Comparison of Individual and Combined Effects of Procainamide and Amiodarone in Patients With Sustained Ventricular Tachyarrhythmias

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To compare the individual and combined electrophysiological effects of amiodarone and procainamide, 35 patients with sustained ventricular arrhythmias underwent programmed stimulation in the control state, after procainamide (mean concentration, 8.7±2.8 μg/ml), after 13±2 days of amiodarone (1,400 mg/day×7 days, then 400 mg/day), and after amiodarone with procainamide (mean procainamide concentration, 7.8±2.2 μg/ml). Sustained ventricular tachycardia (VT) was inducible in all 35 patients during treatment with procainamide alone and with amiodarone alone. Procainamide and amiodarone similarly increased the VT cycle length (+68 vs. +61 msec), the corrected QT interval (+63 vs. +49 msec), and the ventricular effective refractory period measured at paced cycle lengths of 600–550 msec (+23 vs. +21 msec) and 400 msec (+25 vs. +23 msec). Procainamide had a more pronounced effect on QRS duration than amiodarone during sinus rhythm (+18 vs. +8 msec, p<0.01) and during paced cycle lengths of 600–550 msec (+32 vs. +23 msec, p<0.01) and 400 msec (+37 vs. +28 msec, p<0.1) but a similar effect on the QRS duration during VT (+32 vs. +29 msec). During combination therapy, VT initiation was prevented in only two (6%) patients. The combination therapy produced a greater increase (p<0.001) than individual therapy in all the electrophysiological intervals assessed, with the exception of the sinus cycle length. On each drug regimen, a cycle length-dependent increase (p<0.05) in paced QRS duration was noted (400 more than 600–550 msec). The sum of the electrophysiological changes in conduction and refractoriness of the individual agents correlated with the change attributable to combination drug therapy (r=0.58–0.81, p<0.01). The relation of the sum of the change in the cycle length of morphologically similar VT after each agent alone to the change with the combination therapy could be expressed by the regression equation of combined effect = 0.67×sum of the individual effects + 40 msec, with r=0.85, p<0.001. In summary, with the dosing regimen described, 1) procainamide and amiodarone have similar effects on the cycle length of morphologically similar VT and on indexes of refractoriness, but procainamide has a greater effect on paced QRS duration; 2) amiodarone with procainamide does not affect the ability to initiate VT; and 3) knowledge of the change in cycle length of VT after treatment with the individual agents alone permits estimation of the cycle length of morphologically similar VT on the combination therapy. (Circulation 1988;78:583–591)

The use of combination antiarrhythmic agent therapy in the management of serious ventricular arrhythmias is becoming more common.1–5 Combination therapy may provide more effective arrhythmia control than single-agent therapy.1–5 While the use of combination therapy may increase the risk for adverse reactions,6,7 a

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lower dosing regimen for each agent may limit side effects of considered agents but still afford arrhythmia control.\textsuperscript{2,3} Because the dosing regimens used with combination therapy are usually different from those used when therapy with the individual agents is used, it is not possible to deduce from previous studies how individual agents may interact to promote or inhibit their antiarrhythmic effects.\textsuperscript{1–5} Although the electrophysiological effects of both amiodarone and procainamide have been described,\textsuperscript{8–14} the comparative effects of each agent in the same patient have been studied only in a limited fashion.\textsuperscript{15} In addition, little is known about the effects of the combination of amiodarone and procainamide on basic electrophysiological parameters and inducibility of sustained ventricular arrhythmias. The purpose of this study was to compare the electrophysiological effects of amiodarone and procainamide used alone and in combination in patients with refractory sustained ventricular tachyarrhythmias.

**Patients and Methods**

**Patient Population**

We studied 33 men and two women who ranged in age from 34 to 78 years with a mean age of 60 years. Thirty-three patients had documented coronary artery disease with previous myocardial infarction, and two patients had idiopathic dilated cardiomyopathies. Twenty-five of the 35 patients presented with a cardiac arrest, and 10 patients presented with symptomatic but hemodynamically tolerated sustained ventricular tachycardia. All patients had inducible sustained ventricular tachycardia (33 patients) or ventricular fibrillation (two patients) in the baseline state, after procainamide alone (all ventricular tachycardia), and after amiodarone alone (all ventricular tachycardia). Seventeen of the 35 patients have been reported previously in a study that assessed the clinical outcome of amiodarone versus amiodarone plus procainamide or quinidine as chronic therapy for rapid ventricular tachycardia.\textsuperscript{6}

**Antiarrhythmic Agent Administration**

All patients underwent programmed stimulation in the baseline state after all antiarrhythmic agents had been stopped for at least five drug half-lives. The patients then received procainamide intravenously at a loading dose of 15 mg/kg infused at a rate of 50 mg/min followed by a continuous infusion of 4–8 mg/min during repeat programmed stimulation. The mean serum procainamide concentration at the time recordings were made was 8.7 ± 2.1 μg/ml (range, 4.9–14.0 μg/ml). The patients were then studied during therapy with amiodarone alone. Amiodarone was administered orally as a loading dose of 1,400 mg/day × 7 days followed by an oral regimen of 400 mg daily. The mean duration of therapy at the time of electrophysiological testing was 13 ± 2 days (range, 9–19 days). The mean serum amiodarone and desethyl amiodarone concentrations measured in 17 of the patients equaled 1.2 ± 0.4 and 0.7 ± 0.2 μg/ml, respectively. Finally, immediately after stimulation during therapy with amiodarone, procainamide was added to the amiodarone, and stimulation was repeated. The same dosing regimen was used as that noted when procainamide was administered alone. In three patients, the procainamide loading dose of 50 mg/kg was not tolerated during amiodarone therapy because of the development of transient hypotension or severe nausea, and repeat programmed stimulation was undertaken at a dose that was 75–90% that achieved when procainamide was administered in the absence of amiodarone. The mean procainamide serum concentration during amiodarone therapy was 7.8 ± 2.2 μg/ml (range, 4.3–12.4 μg/ml), a level that did not differ significantly from that when the procainamide was administered alone.

**Stimulation Protocol**

All patients underwent the same stimulation protocol on each drug regimen. Our stimulation protocol has been reported.\textsuperscript{16} Briefly, single, double, and triple ventricular extrastimuli were introduced during paced cycle lengths of 600 (or 550) and 400 msec from the right ventricular apex and the right ventricular outflow tract. All stimulation was performed at twice-diastolic threshold with a 1-msec pulse width. A custom-designed programmable stimulator (Bloom Associates) was used for all stimulation. Recordings were made with a 16-channel physiological recorder (VR 16, Electronics for Medicine), and real-time records were obtained with an ink-jet recorder (Siemens Elema Mingograph) at paper speeds of 100–250 mm/sec. The electrophysiological parameters assessed at each study are shown in Table 1. The endpoints for programmed stimulation included the reproducible initiation of sustained

<table>
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<tr>
<th>TABLE 1. Electrophysiological Parameters Assessed in the Control State and on Each Drug Regimen</th>
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<td>Sinus cycle length</td>
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<tr>
<td>QRS duration—sinus rhythm</td>
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<td>QT corrected—sinus rhythm</td>
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<tr>
<td>QRS duration—RVA 600–550*</td>
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<td>VERP—RVA 600–550*</td>
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<td>VERP—RVA 400†</td>
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<td>VT-VF inducibility</td>
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<td>VT cycle length</td>
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<td>VT morphology</td>
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<td>QRS duration—during VT</td>
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<td>VERP, ventricular effective refractory period;VF, ventricular fibrillation;VT, ventricular tachycardia.</td>
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<tr>
<td>*Determined during right ventricular apical pacing at cycle lengths of 600 or 550 msec.</td>
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<td>†Determined during right ventricular apical pacing at cycle lengths of 400 msec.</td>
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Sustained ventricular tachycardia—Tachycardia lasting more than 30 seconds or requiring termination before that time because of hemodynamic collapse.

QRS duration—sinus rhythm—The interval measured from the beginning to the end of the QRS complex simultaneously recorded in leads I, aVF, and VI.

QRS duration during pacing—The interval measured from the stimulus artifact to the end of the QRS complex simultaneously recorded in leads I, aVF, and VI. Measurements were made in triplicate on the eighth paced complex of the drive cycle length.

QTc interval—The interval from the onset of the QRS complex to the end of the T wave recorded in leads I, aVF, and VI during sinus rhythm. The QT interval was corrected for heart rate with Bazett’s formula.

QRS during ventricular tachycardia—The interval determined from the onset to the end of the QRS complex recorded in leads I, aVF, and VI during a stable monomorphic ventricular tachycardia.

Ventricular effective refractory period—The longest coupling interval of the ventricular extrastimulus that failed to evoke a ventricular response. The extrastimulus was introduced after an eight-beat drive train. The coupling interval of the extrastimulus was introduced in 10-msec decrements.

Morphologically similar ventricular tachycardias—Tachycardia displaying the same bundle branch block morphology pattern and a frontal plane axis less than 90° divergent based on analysis of the 12-lead electrocardiogram obtained after arrhythmia induction.

Table of Definitions

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<tr>
<td>Sustained ventricular tachycardia</td>
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<td>QRS duration—sinus rhythm</td>
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<td>QRS duration during pacing</td>
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<td>Ventricular effective refractory period</td>
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<td>Morphologically similar ventricular tachycardias</td>
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uniform morphology ventricular tachycardia or ventricular fibrillation or completion of the stimulation protocol. In eight patients, reproducible initiation of the sustained ventricular arrhythmias was not attempted during at least one study period because of prompt hemodynamic embarrassment with arrhythmia induction, which resulted in the need for immediate cardioversion.

Data Analysis

All intervals were routinely measured at paper speeds of 200–250 mm/sec. Recordings obtained at slower paper speeds (100 mm/sec) were used to assist in identifying onset and offset of measured intervals with well-defined deviations from the baseline noted in leads I, aVF, and VI. Recordings made at 100 mm/sec were used to help identify the onset and offset of the QRS complex. Interobserver and intraobserver variability of QRS, QTc, and cycle length measurements were less than or equal to 5 msec in 95% of intervals. QRS durations or refractory period determinations could not be made at all cycle lengths because of the induction of sustained arrhythmias with a single extrastimulus or because the sinus cycle length became shorter than the longer paced cycle length after the administration of procainamide. The cycle lengths of ventricular tachycardia were compared in two ways. First, the cycle lengths of only morphologically identical sustained ventricular tachycardia were compared in the 22 patients (see below) in whom ventricular tachycardia of the same QRS morphology could be identified at each study period. In addition, the cycle lengths of the first sustained ventricular tachycardia induced during programmed ventricular stimulation were compared. QRS duration during the tachycardia was measured only for patients with tachycardias having the same morphology induced at all four study periods. Values are expressed as mean ± SD. Data at all four study periods were compared with analysis of variance. Serum procainamide concentrations were compared with paired t tests. With linear regression analysis, the combined effects of amiodarone and procainamide were compared with the sum of the effects of each agent alone on indexes of conduction and refractoriness and on the ventricular tachycardia cycle length for arrhythmias having the same morphology. For all statistical analysis, a probability value of less than 0.05 was considered statistically significant.

Results

Comparison of Effects in Sinus Rhythm (Figure 1)

The mean sinus cycle length decreased modestly after the intravenous administration of procainamide from 721 ± 106 msec in the baseline state to 650 ± 85 msec (p < 0.01) (Figure 1A). The sinus cycle length increased after amiodarone administration to 773 ± 146 (p < 0.05) and again shortened significantly after the administration of procainamide (684 ± 114 msec, p < 0.01). The mean QRS duration (Figure 1B) increased significantly from 121 ± 28 during the control state to 139 ± 33 msec after procainamide alone, 129 ± 29 msec after amiodarone alone, and 150 ± 35 msec after the combination of amiodarone and procainamide. The increase in QRS duration after procainamide was greater than that observed after amiodarone. In addition, the increase after the combination therapy was significantly greater than the effect of the procainamide or amiodarone individually. The corrected QT interval increased significantly from 428 ± 37 msec in the control state to 491 ± 40 msec after procainamide, 477 ± 46 msec after amiodarone, and 514 ± 44 msec after the combination therapy. The corrected QT interval on procainamide did not differ significantly from that on amiodarone. The effect of the combination therapy on the corrected QT interval was more than the individual effects of procainamide or amiodarone (Figure 1C).

Effect on Conduction (Figure 2A) and Refractoriness During Pacing (Figures 2 and 3)

The QRS duration (Figure 2A) and the ventricular effective refractory period (Figure 2B) increased at both paced cycle lengths on each drug regimen compared with control. In addition, the effects of the combination therapy on both the QRS duration and ventricular effective refractory period was significantly more than the effect of procainamide or amiodarone alone. The increase in QRS duration (Figure 2A) was more after procainamide than after...
amiodarone at both paced cycle lengths of 600–550 and 400 msec. In contrast, procaainamide and amiodarone each produced a similar increase in the ventricular effective refractory period (Figure 2B) at both paced cycle lengths.

The mean increase in QRS duration (Figure 3A) was significantly ($p < 0.01$) greater at paced cycle length of 400 msec than at 600–550 msec after procaainamide (37 vs. 32 msec), after amiodarone (28 vs. 23 msec), and after the combination therapy (61 vs. 52 msec). There were no significant cycle length dependent effects on the increase in the ventricular effective refractory period (Figure 3B) during therapy with procaainamide (23 vs. 25 msec), amiodarone (21 vs. 23 msec), or amiodarone and procaainamide (43 vs. 40 msec).

**Effect on Inducibility of Ventricular Tachycardia**

The combination of amiodarone and procaainamide prevented induction of all sustained ventricular tachycardia in only two (6%) of the 35 patients.

**Effect on Characteristics of Induced Ventricular Tachycardia**

Of the 33 patients who had inducible ventricular tachycardia in the control state, a morphologically different ventricular tachycardia (Figure 4) was observed in 17 patients after procaainamide, 19 patients after amiodarone, and 17 after amiodarone and procaainamide (Figure 4). Thirteen patients (39%) had a morphologically different ventricular tachycardia observed on all three drug regimens. Twenty-two of the 35 patients had the same ventricular tachycardia morphology observed at all four study periods (Figure 5). In addition to the ventricular tachycardia, which was morphologically similar to that induced at baseline, an additional morphologi-
FIGURE 2. Bar charts of effects of procainamide (P) and amiodarone (A) alone and in combination (A + P) on the QRS duration (Panel A) and the ventricular effective refractory period (VERP) (Panel B) at paced cycle lengths of 600 or 550 msec (open bars, 600 msec) and 400 msec (hatched bars, 400 msec). Comparisons made as indicated by the significance lines (see legend of Figure 1) apply to results at both cycle lengths.

Ventricularally distinct ventricular tachycardia was induced in eight patients on procainamide, 11 patients on amiodarone, and seven patients on the combination of amiodarone and procainamide. The additional morphologically distinct ventricular tachycardia had a similar cycle length (<20 msec difference) in 13 (50%) of the 26 trials and a faster cycle length in nine of the 26 trials.

The mean cycle length of the ventricular tachycardia of the same morphology (Figure 6) increased by 68 msec after procainamide from 248 ± 22 to 316 ± 29 msec, by 61 msec after amiodarone to a mean of 309 ± 33 msec, and by 125 msec to a mean of 373 ± 34 msec after the combination therapy. Procainamide alone and amiodarone alone had a similar effect on tachycardia slowing. The tachycardia cycle length of the first induced sustained tachycardia (without regard to QRS morphology) in the 33 patients with ventricular tachycardia induced at all study periods increased by 61 msec after procainamide from 247 ± 38 to 308 ± 42 msec, by 45 msec after amiodarone to a mean 392 ± 35 msec, and by 108 msec to a mean of 355 ± 61 msec after the combination therapy. The effect of procainamide alone was slightly greater than that with amiodarone alone (p<0.05).

The QRS duration during morphologically identical ventricular tachycardia increased from 135 ± 22 msec in the control state to 167 ± 30 msec (p<0.001) after procainamide, 164 ± 33 msec (p<0.001) after amiodarone, and 196 ± 37 msec (p<0.001) after amiodarone with procainamide. The combined effect of procainamide and amiodarone was more than the individual effect of either agent (p<0.001). Of note, the difference between the effects of amiodarone alone and procainamide alone on the QRS duration during ventricular tachycardia was not significant.
Relation of Combined Effects to Sum of Individual Effects

The sum of the individual effects of procainamide and amiodarone on the cycle length of morphologically similar ventricular tachycardia correlated closely with the effects of the combination therapy on this electrophysiological parameter with an $r$ of 0.85, a slope of the regression equation of 0.67, and SEE of 18 msec (Figure 7). Of note, when the tachycardia morphology was ignored, the sum of the individual effects was less predictive of the combined effects on the tachycardia cycle length with an $r$ value for the regression equation of 0.57 and SEE of 52 msec.

The sum of the individual effects of procainamide and amiodarone on the QRS duration and the ventricular effective refractory period during pacing also correlated with the combined effects on conduction and refractoriness after amiodarone with procainamide (Table 2). The relation was stronger for the effects on QRS duration than for the effects on ventricular effective refractory period. Of note, the slopes for all comparisons were less than 1.0 with a $y$-axis (combined effect) intercept that ranged from 9 to 20 msec for the QRS duration and the ventricular effective refractory period.

Discussion

The use of some combinations of antiarrhythmic therapy in combination has been reported to improve control of ventricular arrhythmias.

Further slowing of tachycardia rates by combination therapies may improve hemodynamic tolerance of the tachycardia and may facilitate the ability to terminate the arrhythmia with pacing techniques. Very few previous studies have compared the effects of different antiarrhythmic agents in the same patients, and no previous work has used the same dosing regimen to assess and compare the electrophysiological effects of a combination of two agents to that of the individual agents alone. The present study evaluated the individual and combined effects of amiodarone and procainamide in a selected group of patients whose sustained ventricular tachyarrhythmias remained inducible after treatment with each antiarrhythmic agent alone. On the dosing regimens described above, procainamide alone and amiodarone alone were shown to have comparable effects on the ventricular effective refractory period during paced cycle lengths of 600 and 400 msec, on the corrected QT interval, and on the ventricular tachycardia cycle length. Procainamide slowed conduction to a greater extent than amiodarone as indexed by the QRS duration during sinus rhythm and during paced cycle lengths of 600–550 and 400 msec. At the shorter cycle lengths observed during
Alone Amiodarone in VT cycle length

darone alone and amiodarone with proca
iological with these agents. However, the combination of amiodarone with procainamide rarely prevents ventricular tachycardia induction if the arrhythmias were also inducible on each of the agents alone. Further, the effect of the combination therapy on certain electrophysiological parameters, particularly the cycle length of a morphologically distinct tachycardia, correlated strongly with the sum of the effects of the individual agents. Although the effects of the agents in combination are not simply additive, regression equations may be used to predict the tachycardia cycle length.

Comparison of Electrophysiological Effects of Amiodarone Alone and Procainamide Alone

Morady et al. also assessed the rate-dependent effects of intravenously administered procainamide and intravenously administered amiodarone and demonstrated a rate-dependent increase in paced QRS duration on each drug. These results are similar to our observations. We noted that the effects on QRS duration are slightly greater at cycle lengths of 400 than at 600–550 msec. This cycle length–dependent difference in QRS duration was not observed in the control state. We also found that after procainamide alone and amiodarone alone, the increase in QRS duration after procainamide alone was more than the increase after amiodarone alone at paced cycle lengths of both 600–550 and 400 msec. It is of interest that after procainamide alone and amiodarone alone, the QRS duration during induced ventricular tachycardia did not differ. Of note, the mean cycle length of the induced ventricular tachycardia during therapy with each of these agents was approximately 310 msec. These results suggest a more pronounced rate-dependent effect on QRS duration for amiodarone. These data must be interpreted with caution, however, because a comparison of QRS durations made during ventricular pacing and that during ventricular tachycardia may not be valid.

No significant difference in the effects of either procainamide or amiodarone alone was found on any index of refractoriness. Furthermore, no cycle length–dependent effect on refractoriness was evident during treatment with either agent alone when paced cycle lengths of 600–550 and 400 msec were compared.

Can the Sum of Individual Effects Predict Combined Effects of Amiodarone and Procainamide?

Frequently, ventricular arrhythmias remain inducible despite antiarrhythmic therapy. We and others have found that hemodynamic tolerance of arrhythmias during amiodarone therapy are predictive of a favorable clinical outcome with respect to the prevention of sudden cardiac death. Although we were not able to demonstrate that treatment with amiodarone and procainamide or quinidine improves overall outcome in a randomized trial in patients with very rapid induced sustained ventricular arrhythmias, the poor outcome during the combination therapy may have been in part related to the persistence of a poorly tolerated arrhythmia in some of the patients treated with the combination therapy. When combination therapy markedly slows the tachycardia such that it is tolerated hemodynamically, this treatment modality may still represent the best therapeutic option in selected patients. In many patients, it may be highly desirable to predict the rate of the tachycardia that may develop on the combination therapy. This is especially the case when arrhythmia recurrence is likely and implantation of an antitachycardia device has been chosen as the therapeutic mode to effect termination of the tachycardia. We found an excellent correlation between the simple addition of the effects of the individual agents on the ventricular tachycardia cycle length and the effect of the combination therapy on this same electrophysiological parameter. Of note, the slope of the regression line was 0.67 with an intercept of 40, suggesting a tendency for the effects of the combination therapy to be overestimated by the simple addition of large changes noted with the individual agents and underestimated when the effects of the individual agents are small (Figure 7). These findings suggest a complex pharmacocellular interaction of procainamide and amiodarone without a defined limit on the maximum electrophysiological effects resulting from the combination therapy on the dosing regimen described.
It thus appears that by characterizing the electrophysiological response of the individual agents and the combination therapy on the ventricular tachycardia cycle length, a regression line can be determined that can be used to predict the effects of the combination therapy on tachycardia cycle length. Of note, the frequent initiation of multiple or new tachycardia morphologies during antiarrhythmic drug therapy (more than 50% of the study population) may limit the clinical usefulness of our observations.

Limitations

Our patient population represents a selected population whose arrhythmias remained inducible on procainamide alone and amiodarone alone. This fact may account in part for the limited success rate (67%) of the combination therapy in preventing ventricular tachycardia induction. Also of note, we and others have demonstrated that the effects of amiodarone on ventricular tachycardia cycle length and other electrophysiological parameters increase over several months of continued therapy.\textsuperscript{19,20} Thus, it is not possible to infer that our results would be the same if different dosing regimens or durations of therapy were used. In addition, this study assessed the effect of procainamide with a single intravenous dosing regimen that resulted in a relatively narrow

\begin{table}[h]
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Parameter compared & Slope & \textit{y} intercept & \textit{r} & \textit{p} \\
\hline
\(\Delta\text{QRS-RVA 600–550}^{*}\) & 0.66 & 16.6 & 0.76 & <0.001 \\
\(\Delta\text{QRS-RVA 400}^{†}\) & 0.72 & 18.5 & 0.81 & <0.001 \\
\(\Delta\text{VERP-RVA 600–550}^{*}\) & 0.73 & 8.7 & 0.70 & <0.01 \\
\(\Delta\text{VERP-RVA 400}^{†}\) & 0.43 & 20.7 & 0.58 & <0.01 \\
\hline
\end{tabular}
\caption{Relation of the Sum of the Effects of Procainamide Alone and Amiodarone Alone (x Axis) to the Combined Effects of Amiodarone With Procainamide (y Axis)}
\end{table}

\textsuperscript{*}Determined during right ventricular apical pacing at cycle lengths of 600 or 550 msec.

\textsuperscript{†}Determined during right ventricular apical pacing at a cycle length of 400 msec.
range of serum concentrations. The intravenous dosing regimen also precluded our ability to assess the effects of N-acetyl procainamide, which may contribute to electrophysiological changes when procainamide is administered in a chronic oral form. However, significant additional effects related to N-acetyl procainamide were not noted in a study comparing intravenous and oral procainamide administration. In addition, the intravenous administration of procainamide, although in general well tolerated (see above), is characteristically associated with a 10–20 mm Hg decrease in systolic pressure. Some of the observed changes, such as the observed modest shortening of the sinus cycle length, may, in part, represent reflex autonomic (rather than direct) effects of procainamide. Autonomic changes related to the duration of study protocol also may alter sinus cycle length, making this parameter the least likely to reflect direct drug effect. Finally, although we attempted to achieve the same serum concentration of procainamide when the drug was administered alone and in combination with amiodarone, small differences in the serum concentration did exist (mean difference, 1.9 µg/ml; range, 0–5.6 µg/ml). These differences may have contributed to some of the discrepancy noted between the sum of the individual electrophysiological effects and the effects of the combination therapy.

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References

Key Words: frequency-dependent effects • amiodarone • combination antiarrhythmic therapy • ventricular tachycardia • procainamide
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