Antiarrhythmic Drug Therapy in Survivors of Prehospital Cardiac Arrest: Comparison of Effects on Chronic Ventricular Arrhythmias and Recurrent Cardiac Arrest

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SUMMARY We studied the long-term effects of membrane-active antiarrhythmic agents on chronic ventricular arrhythmias in patients who have survived prehospital cardiac arrest. Among 16 patients treated with a dose-adjusted, plasma level-monitored antiarrhythmic regimen, eight have survived for longer than 12 months and eight have had recurrent cardiac arrests (RCAs). Monthly Holter monitor tapes (HM) recorded during the 4 months before the eight RCAs were compared with monthly HM tapes matched for time of entry and duration of follow-up in the eight patients who did not have RCAs. Transient or persistent complex ventricular ectopic depolarizations (VEDs) have been recorded on 47 of the 63 monthly HM tapes (75%). The difference between VEDs in the RCA patients (mean 153 VEDs/hr, median 19 VEDs/hr) and VEDs in the patients who have not had RCA (mean 122 VEDs/hr, median 8 VEDs/hr) was not significant ($p > 0.2$); nor was there a predictable relationship between therapeutic plasma levels of antiarrhythmic agents and the frequency and complexity of chronic asymptomatic VEDs (therapeutic levels — mean 104 VEDs/hr, median 6 VEDs/hr; subtherapeutic levels — mean 184 VEDs/hr, median 21 VEDs/hr). Differences were not significant ($p > 0.1$). In contrast, all eight RCA patients had unstable plasma levels (21 of 31 determinations subtherapeutic) while six of the eight patients who have not had RCA had consistently therapeutic levels ($p < 0.01$). Thus, adequate plasma levels of antiarrhythmic agents may protect against RCA, despite failure to suppress VEDs predictably. The apparent dissociation between predictable suppression of chronic VEDs and protection against RCA suggests that clinical effectiveness of these agents may not be best measured by their effect on chronic VEDs.

PATIENTS RESUSCITATED from prehospital cardiac arrest who return to the community after hospitalization have a high incidence of chronic complex ventricular arrhythmias and recurrent prehospital cardiac arrest. In long-term clinical and electrophysiologic studies of such patients, we have observed that chronic asymptomatic complex ventricular arrhythmias were resistant to standard dosages of various antiarrhythmic drugs, so we began to use a dose-adjusted, plasma level-monitored antiarrhythmic drug management protocol. We used plasma levels generally accepted as therapeutic, rather than suppression of chronic ventricular arrhythmias, as the end point of therapy. A subgroup of patients who have had a recurrent cardiac arrest while on this therapy may be compared with patients continuing as long-term survivors without recurrent arrest. In this report we describe the relationship of antiarrhythmic drug plasma levels to suppression of chronic asymptomatic complex ventricular arrhythmias and to recurrent cardiac arrest.

Methods

Emergency medical rescue teams of the City of Miami Fire Department and the Metropolitan Dade County Fire Department, distributed within the city so that they are able to reach 80% of emergency calls within 4 minutes of initial contact, have been described previously. The rescue personnel telemeter a rhythm strip to Jackson Memorial Hospital, the base hospital for the program, and the resuscitative procedures are guided by voice contact with a physician using a two-way radio system. Patients who were successfully resuscitated and transported to the base hospital alive were candidates for the study.

Long-Term Rhythm Analysis

Patients who survive hospitalization are monitored for posthospital arrhythmias during long-term follow-up by two techniques: 1) a 24-hour Holter monitor recording once monthly, and 2) a 30–60-second daily telephone transmission ECG strip. Ventricular arrhythmias on the 24-hour Holter monitor recordings are quantitated by standard scanning techniques.

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to provide a count of the total number of ventricular ectopic depolarizations (VEDs) per 24-hour tape, and a calculation of the mean frequency of VEDs/hr. In addition, we count the number of VEDs on a display of the first 32 seconds of each 10-minute segment on the 24-hour tape (approximately 144 samples in 24 hours). The ventricular ectopic activity count on each 32-second segment of tape then is extrapolated to the number of VEDs/min, and collated into four groups — the number of segments free of any VEDs, and those having 1–5, 6–10, 11–20 and more than 20 VEDs/min. Bar diagrams are constructed to display the percent of segments falling into each frequency category (fig. 1), and the frequency of patterns of advanced grades are also recorded. These bar diagrams indicate the frequency of transient VEDs and the relative frequency of various classification grades.

Antiarrhythmic Drug Therapy and Plasma Levels

The study design calls for use of two membrane-active antiarrhythmic drugs, procainamide hydrochloride and quinidine gluconate. If neither drug is tolerated by the patient, or if the patient develops symptomatic ventricular arrhythmias, other antiarrhythmic drugs are used at the discretion of the primary physician. We report arrhythmia data only for patients who took either procainamide or quinidine, with or without digoxin and diuretics, but without propranolol or other antiarrhythmic drugs.

Plasma levels of procainamide were measured by a spectrophotometric technique,6 plasma levels of quinidine were measured by a double extraction spectrophotofluorimetric technique.7 Blood samples were taken during the 1-hour period before a scheduled dose on the same day of each Holter recording, and were assumed to reflect equilibrium-state plasma levels as long as the dosage of the drug was not changed within 1 week. The mean frequency of VEDs was then matched to the antiarrhythmic drug plasma level determined on the same day.

The management protocol for quinidine gluconate assumes a therapeutic range of 2.3–6.0 µg/ml,8 and 4–8.0 µg/ml for procainamide.9 Dosages are adjusted in an attempt to achieve these plasma levels in all patients during the 1 hour before a scheduled dose (i.e., at the nadir of equilibrium-state fluctuation), and dosages ranged from 2–5 g/day of procainamide and 1.6–3 g/day of quinidine gluconate, as determined by the ability to achieve therapeutic blood levels or the limits of drug tolerance.

Data Analysis

Patients who had had recurrent prehospital cardiac arrests, with or without a second successful resuscitation, during posthospital follow-up after the initial cardiac arrest were compared with those who had been followed for a minimum of 12 months (range 13–32 months) without a recurrent arrest. Among those who died suddenly or had a successfully resuscitated recurrent cardiac arrest, the last four Holter monitor tapes before the recurrent event were analyzed for the frequency of ventricular ectopic activity and matched with the corresponding plasma levels of antiarrhythmic drugs. Among patients who did not have a recurrent cardiac arrest, the four Holter monitor tapes and corresponding plasma levels providing the closest match for time of entry and follow-up to tapes in the recurrent arrest group were analyzed.

Results

Thirty-four patients survived prehospital cardiac arrest, were hospitalized, and were discharged in the past 2.5 years. Of the 28 patients who entered and remained in the long-term follow-up protocol, 16 were in one of the two categories in this report: 1) eight patients have been followed for 12 months or longer after prehospital cardiac arrest and were alive at last follow-up, with no recurrent cardiac arrest; and 2) eight patients have had a recurrent cardiac arrest. In the latter category, six patients were classified as sudden deaths at the scene of the recurrent cardiac arrest, and two are alive after a second successful prehospital resuscitation. Of the remaining patients who entered long-term follow-up during the study period, two were excluded from our analysis because they died non-sudden deaths, four were excluded because they could not tolerate either of the study drugs or had comorbidity exclusions, and six have been followed as survivors for less than 12 months.

The 16 patients ranged in age from 21–74 years at the time of their initial cardiac arrest, with a mean age of 60 ± 13 years (mean ± SD) and a median of 62 years. The recurrent cardiac arrest group (mean 53 years, median 55 years) was younger than the survivors (mean 68 years, median 68 years). There were 12 males and four females; all of the females were in the surviving group. Twelve patients (75%) had coronary artery disease as the dominant underlying pathology, two of whom had acute myocardial infarctions at the time of the index event; one had a ventricular aneurysm. One coronary artery disease patient also had asymmetric septal hypertrophy. Two of the remaining four patients had cardiomyopathies and two had hemodynamically significant aortic regurgitation, one of whom also had coronary artery lesions. Most of the patients were in functional class II or III, none in class IV, and none had coexisting renal or hepatic disease. Only four patients were surgical candidates, based upon etiology of heart disease or anatomy. One in the recurrent cardiac arrest group (HLL) refused aortic valve replacement for isolated aortic insufficiency. Two others in that group had surgery — one patient (GR) had an aneurysmectomy with a left anterior descending bypass, and another (DS) had aortic valve replacement with a single bypass and lesions that could not be bypassed in the other two vessels. One patient in the long-term survivors group had a triple-bypass procedure. Ten patients (four in the recurrent cardiac arrest group and six in the long-term survivors group) were not considered for surgery because of inoperable multiple-vessel disease and/or severe left ventricular dysfunction.
The recurrent cardiac arrest group had been followed for 4–27 months (mean 13.6 months, median 13.5 months) between the index event and the recurrent arrest, while those without recurrent events have been followed 13–32 months (mean 23.6 months, median 25 months) at the time of this report.

Figure 1 illustrates the two general types of responses of chronic ventricular arrhythmias to antiarrhythmic therapy which we observed. In panel A (top), the six Holter monitor recordings at monthly intervals demonstrate a beneficial effect of the antiarrhythmic agent, quinidine gluconate, in suppressing frequency of chronic asymptomatic ventricular arrhythmias. The pre-dose equilibrium-state quinidine plasma level was 1.8 μg/ml at the time of the first recording, 1.6 μg/ml at the second, and 2.4, 3.7, 4.3 and 4.3 μg/ml on the days of the next four recordings. As therapeutic plasma levels of quinidine were achieved, VEDs were almost completely suppressed.

In the lower half of panel A, a corresponding decrease in the Lown classification accompanies the decrease in VED frequency. In panel B, six Holter monitor tapes recorded from a patient taking procainamide hydrochloride are shown. The first two Holter tapes were recorded when the plasma levels were 1.4 μg/ml and 3.1 μg/ml, respectively. The last four tapes were recorded when plasma procainamide levels were within therapeutic range (≥ 4.0 μg/ml). The lower half of panel B again shows that frequency tends to be paralleled by grade, although transient periods of advanced grade with low overall frequency did occur. The type of response shown in panel B, in which chronic asymptomatic ventricular ectopic activity was not suppressed or was incompletely suppressed, independent of the plasma levels of antiarrhythmic agents, was the most common response (tables 1 and 2).

Table 1 demonstrates plasma level data and corres-
TABLE 1. Recurrent Prehospital Cardiac Arrest

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis (functional classification)</th>
<th>Follow-up to RCA (Mon)</th>
<th>Plasma level of antiarrhythmic drugs</th>
<th>Mean VEDs/hr on 24-hour tape</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Therapeutic range: PA = 4.0–8.0 µg/ml, QU = 2.3–6.0 µg/ml</td>
<td>Subtherapeutic PA or QU, µg/ml</td>
</tr>
<tr>
<td>JC*</td>
<td>66</td>
<td>M</td>
<td>CAD (class II)</td>
<td>4</td>
<td>PA 7.0, PA 4.5</td>
<td>PA 0.3, 2/hr</td>
</tr>
<tr>
<td>BL</td>
<td>21</td>
<td>M</td>
<td>CM (class I)</td>
<td>18</td>
<td>QU 1.8, QU 1.1</td>
<td>QU 2.4, 2/hr†</td>
</tr>
<tr>
<td>GR</td>
<td>55</td>
<td>M</td>
<td>CAD, VA (class III)</td>
<td>9</td>
<td>PA 7.1, PA 4.0</td>
<td>438/ hr†</td>
</tr>
<tr>
<td>HLI</td>
<td>55</td>
<td>M</td>
<td>AI (class II)</td>
<td>13</td>
<td>PA 6.6, PA 2.2, PA 1.5, PA 0</td>
<td>14/ hr†, 16/ hr†, 29/ hr†, 23/ hr†</td>
</tr>
<tr>
<td>NC</td>
<td>64</td>
<td>M</td>
<td>CAD (class III)</td>
<td>27</td>
<td>PA 4.5, PA 5.0</td>
<td>980/ hr†, 94/ hr†</td>
</tr>
<tr>
<td>DS</td>
<td>60</td>
<td>M</td>
<td>AI, CAD (class III)</td>
<td>20</td>
<td>PA 2.8, PA 1.5, PA 2.1</td>
<td>3/ hr, 26/ hr†, 180/ hr†</td>
</tr>
<tr>
<td>EC*</td>
<td>54</td>
<td>M</td>
<td>CAD (class II)</td>
<td>14</td>
<td>PA 5.5, PA 2.0</td>
<td>1/ hr, 4/ hr†</td>
</tr>
<tr>
<td>JF</td>
<td>48</td>
<td>M</td>
<td>CAD (class II)</td>
<td>4</td>
<td>PA 5.9, PA 2.0</td>
<td>2/ hr, 5/ hr†</td>
</tr>
<tr>
<td>Total</td>
<td>53 = 14</td>
<td>M = 8</td>
<td>F = 0</td>
<td>13.6 ± 8.0</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median = 19/ hr</td>
</tr>
</tbody>
</table>

*Recurrent prehospital cardiac arrest with second successful resuscitation.
†Includes periods of frequent or advanced VEDs.

Abbreviations: CAD = coronary artery disease; CM = cardiomyopathy; VA = ventricular aneurysm; AI = aortic insufficiency; RCA = recurrent cardiac arrest; VED = ventricular ectopic depolarization; PA = procainamide; QU = quinidine.

Corresponding ventricular arrhythmia frequency (mean VEDs/hr during a 24-hour Holter tape) for the patients who had recurrent cardiac arrest with either sudden death or a second successful resuscitation; table 2 provides the corresponding data for the group that did not have recurrent cardiac arrests. There is a striking absence of the expected correlation between mean hourly frequency of VEDs and the corresponding plasma levels. The lack of correlation occurred between the groups as a whole and for individuals within either group. We observed, as expected, consistently low or absent ventricular arrhythmic activity in some patients who maintained stable therapeutic plasma levels of the drugs (patients MK and TK), or an inverse relationship between plasma levels and frequency of ventricular arrhythmias (patient FM), in some patients. However, this dose-response relationship was absent or markedly variable in many patients (NC, MN, JG, GR, DS and MO). Moreover, two patients (BL and EC) who were intermittently subtherapeutic maintained consistently low levels of ectopic activity, while two others had as much or more ectopic activity when they had therapeutic plasma levels than when they did not (GR and NC).

A low mean frequency of VEDs/hr on a 24-hour tape did not necessarily reflect the absence of periods of advanced ectopic activity. Thirty of the 63 tapes (48%) analyzed by the sampling methods used for this study recorded mean frequencies of ventricular ectopic activity defined as infrequent (mean < 10 VEDs/hr). This may be misleading, however, because frequent or complex ectopic activity did not occur uniformly through the 24-hour period, and in 14 of the 30 “infrequent” tapes (47%), there were one or more periods of transient advanced ectopic activity (frequency ≥ 10 beats/min and/or Lown grades 3–5) when the tapes were evaluated by both scanning techniques described in the Methods section. Thus, 75% (47 of 63) of the tapes met criteria for advanced arrhythmias, either transiently or persistently. In con-
Table 2. Long-term Survivors Without Recurrent Cardiac Arrest (>12 Months)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis (functional classification)</th>
<th>Follow-up post-arrest (Mon)</th>
<th>Plasma level of antiarrhythmic drugs</th>
<th>Mean VED on 24-hour tape</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM</td>
<td>69</td>
<td>M</td>
<td>CAD (class II)</td>
<td>32</td>
<td>PA 6.9</td>
<td>125/hr*</td>
</tr>
<tr>
<td>MN</td>
<td>66</td>
<td>M</td>
<td>CAD (class II)</td>
<td>20</td>
<td>PA 4.1</td>
<td>156/hr*</td>
</tr>
<tr>
<td>GO</td>
<td>73</td>
<td>F</td>
<td>CAD, ASH (class III)</td>
<td>32</td>
<td>PA 5.0</td>
<td>20/hr*</td>
</tr>
<tr>
<td>HLa</td>
<td>60</td>
<td>F</td>
<td>CAD (class III)</td>
<td>30</td>
<td>QU 4.0</td>
<td>1/hr</td>
</tr>
<tr>
<td>MK</td>
<td>74</td>
<td>F</td>
<td>CAD, (AMI) (class II)</td>
<td>12</td>
<td>QU 0.0</td>
<td>0/hr</td>
</tr>
<tr>
<td>MO</td>
<td>59</td>
<td>F</td>
<td>CM (class II)</td>
<td>26</td>
<td>QU 3.5</td>
<td>0/hr</td>
</tr>
<tr>
<td>JG</td>
<td>74</td>
<td>M</td>
<td>CAD, (AMI) (class II)</td>
<td>13</td>
<td>QU 1.1</td>
<td>1/hr*</td>
</tr>
<tr>
<td>TK</td>
<td>67</td>
<td>M</td>
<td>CAD (class II)</td>
<td>24</td>
<td>PA 12.2</td>
<td>5/hr*</td>
</tr>
<tr>
<td>Total</td>
<td>68 ± 6</td>
<td>M = 4</td>
<td>F = 4</td>
<td>23.6 ± 8.0</td>
<td>27</td>
<td>5 Mean = 122/hr</td>
</tr>
</tbody>
</table>

*Includes periods of frequent advanced VEDs.

Abbreviations: CAD = coronary artery disease; CM = cardiomyopathy; ASH = asymmetric septal hypertrophy; AMI = acute myocardial infarction; VED = ventricular ectopic depolarization; PA = procainamide; QU = quinidine.

Contrast to the inability to predict periods of advanced grades of arrhythmias when overall frequency of VEDs was low, there was a general relationship between persistent high frequency and persistent advanced grades. In figure 1, the percent of time in which the higher frequencies occurred were closely paralleled by advancing grade, using the Lown classification.

Our interpretation of the data in tables 1 and 2 is based on the assumption that the plasma levels, drawn within the 1-hour period before a scheduled dose, represent uniform antiarrhythmic activity in plasma during the 24-hour period of each Holter tape, regardless of fluctuations between doses. The validity of this assumption, as it relates to VED frequency and complexity, was tested in four subjects in whom serial plasma levels of antiarrhythmic agents (two quinidine and two procainamide) were determined from blood samples obtained during the recording of an 8-hour Holter tape. Figure 2 demonstrates the results from two of these subjects. Panel A was recorded from patient JG and panel B from patient MK (table 2).

Each bar represents the total number of VEDs during a 30-minute interval. The black dots represent plasma procainamide (panel A) or quinidine (panel B) levels at the times indicated, determined in all but one instance 15 minutes into the 30-minute period. The cross-hatched bars indicate complex forms of VEDs (multifocality, bigeminal patterns, salvos or runs of ventricular tachycardia, and/or the R-on-T phenomenon) in addition to frequency, while solid bars indicate the presence of only unifocal forms of VEDs and their frequency. The time and dosage of oral procainamide (panel A) or quinidine (panel B) are indicated by the open arrows. Both panels A and B show that the frequency of VEDs is varying independently of plasma level variations between doses, indicating the absence of predictable changes in the frequency or complexity of chronic ventricular ectopic activity associated with plasma level variations during the equilibrium state of oral therapy. This observation applied to all four patients so tested.

When arrhythmias on the Holter monitor tapes for
the two conditions — therapeutic plasma levels vs subtherapeutic plasma levels — were analyzed for frequency of VEDs/hr, the 37 tapes recorded at the time of documented therapeutic plasma levels had a mean (±SD) of 104 ± 234 VEDs/hr, while the 26 tapes which were recorded at the time of subtherapeutic plasma levels had a mean of 184 ± 566 VEDs/hr. Because of the very skewed distributions, however, median frequency values were determined for the two groups (median 6 VEDs/hr for therapeutic levels and 21 VEDs/hr for subtherapeutic levels), and the significance of the differences tested by the Wilcoxon two-sample rank test. While the means and medians of the frequencies were somewhat higher in the subtherapeutic group, the differences were not statistically significant (0.2 > p > 0.1).

In the recurrent arrest/sudden death group (table 1), all eight patients had subtherapeutic levels at least two of the last four plasma level determinations immediately before recurrent arrest, with only one patient having a therapeutic level on the last determination before recurrent cardiac arrest. Moreover, a total of 21 of the 31 determinations in this group were subtherapeutic, while only 10 were within the therapeutic range. Table 2 demonstrates that, among the eight patients who have not had recurrent cardiac

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**Figure 2.** Plasma levels of antiarrhythmic drugs and corresponding frequencies of ventricular ectopic depolarizations (VEDs) between oral doses. Each bar represents a 30-minute period from a Holter tape, with the figure inserted representing the total number of VEDs. Serial plasma levels were obtained at the times indicated. The cross-hatched bars indicate complex VEDs (Lown grade 3–5), and the solid bars indicate unifocal VEDs. Panel A was recorded from patient JG (procainamide), and panel B from patient MK (quinidine gluconate).
arrest, only two had subtherapeutic antiarrhythmic drug levels during any of the four determinations. In the recurrent cardiac arrest group, the mean frequency of chronic VEDs was 153 ± 314 per hour and the median value was 19 per hour, while the patients who have not had a recurrent arrest had a mean of 122 ± 479 per hour and the median value of 8 per hour. The Wilcoxon two-sample rank test using the median values showed no significant difference ($p > 0.2$). The data in tables 1 and 2 were also collated to identify any influence of repeated measurements on the same individuals on the analyses. The mean ± SD of the data in table 1, after a mean value for VEDs/hr was calculated for each patient, was 148 ± 265 VEDs/hr for the eight entries. For the eight entries in table 2 (no recurrent cardiac arrest), the corresponding values were 119 ± 281 VEDs/hr. There were no significant differences between the groups using this method, nor for the intrapatient median value analyses.

The absence of a predictable dose-response relationship for VEDs is further underscored by our experience with the recurrent cardiac arrest group (table 1). The frequency of VEDs on the 10 tapes recorded when plasma levels of antiarrhythmic drugs were in the therapeutic range tended to be paradoxically higher (mean 301 per hr, median 38 per hr) than the frequency on the 21 tapes recorded when plasma levels were subtherapeutic (mean 82 per hr, median 16 per hr), although these differences did not achieve statistical significance.

Table 3 demonstrates the relationship between plasma levels of antiarrhythmic drugs and recurrent cardiac arrest. None of the six patients who maintained stable therapeutic plasma levels had a recurrent cardiac arrest, while eight of the 10 patients who had variable plasma levels on at least two of the four determinations had a recurrent cardiac arrest or sudden death. Patients who maintained stable therapeutic plasma levels on the four matched tapes analyzed for this report (table 2), after their proper dosages had been determined by dose adjustment (3–5 months), usually had therapeutic plasma levels at the times of their other determinations (43 of 48 (90%) determinations). A test of the significance of the plasma level vs recurrent cardiac arrest data, using the Fisher’s exact test, was significant ($p < 0.01$). While stability of therapeutic plasma levels of antiarrhythmic drugs appears to separate survivors from non-survivors, frequency of VEDs on Holter tapes did not separate these two groups.

### Table 3.

<table>
<thead>
<tr>
<th>Antiarrhythmic plasma levels</th>
<th>Recurrent cardiac arrest</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable, therapeutic</td>
<td></td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Variable, subtherapeutic</td>
<td></td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>

**Discussion**

Chronic ventricular arrhythmias are a risk factor for total cardiac mortality and for sudden cardiac death in clinically overt or subclinical heart disease, and the frequency and classification of VEDs may be helpful in determining relative risk. However, it has not been determined whether suppression of chronic arrhythmias will reduce risk of death. In the one clinical setting of acute ischemic events, antiarrhythmic agents appear both to suppress acute ventricular arrhythmias effectively and reasonably predictably; and, presumably in a related manner, decrease the propensity to potentially lethal ventricular arrhythmias. Many clinicians attempt to suppress chronic ventricular arrhythmias in the setting of heart disease to decrease the risk of triggering a potentially lethal arrhythmia; and we often assume that failure to suppress chronic ventricular arrhythmias in the presence of antiarrhythmic agents may carry a particularly ominous prognosis. Scientific confirmation of the validity of these assumptions is not yet available.

The patient group that we report is a very specific and carefully defined subsegment of the clinical population who have a risk for sudden death defined by the coexistence of chronic ventricular arrhythmias and organic heart disease. The proportion of the total population at risk for sudden cardiac death is very small, but is of value for clinical studies because of an ordinarily high risk over a short period (approximate 30% 1-year mortality on standard, low-dose or no antiarrhythmic therapy). While the long-term survivors and recurrent cardiac arrest groups were not matched for etiology and sex, possibly influencing outcome, they were similar in functional classification, the survivors were unexpectedly older than the recurrent arrest patients, and the extent of coronary artery disease was similar in the two groups.

During our initial studies of prehospital cardiac arrest victims who were successfully resuscitated and discharged from the hospital, more than 75% had chronic asymptomatic complex ventricular arrhythmias which were resistant to various antiarrhythmic drug regimens. Because of the failure of either of the drugs used in the present study or other drugs or drug combinations to suppress predictably the chronic arrhythmias, and the previously observed high recurrent cardiac arrest rate in this population, we changed our therapeutic strategy and began using therapeutic plasma levels of antiarrhythmic drugs as the end point for determining dosages. The protocol was restricted to those membrane-active agents for which plasma level determinations were available to us, unless the chronic asymptomatic arrhythmias became symptomatic (i.e., symptoms of low cardiac output during arrhythmias or sustained ventricular tachycardia). If the latter occurred, the strategy would be abandoned and the patient treated with whatever drug or combination of drugs best controlled symptomatic arrhythmias. To date, the drug protocol appears unpredictable for suppressing...
chronic arrhythmias in these patients, but may be decreasing mortality.

Our inability to achieve predictably stable therapeutic plasma levels in the recurrent cardiac arrest group can be only partially explained. One patient stopped taking his medication, another may have stopped, and one other was advised to stop by a physician. In the other patients with variable levels, however, we cannot explain the low levels. Noncompliance is always uncertain, and metabolic variations such as rapid acetylation of procainamide or the rate of hydroxylation and excretion of quinidine cannot be excluded. Variability of clinical status may further influence absorption, distribution or excretion of the drugs. Measurement of plasma levels of both procainamide and N-acetylprocainamide would have been desirable during the course of these studies, but determination of the N-acetyl metabolite was only recently available to us. Nonetheless, the specific relationship between plasma procainamide levels and the VED frequencies which we are reporting, and the multiple determinations which can be compared with one another in each patient, suggest that the absence of this information may not be critical to interpreting our observations.

Regardless of the reason for unstable or consistently low plasma levels, it appears to be clinically important. The lack of a predictable relationship between the ability to achieve therapeutic levels of antiarrhythmic agents and suppression of chronic asymptomatic complex ventricular arrhythmias was unexpected, although consistent with recent observations regarding variability of ectopic activity on Holter monitor tapes. However, more intriguing is the implication that therapeutic plasma levels of antiarrhythmic agents may protect against potentially lethal arrhythmias, independent of their effectiveness or lack of effectiveness in suppressing advanced chronic arrhythmias. This observation must be interpreted cautiously because of the small number of patients in the analysis and the lack of strict comparability of the groups. The data in table 3 are barely significant, indicating need for a larger population base to validate our initial considerations. A population of such patients large enough to allow comparability will probably require a multicenter study, possibly including patients with similar risk but higher prevalence than prehospital cardiac arrest survivors. Nonetheless, our data do suggest a dissociation between the effect of antiarrhythmic agents on the genesis of chronic ventricular arrhythmias, and the ability of these chronic arrhythmias (probably coexisting with other partially clarified electrophysiological, neural and psychological events) to entrain the ventricular muscle mass into potentially lethal ventricular arrhythmias (symptomatic ventricular tachycardia or ventricular fibrillation). We can only speculate whether this means that antiarrhythmic agents exert their major influence between a “site” of initiation of ventricular ectopic activity and the remaining ventricular muscle, or impair the likelihood of normal muscle and conducting tissue from participating in a potentially lethal arrhythmia. However, suppression of chronic ventricular ectopic activity may not necessarily provide the best measure of effectiveness of antiarrhythmic agents in this clinical setting, and should be evaluated in other settings.

Acknowledgments

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