ALTHOUGH premature ventricular complexes (PVCs) are a risk factor for total cardiac mortality and for sudden cardiac death in patients with chronic heart disease,1-9 no studies to date have determined whether effective suppression of chronic PVCs directly results in a reduction of potentially lethal arrhythmias or sudden death.10 In acute ischemic injury to the myocardium, antiarrhythmic agents suppress various forms of PVCs effectively and predictably; and, presumably related to this, they also decrease the propensity to potentially lethal arrhythmias.11 Even in this setting, however, there is evidence that the relationship between the PVC and potentially lethal arrhythmias is variable.12-14

In chronic heart disease complicated by PVCs, antiarrhythmic agents are generally used in an attempt to suppress PVCs on the assumption that successful suppression will lead to a decreased risk of potentially lethal arrhythmias. Conversely, it is often assumed that failure to suppress chronic ventricular arrhythmias may carry an ominous prognosis. Neither of these assumptions has received scientific confirmation.10,15

In survivors of prehospital cardiac arrest, who are at high risk for recurrent cardiac arrest, antiarrhythmic agents may protect against recurrent cardiac arrest, even without predictable or uniform suppression of chronic PVCs.16,17 The present study was carried out to expand our data base on the relationship between antiarrhythmic agents and acute and chronic ventricular arrhythmias. We compared the concentration-response relationships between plasma levels of antiarrhythmic agents and PVCs in acute myocardial infarction and in stable chronic ischemic heart disease. We also compared effectiveness against acute paroxysms of sustained ventricular tachycardia with effectiveness against the background chronic PVCs in the same patients. The results suggest that the relationship between plasma levels of an antiarrhythmic agent and effectiveness against ventricular arrhythmias varies with the form and the clinical setting of the arrhythmias.

Methods

We studied 18 patients with ventricular arrhythmias. Because of its short half-life, procainamide was the membrane-active antiarrhythmic drug used to determine the dose-response relationship between membrane-active agents and PVCs or sustained ventricular tachycardia. Our observations are based on continuous Holter monitor recordings of patients during the period of observation, and plasma levels of procainamide were determined as described below.

Patient Population

The 18 patients included six who had PVCs during the first 48 hours after the onset of acute myocardial infarction, six who had chronic PVCs in the presence of stable chronic ischemic heart disease, and six who had chronic heart disease with recurrent episodes of symptomatic sustained ventricular tachycardia (table 1). The latter group also had a background of PVCs occurring between the episodes of sustained ventricular
TABLE 1. Relationship of Plasma Procainamide Levels and Suppression of Ventricular Arrhythmias

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Arrhythmia</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Threshold level for prevention of spontaneous RVT</th>
<th>Level for 85% suppression of PVCs</th>
<th>Maximum plasma level tolerated</th>
<th>Premature ventricular complexes/30 minutes</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At minimum plasma level of procainamide</td>
<td>At threshold plasma level for preventing RVT</td>
<td>At maximum plasma levels of procainamide attained</td>
<td></td>
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<tr>
<td>1</td>
<td>72</td>
<td>M</td>
<td>AMI</td>
<td>PVCs</td>
<td>1.3</td>
<td>10.3</td>
<td>5.1</td>
<td>ND</td>
<td>34</td>
<td>0</td>
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<tr>
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<td>AMI</td>
<td>PVCs</td>
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<td>ND</td>
<td>45</td>
<td>1</td>
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<td>AMI</td>
<td>PVCs</td>
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<td>8.4</td>
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<td>8.8</td>
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<td>AMI</td>
<td>PVCs</td>
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<td>7.6</td>
<td>5.4</td>
<td>ND</td>
<td>36</td>
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<tr>
<td>6</td>
<td>68</td>
<td>F</td>
<td>AMI</td>
<td>PVCs</td>
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<td>7.5</td>
<td>4.3</td>
<td>ND</td>
<td>40</td>
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<td></td>
<td>1.5 ± 0.6</td>
<td>8.7 ± 1.1</td>
<td>5.0 ± 0.5</td>
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<td>0.7 ± 0.8</td>
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<td>PVCs</td>
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<td>10.6</td>
<td>9.5</td>
<td>ND</td>
<td>42</td>
<td>3</td>
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<tr>
<td>8</td>
<td>50</td>
<td>M</td>
<td>CIHD</td>
<td>PVCs</td>
<td>1.6</td>
<td>10.3</td>
<td>8.0</td>
<td>ND</td>
<td>35</td>
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<tr>
<td>9</td>
<td>63</td>
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<td>CIHD</td>
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<td>PVCs</td>
<td>1.0</td>
<td>9.1</td>
<td>9.1</td>
<td>ND</td>
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<tr>
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<td>1.3 ± 0.4</td>
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<tr>
<td>13</td>
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<td>CIHD</td>
<td>RVT, PVCs</td>
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<td>7.0</td>
<td>&gt;15.7 (ND)</td>
<td>72</td>
<td>41</td>
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<tr>
<td>14</td>
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<td>CM</td>
<td>RVT, PVCs</td>
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<td>20.8</td>
<td>8.2</td>
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<tr>
<td>15</td>
<td>76</td>
<td>M</td>
<td>CIHD (CM)</td>
<td>RVT, PVCs</td>
<td>0</td>
<td>30.0</td>
<td>14.9</td>
<td>18.8</td>
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<tr>
<td>16</td>
<td>74</td>
<td>M</td>
<td>CIHD</td>
<td>RVT, PVCs</td>
<td>3.2</td>
<td>11.6</td>
<td>5.5</td>
<td>&gt;11.6 (ND)</td>
<td>62</td>
<td>55</td>
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<tr>
<td>17</td>
<td>64</td>
<td>M</td>
<td>CIHD</td>
<td>RVT, PVCs</td>
<td>0</td>
<td>24.5</td>
<td>7.9</td>
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<tr>
<td>18</td>
<td>70</td>
<td>M</td>
<td>CIHD (CM)</td>
<td>RVT, PVCs</td>
<td>5.8</td>
<td>34.0</td>
<td>11.0</td>
<td>16.4</td>
<td>15.0-18.0</td>
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<tr>
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<td>1.9 ± 2.4</td>
<td>22.8 ± 8.5</td>
<td>9.1 ± 3.4</td>
<td>40.3 ± 21.5</td>
<td>2.0 ± 2.1</td>
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</tr>
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</table>

Subtotals are mean ± SD.
Abbreviations: AMI = acute myocardial infarction; CIHD = chronic ischemic heart disease; CM = cardiomyopathy; PVC = premature ventricular complexes; RVT = recurrent ventricular tachycardia; ND = not determined.
tachycardia. Criteria for acute myocardial infarction included a typical clinical history, ECG patterns of transmural or subendocardial infarction, and positive enzymes, including CK-MB. Criteria for chronic ischemic heart disease included a history of angina pectoris, plus either a documented myocardial infarction at least 6 months earlier, a positive treadmill stress test, or coronary atherosclerosis identified by coronary angiography.

None of the acute myocardial infarction patients or chronic ischemic heart disease patients with PVCs had received antiarrhythmic therapy for at least 48 hours before starting procainamide. The studies in the ventricular tachycardia patients were carried out after each patient had been off all antiarrhythmic agents except procainamide for at least 48 hours. The six acute myocardial infarction patients and the six chronic ischemic heart disease patients were hemodynamically stable throughout the period of observation; hemodynamically unstable patients were excluded. The six recurrent ventricular tachycardia patients had stable hemodynamics except during periods of sustained ventricular tachycardia, when blood pressure and cardiac output fell. In three of the six patients, cardiac output and blood pressure also fell at the highest procainamide levels achieved.

Lidocaine is routinely used in our coronary care unit in suspected or documented acute myocardial infarction patients who have any periods of frequent or complex ventricular arrhythmias, so the study was limited to patients who had an average of only one or two PVCs per minute during a 2-hour pretreatment phase of the evaluation. To allow for comparability of the groups, observations on chronic PVC patients (stable ischemic heart disease) were limited to patients who also had only one or two PVCs per minute during the pretreatment phase. Exclusion of high-frequency-PVC patients could have altered dose requirements, but should not alter relationships between acute myocardial infarction patients and chronic ischemic heart disease patients. The ventricular tachycardia patients did have higher frequencies of background PVCs (table 1).

Procainamide Plasma Level Determinations

Procainamide concentrations were measured in blood samples obtained by direct venipuncture or from an indwelling heparin lock after discard of 2 ml of blood. N-acetyl procainamide (NAPA) levels were also determined in five of six recurrent ventricular tachycardia patients. Assays were routinely performed using a commercially available quantitative enzyme immunoassay (Emit-cad, Syva). Selected samples were verified by gas-liquid chromatography (GLC) using a nitrogen-phosphorus detector. The latter technique, adapted from Valentine et al.,14 involves the addition of 0.5 ml of 5% NaOH to 0.5 ml of serum and double extraction in methylene chloride. The samples are dried under nitrogen, reconstituted in 50 µl of ethyl acetate and 4 µl are injected into the GLC. All samples were quantitated in duplicate and quinidine was used as the internal standard for the GLC method.

Study Protocol

Identical protocols were used in the six acute myocardial infarction patients and the six chronic ischemic heart disease patients. A 2-hour baseline Holter monitor recording was obtained before administration of procainamide. The Holter recording was continued while 500 mg of procainamide were given intravenously in 100-mg infusions every 5 minutes for 25 minutes, similar to the dosing regimen suggested by Giardina et al.16 An oral dose of 500 mg of procainamide was given 4½ hours after the initial i.v. infusion. The protocol was performed with patients in the resting state, limited to bed rest and a chair at bedside. No higher levels of activity were permitted.

Plasma levels of procainamide were measured 30 and 60 minutes after the beginning of the initial 100-mg infusion and at 2-hour intervals thereafter. The Holter monitor recording was continued for 4 or more hours after the oral dose was given, and then analyzed in 30-minute segments from the beginning of the pretreatment phase to the end of the recording. The PVCs were counted during each 30-minute segment of the tapes. Bar graphs (fig. 1) were constructed demonstrating the PVC count during each 30-minute period for the 2 hours before procainamide and continuing through the 8 hours after the initiation of the i.v. dosing. Plasma level determinations were plotted on the same graph to compare frequency of PVCs with plasma levels of procainamide (fig. 1).

The clinical state of the patients who had recurrent sustained ventricular tachycardia, in addition to PVCs between episodes of ventricular tachycardia, required a more aggressive treatment protocol on clinical grounds. Each patient had had at least two episodes of sustained ventricular tachycardia daily for at least 3 days before entry into the study. The plasma level determined to be protective against ventricular tachycardia was the minimum level associated with freedom from spontaneous ventricular tachycardia for more than 48 hours. We could not perform multiple titrations in the range of the threshold of effectiveness, so the threshold levels reported represent maximum values. The true threshold levels may have been lower. The protocol for these patients included continuous 24-hour Holter monitoring during the period of observation in each patient. Plasma level fluctuations of procainamide were compared with the grade and frequency of ventricular ectopic activity and/or the occurrence of ventricular tachycardia.17 These studies were also performed in the coronary care unit, with patient activity limited to bed rest and a chair at bedside during the periods of data collection. Larger initial doses of procainamide were used (up to 1000-mg initial infusion), and oral dosing was varied according to clinical indications. The maximum oral dose attempted was 1 g every 4 hours. Plasma levels of procainamide were determined during the interval from 1 hour before an oral dose, through the inter-
dose period, to 2 hours after the subsequent oral dose on sequential days. This protocol was carried out at different dosages, which provided data on the relationship between various forms of ventricular arrhythmias and plasma levels of antiarrhythmic agents (see Results section).

**Collection of Data and Statistical Analysis**

The relationship between plasma levels of procainamide and frequency of PVCs was determined by counting the PVCs during the 30-minute period closest to when the blood was drawn. When possible, the PVC count included the 15 minutes before and 15 minutes after blood was drawn. For patients in the acute myocardial infarction and chronic ischemic heart disease groups, who were being studied solely for the relationship between PVCs and plasma levels of procainamide, we plotted the concentration-response data from the data points beginning with the determination 5 minutes after completion of the intravenous dosing protocol, and then subsequent determinations as plasma levels were changing rapidly, as shown in figure 1. The six data points from each of the six patients in the acute myocardial infarction group and in the chronic ischemic heart disease group were each plotted as individual patient curves and also on a scattergram (36 points per group), and best-fit regression analysis was performed. For the purpose of data analysis, PVC suppression resulting in 4 PVCs/hour or less, or more than 95% suppression, was considered equivalent to complete suppression.

In the group with recurrent ventricular tachycardia in the presence of chronic heart disease, all patients had been on procainamide at some time before the study; but three of the six had had a long enough dosing interval before initiation of our studies to give a zero value of plasma procainamide level. The analysis of PVC frequency was carried out by the same techniques described for the other two groups of patients, but the dosages and plasma levels of procainamide were significantly higher (see Results section and table 1). In addition to best-fit regression analysis relating PVC frequency to plasma levels of procainamide, patients in this category were also analyzed for the lowest plasma level of procainamide that provided complete protection against paroxysms of ventricular tachycardia, the degree of suppression of PVCs at the plasma levels that protected against ventricular tachycardia, and the plasma level required to achieve 85% suppression of PVCs.
The statistical analyses carried out for significance of differences between the three groups and matched pairs are outlined in Table 2. In regard to statistical tests among the three groups, three two-sample t tests were performed on each data set using unpoled variance estimates and adjusted degrees of freedom to account for the difference in variances among the groups. To preserve an overall experimentwise error rate of 0.05, each test was made at the 0.017 level of significance in accordance with the Bonferroni procedure.

Correlation coefficients were calculated for each patient and for groups of patients for the data relating PVC frequency to plasma levels of procainamide. The significance of differences between acute and chronic ischemic heart disease groups was calculated by an analysis of covariance. For data in which comparisons of functions in individual patients were possible (e.g., threshold level for prevention of spontaneous ventricular tachycardia vs level for 85% suppression of PVCs), a matched-pair t test was performed.

Results

Concentration-Response Relationships In Acute Myocardial Infarction and Chronic Ischemic Heart Disease

Our observations demonstrate that PVCs in the acute phase of myocardial necrosis are more effectively and predictably suppressed at lower plasma levels of procainamide than are PVCs in the setting of chronic stable ischemic heart disease (Fig. 1). In the acute myocardial infarction patient, nearly complete suppression of PVCs occurred after the i.v. infusion, and PVCs returned as plasma levels fell until after the oral dose was given and absorbed. The lag between the time of the oral dose and subsequent complete suppression is presumably accounted for by the time required for absorption of procainamide. In a chronic ischemic heart disease patient with PVCs who achieved comparable plasma levels during the intravenous and oral dosing and had a comparable baseline frequency of PVCs, there was a tendency for suppression of PVCs in the presence of procainamide, but the degree and uniformity of suppression at the plasma levels achieved were less than those observed in the acute myocardial infarction patient.

Figure 2 shows cumulative data recorded from six acute myocardial infarction patients and six chronic ischemic heart disease patients. In each patient, six data points were recorded. Six plasma levels of procainamide were measured after completion of the i.v. dosing schedule (see Methods section), providing data points as plasma levels were falling from a peak after the completion of the i.v. dosing, and as plasma levels were rising again after the oral dose. Each plasma level was matched to the total number of PVCs occurring during the closest 30-minute period. The cumulative data were subjected to a best-fit regression analysis, and the linear regressions shown in figure 2 resulted. In addition, covariance analysis of the data points for each of the six patients in each group demonstrated the absence of significant differences between the six slopes in each group (i.e., acute myocardial infarction and chronic ischemic heart disease).

The relationship between plasma levels of procainamide and frequency of PVCs was different for the acute myocardial infarction patients and the chronic ischemic heart disease patients (Fig. 2). In the acute myocardial infarction patients, no point >6.2 µg/ml

Table 2. Statistical Analysis

<table>
<thead>
<tr>
<th>Plasma levels of procainamide</th>
<th>Frequency of PVCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum plasma levels</td>
<td>PVCs/30 minutes at minimum plasma levels</td>
</tr>
<tr>
<td>AMI vs CIHD — NS†</td>
<td>AMI vs CIHD — NS†</td>
</tr>
<tr>
<td>AMI vs VT — NS†</td>
<td>AMI vs VT — NS†</td>
</tr>
<tr>
<td>CIHD vs VT — NS†</td>
<td>CIHD vs VT — NS†</td>
</tr>
<tr>
<td>Maximum plasma levels</td>
<td>PVCs/30 minutes at maximum plasma levels</td>
</tr>
<tr>
<td>AMI vs CIHD — p = NS†</td>
<td>AMI vs CIHD — NS†</td>
</tr>
<tr>
<td>AMI vs VT — p &lt; 0.05†</td>
<td>AMI vs VT — NS†</td>
</tr>
<tr>
<td>CIHD vs VT — p &lt; 0.05†</td>
<td>CIHD vs VT — NS†</td>
</tr>
<tr>
<td>Plasma level for 85% suppression of PVCs</td>
<td>PVCs/30 minutes at minimum vs maximum plasma levels</td>
</tr>
<tr>
<td>AMI vs CIHD — p &lt; 0.05†</td>
<td>AMI — p &lt; 0.001*</td>
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<tr>
<td>AMI vs VT — p &lt; 0.05†</td>
<td>CIHD — p &lt; 0.001*</td>
</tr>
<tr>
<td>CIHD vs VT — p &lt; 0.05†</td>
<td>VT — p &lt; 0.01*</td>
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<td>Plasma levels for prevention of VT vs 85% suppression of PVCs p &lt; 0.01*</td>
<td>PVCs/30 minutes in VT group</td>
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<tr>
<td>Minimum plasma level vs VT threshold plasma level — p &lt; 0.01*</td>
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<td>VT threshold plasma level vs maximum plasma level — p &lt; 0.01*</td>
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<tr>
<td>Minimum plasma level vs maximum plasma level — p &lt; 0.01*</td>
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</table>

*Matched-pair t test.
†Two-sample t test with significance level set at α/3 by Bonferroni procedure. See text.
Abbreviations: PVC = premature ventricular complex; for other abbreviations, see Table 1.
ACUTE MYOCARDIAL INFARCTION

\[ y = 46.0 - 8.7x \]
\[ r = 0.81 \]

CHRONIC PVCs

\[ y = 46.1 - 4.3x \]
\[ r = 0.92 \]

Figure 2. Comparison of effectiveness of procainamide in suppressing premature ventricular complexes (PVCs) in acute myocardial infarction and in chronic ischemic heart disease. (top) Plasma levels of procainamide and total PVC count on 30-minute segments of a Holter monitor tape in six acute myocardial infarction patients. (bottom) Similar data for six patients with stable chronic ischemic heart disease. The frequency of PVCs at minimum plasma levels of procainamide is similar in both groups of patients (y-intercepts = 46.0 and 46.1 PVCs/30 minutes, respectively). However, the slopes are significantly different in the two patient groups (p < 0.02), suggesting that PVCs in acute myocardial infarction are more sensitive to suppression by procainamide at comparable plasma levels than are PVCs in the setting of chronic ischemic heart disease. Linear regressions were calculated for all points producing 95% or less PVC suppression. The data for each of the six patients in each group are indicated by the six symbols in the top panel.

was associated with less than 95% suppression, or more than 4 PVCs/hour, and most were 0 or 1 per 30 minutes. Linear regressions using data points at cutoffs ≤4 µg/ml, ≤5 µg/ml, or ≤6 µg/ml were not significantly different. The slope of the linear regression is different from that in the acute myocardial infarction patients (fig. 2). It is clear that the relation between PVC count and procainamide level is not linear for acute myocardial infarction patients over the entire range of decreasing procainamide levels. However, in the range of 0.8–5.0 µg/ml of procainamide, the regression is linear for both the acute and chronic groups. Covariance analysis was used to compare the slopes for the two groups over this range, and they were significantly different (p < 0.02).

Table 1 shows comparisons of the effect of procainamide on PVCs in acute myocardial infarction patients and in chronic ischemic heart disease patients at various plasma levels. The mean minimum and mean maximum plasma levels attained during the dosing interval in the two groups were not different, nor was the frequency of PVCs different in the two groups at minimum plasma levels measured in the time interval between the intravenous and oral doses (table 2). The frequencies at maximum plasma levels achieved were 0.7 ± 0.8 PVCs/30 minutes in the acute myocardial infarction group and 6.3 ± 6.0 PVCs/30 minutes in the chronic ischemic heart disease group (table 1) (NS). More important, however, the plasma level of procainamide required for at least 85% suppression of PVCs, derived from linear regressions for each patient, and then averaged for the group, was 5.0 ± 0.5 µg/ml for the acute myocardial infarction patients and 9.3 ± 0.7 µg/ml for the chronic ischemic heart disease patients (p < 0.05). We did not try to determine the maximum plasma level tolerated in these two groups.

Recurrent Sustained Ventricular Tachycardia and Chronic PVCs

In the six patients who had recurrent episodes of symptomatic sustained ventricular tachycardia, a background of PVCs was present at a mean frequency of 63 ± 27 PVCs/30 minutes at minimum plasma levels of procainamide (table 1). All six patients had been referred because of recurrent sustained ventricular tachycardia, and had the following characteristics: (1) chronic ventricular ectopic activity in the form of frequent and/or complex PVCs as a background between episodes of sustained ventricular tachycardia; (2) ventricular tachycardia controllable by procainamide; and (3) sufficient data available to compare the effects of procainamide on ventricular tachycardia and chronic PVCs in each patient. The threshold plasma level for prevention of ventricular tachycardia and for 85% suppression of complex or frequent PVCs in the six patients in this category are shown in table 1. The mean plasma level required for prevention of ventricular tachycardia was 9.1 ± 3.4 µg/ml (range 5.5–14.9 µg/ml). In contrast, the mean plasma level required to suppress 85% of chronic PVCs in these six patients was 14.9 ± 3.8 µg/ml (range 9.3–18.8 µg/ml). The differences between plasma levels required to prevent ventricular tachycardia and those required to suppress 85% of the PVCs were statistically significant (p < 0.01) by a matched-pair t test (table 2). To achieve trough levels in the range required for more than 85% PVC suppression, dosages causing peak levels of 13.7–34.0 µg/ml were required (table 1). Four of the six patients (nos. 14, 15, 16 and 18) could not tolerate the peak plasma levels required to suppress chronic PVCs, but all six could tolerate the plasma levels required to prevent ventricular tachycardia. Finally, serial NAPA levels were measured in five of the six patients in this group (nos. 13, 14, 15, 16 and 18). The interdose fluctuations of NAPA were much lower than those of the parent compound (mean fluctuation 2.7 ± 2.1 µg/ml), and neither the fluctuation nor the absolute levels of NAPA correlated as well with clinical effectiveness.
against ventricular tachycardia or PVCs as did levels and variations of the parent compound.

Electrocardiographic rhythm strips, with corresponding plasma levels of procainamide, in one of the ventricular tachycardia patients (patient 18), are shown in figure 3. At a procainamide plasma level of 7.0 µg/ml, the patient had an episode of ventricular tachycardia that was accompanied by a fall in blood pressure. At plasma levels of 10.7–14.2 µg/ml, various forms of advanced ventricular ectopic activity occurred, but the patient remained free of sustained ventricular tachycardia. At plasma levels of 17.9 and 19.8 µg/ml, the patient had occasional unifocal PVCs, no advanced ventricular ectopic activity, and no ventricular tachycardia. However, he could not tolerate these highest levels of procainamide because of myocardial depression and hypotension.

Figure 4 shows rhythm strips and corresponding procainamide plasma levels recorded from patient 15, who had a programmable permanent transvenous pacemaker implanted before referral to our institution. All antiarrhythmic treatment had been stopped because of “intolerance.” When the patient was receiving no procainamide, he had frequent episodes of sustained ventricular tachycardia at a cycle length of 255 msec, associated with a fall in blood pressure and cardiac output. As his plasma level of procainamide was increased, the rate of ventricular tachycardia slowed and was finally suppressed at a plasma level of 14.9 µg/ml. At this point he reverted to a paced rhythm. Figure 5 demonstrates the relationship between dosage of procainamide, interdose fluctuation of plasma levels, and suppression of ventricular tachycardia in this patient. A level of 14.9 µg/ml was required to effectively suppress ventricular tachycardia, and this level was adequately tolerated. However, he continued to have advanced forms of PVCs that could not be suppressed below a level of 18.8 µg/ml. The dose of procainamide required to achieve this trough level was 750 mg every 4 hours, which resulted in peak levels of 24–30 µg/ml. This peak level was not tolerated because of myocardial depression. At 625 mg every 4 hours, acceptable peak
levels and effective trough levels were obtained, even though the patient continued to have frequent PVCs.

Thirty-four data points relating PVCs, recurrent sustained ventricular tachycardia, and procainamide plasma levels in patient 14 are plotted in figure 6. The 34 points were recorded over a 5-day period of treatment. Plasma levels were determined half-way through a 30-minute recording period, giving a PVC count during 15 minutes before and after plasma level determinations. There was a tendency for a decrease in frequency of PVCs at plasma levels of procainamide < 15.0 µg/ml, but the degree of suppression was limited. Best-fit regression analysis in the range from 2–15 µg/ml was linear (y = 96.9 – 3.24x; r = 0.86). In the range from 15.0–19.0 µg/ml, the data points departed abruptly from the linear regression line, suggesting a threshold effect. No nonlinear analysis provided a better fit to all of the data points. At plasma levels of procainamide < 8.2 µg/ml, the patient had recurrent episodes of sustained ventricular tachycardia; and in excess of this plasma level, there were no episodes of sustained ventricular tachycardia. Thus, the data suggest that procainamide has two thresholds of effectiveness: a threshold for prevention of ventricular tachycardia and a threshold for suppression of PVCs. The data in the other five patients were qualitatively similar, although the range of threshold levels was wide (table 1). For the group of six patients, the mean frequency of PVCs at minimum plasma levels of procainamide measured was 63.0 ± 27.0 PVCs/30 minutes. At the mean plasma level required to prevent ventricular tachycardia (i.e., 9.1 ± 3.4 µg/ml), the mean frequency of PVCs was reduced by only 36%, to 40.3 ± 21.5 PVCs/30 minutes (range –11.3% to –63.0%). However, 85% suppression occurred at 14.9 ± 3.8 µg/ml, and a mean of >97% suppression was achieved at maximum plasma levels attained (i.e., 20.8 ± 8.5 µg/ml). Thus, suppression of PVCs was achievable, but only at plasma levels of procainamide well in excess of those required to prevent spontaneous ventricular tachycardia. Tolerance was a major problem at these higher levels.
Discussion

The data from these highly selected groups of patients suggest that the relationship between plasma levels of procainamide and the effect of the drug on various forms of ventricular arrhythmias may depend on the nature of the arrhythmia and the clinical setting. Although few patients were included in our initial observations, PVCs in acute ischemic events appear to have a different concentration-response relationship to procainamide than do similar PVCs in stable chronic ischemic heart disease. In the study by Giardina et al.,19 from which we derived the design of the i.v. dosing program in our studies, the authors did not design their study to test for differences in the relationship between plasma concentration required for abolishing arrhythmias in acute myocardial infarction vs other clinical settings. However, analysis of their data suggests that procainamide may be more effective at lower plasma levels in the acute myocardial infarction patients than in the remainder of their patients. Our study had been designed to look specifically for any such differences.

Our data also demonstrate that background PVCs in patients with a propensity to sustained ventricular tachycardia respond differently to varying procainamide levels than do the episodes of ventricular tachycardia themselves. In the ventricular tachycardia patients, there appear to be two thresholds of antiarrhythmic effectiveness, one for the prevention of paroxysms of sustained ventricular tachycardia and a second for suppression of background PVCs. The data suggest that it may not be necessary to suppress chronic PVCs, which tend to be more resistant to antiarrhythmic therapy, in order to protect against paroxysmal sustained ventricular tachycardia in patients subject to chronic recurrent ventricular tachycardia. The average percent suppression achieved at plasma levels sufficient to protect against ventricular tachycardia was only -36%, with a range of -11.3% to -63.0% in the individual patients. These observations, however, should not be extrapolated to ventricular tachycardia occurring in acute myocardial infarction, which we did not study.

Ventricular arrhythmias in the two "acute" clinical settings, acute myocardial infarction with PVCs and acute paroxysms of sustained ventricular tachycardia, appear to be more sensitive to the effects of procainamide than do the two "chronic" settings, PVCs in the setting of chronic stable ischemic heart disease and the background PVCs in patients prone to paroxysms of sustained ventricular tachycardia. A therapeutic effect against PVCs can be achieved in both chronic settings, but only at higher plasma levels. Moreover, the necessity for achieving such levels in order to protect against more serious arrhythmias is questionable by our observations. In another study of patients with ventricular arrhythmias associated with obstructive cardiomyopathy, Canedo et al.20 also observed that potentially lethal ventricular arrhythmias may be suppressed by propranolol, without necessarily suppressing PVCs.

Procainamide was selected for these studies for several reasons. First, procainamide is a safe and effective alternative to lidocaine for PVC suppression in acute ischemia;19, 21 and, in our experience, it can be an effective drug for treating potentially lethal arrhythmias,13 particularly under carefully controlled circumstances. Second, its short half-life, which is a clinical disadvantage, makes it the best drug available for this type of study. It can be used intravenously or orally, and blood levels may fluctuate widely over short periods of time, so we could achieve a broad range of data points using standard clinical dosing protocols in the three patient groups. Reports of hysteresis between plasma concentration and procainamide effects,22 and of differences in peak concentrations in normal vs experimentally acute ischemic tissue,28 must be considered in interpreting our data. The hysteresis problem in relating suppression of PVCs to plasma procainamide levels is theoretically of concern, but the data reported by Galeazzi et al.22 included only observations on ΔQT intervals. No arrhythmia data were available. In regard to heterogeneous distribution during experimental acute ischemia,28 the differences had become very small by 25 minutes after bolus. Furthermore, the relationship between tissue concentration gradients and antiarrhythmic effect was not studied.

Our observations are based on studies using only procainamide, but major emphasis must remain on principles of management derived from these studies, rather than the value of this single antiarrhythmic agent. Other antiarrhythmic agents and experimental drugs under study could be equally effective, and they could also demonstrate different thresholds for preventing spontaneous recurrent sustained ventricular tachycardia and suppressing PVCs. These assumptions remain to be tested.

Our six patients in the ventricular tachycardia group had a lower threshold for prevention of ventricular tachycardia than for suppression of chronic PVCs, but it is conceivable that the threshold relationships could be reversed. Herling et al.24 observed some instances in which chronic PVCs were suppressed in patients who continued to have episodes of ventricular tachycardia (inducible or spontaneous). Based on our experience, however, the latter is less common than the relationship in which lower plasma levels are required to suppress ventricular tachycardia than chronic PVCs.

Programmed stimulation studies, carried out before and after therapeutic interventions in patients who have inducible sustained ventricular tachycardia, appear to be of value in predicting effectiveness of a drug and identifying therapeutic levels during long-term follow-up.26-28 Our data may support the value of this approach in managing patients with potentially life-threatening arrhythmias. Suppression of PVCs did not parallel prevention of spontaneous ventricular tachycardia in our patients, with PVCs persisting at plasma levels at which sustained symptomatic ventricular tachycardia was preventable, so the use of PVC suppression as an end point of therapy appears in-
adequate. In addition, the patients in this study presented with sufficiently frequent episodes of spontaneous ventricular tachycardia to provide a satisfactory end point by monitoring alone. However, many patients who have less frequent episodes of recurrent sustained ventricular tachycardia require an objective measure of effectiveness of therapy other than monitoring or direct clinical observation. PVC suppression does not appear to provide this measure of effectiveness consistently and predictably, so we believe that the case made by the advocates of invasive methods for determining drug effectiveness in selected patients may be supported by our data.

Our data are consistent with our previous reports in survivors of prehospital cardiac arrest. In those studies\(^6\), we observed a dissociation between the effect of antiarrhythmic agents on PVCs and on prevention of recurrent prehospital cardiac arrest (i.e., antiarrhythmic effect vs antibrillarrrhythmic effect). The present data, in a more controlled clinical setting, support our hypothesis that potentially lethal arrhythmias have a different relationship to plasma levels of antiarrhythmic agents than do chronic PVCs. An analogy can be made in which drug effect on a "trigger" event (i.e., the PVC) may be quantitatively or qualitatively different from the effect on a potential "circuit" (i.e., ventricular tachycardia or ventricular tachycardia leading to ventricular fibrillation). Further, the pharmacologic dissociation between the two forms of ventricular arrhythmias may reflect an electrophysiologic difference that has not been defined.

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References

Clinical Pharmacology and Antiarrhythmic Efficacy of Encainide in Patients with Chronic Ventricular Arrhythmias

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SUMMARY We determined the pharmacokinetics, efficacy and therapeutic plasma concentration of encainide, a new antiarrhythmic drug that affects His-Purkinje conduction but not ventricular refractoriness. Nine patients with frequent and complex premature ventricular complexes were studied in a 3-day double-blind protocol. Each day, each patient received 75 mg of i.v. or oral encainide or placebo. Frequent blood samples for encainide plasma concentration determination and continuous ambulatory ECGs were obtained. There was a marked intersubject variation in bioavailability (mean 42 ± 24%, range 7.4-82%), clearance (13.2 ± 5.6 ml/min/kg), and half-life (3.4 ± 1.7 hours i.v., 2.5 ± 0.8 hours oral). Eight of nine patients had more than 90% suppression of premature ventricular complexes for 3-36 hours. Minimal antiarrhythmic plasma concentration was higher (39 ± 54 ng/ml, range 3.5-170 ng/ml) after i.v. dosing than after oral dosing (14 ± 16 ng/ml, range 1.5-48 ng/ml), suggesting an active metabolite after oral dosing in many patients. Minimal side effects were seen despite high peak plasma concentrations (range 794-1556 ng/ml i.v., 36-495 ng/ml oral). The minimal ratio of toxic to therapeutic plasma concentration ranged from 4.3-326 (median 23) after oral dosing. Antiarrhythmic action was associated with an 11-44% widening of the QRS complex that was not associated with other adverse effects. We conclude that encainide effectively suppresses ventricular arrhythmias. Despite a variable bioavailability, high clearance and short half-life, its wide ratio of toxic to therapeutic concentration and probable active metabolite permit a long duration of action, which should allow a reasonable dose schedule in most patients during chronic oral dosing.

ENCAINIDE (4-methoxy-2-[2-(1-methyl-2-piperidyl)ethyl] benzanilide hydrochloride) is a new compound with antiarrhythmic activity. In a canine Purkinje fiber preparation, the drug depresses the rate of rise of phase 0 of the action potential, shortens the action potential duration without significantly changing the effective refractory period and decreases the rate of spontaneous phase 4 depolarization. Encainide abolishes aconitine-induced atrial fibrillation and ventricular arrhythmias induced by digitalis and coronary artery ligation in a variety of animal species. The drug also elevates the ventricular fibrillation threshold in the dog. In a closed-chest anesthetized dog model, encainide caused a plasma-concentration-dependent prolongation of the HV interval and QRS complex. The drug had no effect on other electrophysiologic measurements, including ventricular refractoriness. In man, i.v. encainide in doses of 0.6 and 0.9 mg/kg over 15 minutes resulted in a 31% prolongation of the HV interval and a 17% increase of QRS duration associated with peak plasma concentrations of 110-1150 ng/ml.

Encainide is of value for treating some patients with refractory life-threatening recurrent ventricular tachycardia and fibrillation and effectively suppressed ventricular ectopic beats in a fixed-dose comparison with quinidine. Kesteloot and Stroobandt found that single i.v. doses of encainide abolished ventricular ectopic beats in 31 of 33 patients, and Roden et al. reported complete suppression of ventricular arrhythmias in 10 of 11 patients after oral dosing. The present study was performed to provide further data about the efficacy and clinical pharmacology of encainide.

Methods

Nine patients (six males and three females) with frequent and complex ventricular ectopy were studied. The average age of the patients was 60.5 ± 7.6 years (range 49-77 years). The clinical characteristics of the patients are listed in table 1.

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