained. The severity of drug toxicity was defined as mild, symptoms present but tolerable; as moderate, patient required persuasion to continue therapy; or as severe, side effects were intolerable. Statistical analysis was performed by Chi square method, using Yates correction where appropriate. Means of group data were compared by using Student’s t-test.

Results

Control Studies

Prior to initiating drug therapy, 21 of 23 patients had at least one exercise or one monitoring session. In the two other cases, gravity of the arrhythmia precluded baseline studies before commencement of drug therapy. These 21 patients performed 42 baseline exercise tests. The mean exercise tolerance for the group was 8.1 minutes and the mean maximum heart rate achieved was 149 beats/min (table 4). Ten patients showed ventricular tachycardia (VT) on at least one control exercise test; six others had couplets; while the five remaining had frequent VPBs but no repetitive arrhythmia. Of the 21 patients, 14 had 22 control monitoring sessions prior to drug testing. Three had episodes of VT, seven exhibited couplets, three had frequent VPBs and one was entirely free of arrhythmia.

Procaine Amide

All 23 patients received the 3.0 g daily dose of procaine amide. One patient, because of toxicity, had to discontinue therapy before objective assessment could be accomplished of antiarrhythmic status (patient 9). Only four of the 22 patients exhibited arrhythmia suppression; however, one of these exhibited moderate toxicity (table 5). The mean serum procaine amide level was 5.3 mcg/ml, ranging from 2.2 to 11.5 mcg/ml. The mean concentration in the three successfully treated patients was 4.9 mcg/ml. Drug toxicity during the three days of therapy developed in 8 of 23 patients who demonstrated a mean blood procaine amide level of 5.6 mcg/ml. In five, the adverse reactions were mild and additional drug could be tolerated. A dose of 6.0 g of procaine amide was administered to 16 of the 23 patients. In seven patients, no further testing at a higher dose was indicated: three because of success at a lower drug level, three because of toxic reactions, and one because both arrhythmia suppression and toxicity occurred simultaneously. Of the 16 patients, four showed antiarrhythmic effect. However, at this dose level, procaine amide could not have been continued in three patients because of disabling toxicity (table 5). The mean procaine amide blood level in the 16 patients was 9.7 mcg/ml with a range of 4.4 to 16.5 mcg/ml. Drug toxicity was encountered in a total of ten patients; among eight of these who had appropriate blood levels drawn, the mean procaine amide level was 8.3 mcg/ml.

Quinidine Sulfate

Twenty-one patients received 1.2 g of quinidine per day. Two other patients had taken a similar dose of quinidine prior to referral without either therapeutic or toxic effect and hence, were tested on the larger dose schedule only. Of the 21 patients treated for three days with quinidine in a dose of 1.2 g daily, three had a satisfactory response. Eight patients developed some toxic manifestations. The

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>No arrhythmia</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Isolated unifocal VPBs</td>
</tr>
<tr>
<td></td>
<td>Less than 30/hr or 1/min</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Isolated unifocal VPBs</td>
</tr>
<tr>
<td></td>
<td>More than 30/hr or 1/min</td>
</tr>
<tr>
<td>Grade 3</td>
<td>a.) couplets</td>
</tr>
<tr>
<td></td>
<td>b.) ventricular tachycardia</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Early cycle VPBs</td>
</tr>
</tbody>
</table>

Table 3

Grading of Ventricular Ectopic Activity with 24 Hours Ambulatory Monitoring and with Treadmill Exercise
mean serum quinidine level was 2.9 mcg/ml ranging from 0.2 to 5.6 mcg/ml. The mean serum quinidine level in successfully treated patients was 3.1 mcg/ml. In the six patients exhibiting adverse effects in whom blood was available for analysis the level was 3.2 mcg/ml.

Sixteen patients received 1.8 g of quinidine daily. Seven patients were not given the larger dose of quinidine, three because of control of arrhythmia with 1.5 g daily, and four because of toxicity. In four patients 1.8 g of quinidine controlled the arrhythmia, while in seven toxicity developed. The mean blood level among the 16 patients receiving 1.8 g daily was 4.8 mcg/ml, with a range of 2.7 to 9.7 mcg/ml. In the successfully treated patients, the mean level was 5.3 mcg/ml, whereas the level in those with toxicity was 5.2 mcg/ml (table 5).

**Toxic Effects**

Quinidine and procaine amide had no adverse effect on either exercise tolerance or maximum heart rate. There were no significant alterations in electrocardiographic parameters such as PR interval, QRS duration and QT or QTc duration (table 4). However, extracardiac toxic effects were common and were dose related. Procaine amide produced a multiplicity of side effects particularly at high doses. Insomnia was the commonest complaint (14 episodes). Also observed were malaise (7), fatigue (7), diarrhea (5), nausea (4), and dizziness (4). Hallucinations occurred in two cases. The common side effect of quinidine was diarrhea (14 episodes), but this was not disabling. Other toxic manifestations were infrequent. Moderate or severe side effects occurred in six of the 21 patients (29%) receiving quinidine and in 11 of 23 patients (48%) given procaine amide. Significant toxicity was dose-related for procaine amide; this did not appear to be the case for quinidine.

**Comparison of Monitoring with Exercise**

There were 53 combined ambulatory monitoring and exercise tests performed at the same patient visit during the procaine amide and quinidine study. Using the classification shown in table 3, exercise resulted in a higher grade of arrhythmia than monitoring in 22 sessions (41%); a similar grade in 20 sessions (38%); and a lower grade in 11 sessions (21%). Half of the higher arrhythmia grades associated with exercise occurred with exercise-induced VT (4b) when monitoring merely showed couplets (4a). When class 4a and 4b arrhythmias are grouped together as equivalent, monitoring and exercise resulted in a similar grade.
of arrhythmia in 31 tests (59%), exercise more than monitoring in 12 tests (23%), and exercise less than monitoring in ten tests (18%). One patient consistently showed arrhythmia on effort but not on monitoring, while one other patient consistently showed higher grades of arrhythmia on monitoring.

**Discussion**

Experience in treating ventricular ectopic activity is largely limited to the continuously present arrhythmia or the recurring and sustained disorder which both patient and physician readily recognize. Choice of drug and dosage schedule is guided by abolition of the arrhythmia or prevention of detectable recurrences. This cannot be easily achieved with the sporadic and fleeting ventricular arrhythmias. They are usually not symptomatic, the patient is largely unaware of their presence, and the physician is hard pressed to determine their occurrence. The sole reason for attempting to suppress these arrhythmias is that they may be precursors of sudden death. How then is one to gauge efficacy of an antiarrhythmic regimen? The specific questions relate to choice of a suitable drug, selection of an appropriate dose schedule and determination of an adequate therapeutic endpoint. As the patient susceptible to death is more precisely identified, the importance of these questions will grow more relevant.

Major reliance in the present study for exposing ventricular ectopic arrhythmias (VEA) was by means of exercise stress testing. The physiologic underpinnings for this approach derive from recent and extensive clinical experience in coronary care units. In the setting of the CCU, it has been amply documented that acute myocardial ischemia is associated with a ubiquity of VEA. Since exercise accelerates heart rate, increases blood pressure and augments the heart's requirement for blood, it is reasonable to expect that the minor degrees of acute ischemia thus precipitated may also divulge disturbances in cardiac mechanism. Indeed, a survey of 1,000 treadmill exercise tests in 625 patients has demonstrated that exercise increased the incidence of repetitive VEA of grades 4a and 4b by a factor of nearly eight compared to supine monitoring. Earlier studies by Kosowsky et
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al.12 have demonstrated that exercise yields VPBs
having a higher grade than those exposed by
ambulatory monitoring of nearly 11 hours dura-
tion.

If exercise is to be employed to expose VEA for
determining antiarrhythmic drug efficacy, the pre-
cise objective of therapy still lacks definition.
Obviously the desirable end point is prevention of
sudden death, but this is not readily testable. Two
essential questions, therefore, are which arrhythmias
constitute precursors of sudden death, and which
arrhythmias if suppressed would encourage hope of
effective prophylaxis. Experimental evidence indi-
cates that repetitive VEA constitute prodromes for
ventricular fibrillation.24, 25 Epidemiologic studies
have implicated frequent VPBs, couplets, and
paroxysms of VT as harbingers of sudden death in
patients with ischemic heart disease.7, 8 The ther-
apeutic end points of the present study were deter-
mined by these findings. Drug effectiveness
was defined as the complete abolition of ventricular
couplets and ventricular tachycardia and 75% re-
duction in VPB frequency.

The remarkable and unanticipated result of the
present study was the ineffectiveness of oral
procaine amide and quinidine in suppressing VEA
in the ambulatory patient. These drugs failed in 65% of
the patients tested even though a considerable
incidence of adverse reactions was provoked. This is
especially surprising since procaine amide, at
considerably lower blood levels, proved effective in
controlling ventricular arrhythmias in patients with
acute myocardial infarction.26 In a recent study
procaine amide was administered intravenously to
20 patients with ventricular arrhythmia; complete
success was achieved in 17 and partial suppression
in two other patients.27 These patients received 100
mg every five minutes and the total dose did not
exceed one gram. The mean effective blood level
was 6.5 mcg/ml, which was 67% of the blood level
obtained in the present study when 6 g was the
daily dose and arrhythmia control was achieved in
only four of 16 patients. Another recent study28 also
demonstrated that quinidine when administered
every six hours was effective in materially reducing
VEA in 23 carefully monitored patients with acute
coronary insufficiency. It would appear that oral
antiarrhythmic therapy for sporadically recurring
VEA in the ambulatory subject is not as effective as
when the same drugs are used to suppress
continuous or recurring arrhythmia in the hospital-
ized patient.

The present study was specifically designed to
minimize drug toxicity. Only short courses of drugs
were given, since previous experience had dem-
strated that 30% of patients taking quinidine9 and
54% of patients receiving a low dose of procaine
amide29 had to discontinue therapy because of
untoward side effects. Notwithstanding the fact that
drug intake was limited to three days, at any drug-
dose schedule, toxic effects were more common
than therapeutic successes. The highest therapeutic
efficacy was 25% with the larger dosages of either
procaine amide or quinidine. Yet the lowest
incidence of toxicity was 38% noted with 3.0 g of
procaine amide. The use of either quinidine or
procaine amide for the control of episodic VEA is
therefore unwarranted for such practice promises a
meager harvest of therapeutic success and a high
yield of disabling toxicity. Until the introduction of
better tolerated antiarrhythmic drugs, their use will
be justified only when the arrhythmias are disabling
to the patient.

A key assumption of this study is that in the
patient with CHD, VEA suppression is prerequisite
for prevention of sudden death. The association of
VPBs with an increased risk of sudden death does
not prove that their abolition is essential for
effective prophylaxis. Knowledge of whether anti-
arrhythmic drug treatment will prove effective and
whether this requires VPB suppression must await
large scale epidemiologic studies, preferably utiliz-
ing drugs less toxic than either procaine amide or
quinidine. Until that time, therapy of sporadic VEA
will need adhere to methods similar to those
outlined in the present report.

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