Amiodarone versus amiodarone and a type IA agent for treatment of patients with rapid ventricular tachycardia

FRANCIS E. MARCHLINSKI, M.D., ALFRED E. BUXTON, M.D., JOHN M. MILLER, M.D., JOSEPH A. VASSALLO, M.D., BELINDA T. FLORES, M.S.N., AND MARK E. JOSEPHSON, M.D.

ABSTRACT  Induction of rapid ventricular tachycardia or fibrillation during therapy with amiodarone is associated with an increased risk of sudden death. To determine whether the addition of a type IA antiarrhythmic agent to therapy would improve outcome, 37 patients in whom ventricular tachyarrhythmia of a cycle length less than 350 msec was induced after 14 ± 2 days of amiodarone were randomly assigned to therapy with amiodarone alone (group 1, 20 patients) or amiodarone plus type IA agent (group 2, 17 patients). Type IA therapy consisted of procainamide in 13 patients and quinidine in four procainamide-intolerant patients. To assess the short-term effects of a type IA agent on inducibility of ventricular tachyarrhythmia, cycle length, and hemodynamic tolerance, 16 of 20 patients in group 1 and all patients in group 2 underwent repeat programmed stimulation after the intravenous administration of procainamide during amiodarone therapy (mean procainamide serum concentration 7.2 ± 2.0 μg/ml). Procainamide prevented induction of sustained arrhythmia in only two of 33 patients. Procainamide increased the cycle length of induced ventricular tachycardia from 283 ± 30 to 352 ± 46 msec (p < .001). After the addition of procainamide, 16 of 31 patients vs 10 of 37 patients on amiodarone alone had an induced arrhythmia that was tolerated hemodynamically (p < .05). There were no differences between groups 1 and 2 with respect to patient or arrhythmia characteristics, response to short-term procainamide, or duration of follow-up. The mean follow-up for all patients was 14 ± 10 months. By life table analysis, outcome did not differ between group 1 and group 2 patients with respect to either development of sudden death or syncope (four patients in group 1 vs five patients in group 2) or the development of any arrhythmia event or side effect that required withdrawal of antiarrhythmic therapy (nine patients in group 1 patients vs 12 patients in group 2). Forty percent of group 2 patients developed adverse effects necessitating withdrawal of drug. We conclude in patients in whom rapid ventricular tachycardia is induced on amiodarone (1) type IA agents increase the cycle length and result in improved hemodynamic tolerance but rarely prevent induction of ventricular tachycardia, and (2) outcome is not improved by the addition of a type IA agent to therapy.

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INDUCTION of a rapid, poorly tolerated ventricular arrhythmias during amiodarone therapy has been associated with a poor prognosis. Horowitz et al.1 reported a 50% incidence of sudden death in this patient population during continued amiodarone therapy, with a mean follow-up of 1 year. The effect of the addition of a type IA agent on inducibility of tachycardia and clinical outcome has not been evaluated previously. The present study was undertaken to (1) determine the effect of procainamide on inducibility and rate/hemodynamic tolerance of rapid ventricular arrhythmias induced during amiodarone therapy, and (2) to determine whether the addition of a type IA agent (procainamide or quinidine) to amiodarone therapy results in a better clinical outcome.

Methods

Thirty-seven patients with rapid ventricular tachycardia/ventricular fibrillation (cycle lengths <350 msec) induced at the time of electrophysiologic study after a mean of 14 ± 2 days of amiodarone were the subject of this report. Amiodarone was
administered as a loading dose of 1400 mg/day for 7 days followed by maintenance doses of 400 mg daily.

There were 30 men and seven women in the study population ranging in age from 42 to 77 years (mean 60 ± 9). Thirty-five patients had coronary artery disease with documented previous myocardial infarction, and two patients had idiopathic congestive cardiomyopathy. The mean ejection fraction determined by either gated blood pool scan or left ventriculography during cardiac catheterization was 32 ± 11%. Thirty-one of the patients presented with ventricular tachycardia or fibrillation associated with a cardiac arrest or syncope while six patients presented with a hemodynamically tolerated ventricular tachycardia. The time from myocardial infarction to presentation of arrhythmia varied from 4 days to 23 years (mean 52 ± 78 months); 12 of the 37 patients presented within 3 months of acute myocardial infarction. Three of these six patients were being treated with empiric antiarrhythmic drug therapy at the time of presentation. All 37 patients had inducible ventricular tachycardia or fibrillation while on a type 1A agent alone, and all but two patients had inducible ventricular tachycardia or fibrillation during a baseline study while off all antiarrhythmic agents. The two remaining patients underwent initial study while being treated with procainamide.

**Study protocol.** After initiation of rapid ventricular tachycardia during amiodarone therapy, 33 of the 37 patients underwent repeat ventricular stimulation after receiving intravenous procainamide. Programmed stimulation included one to three ventricular extrastimuli from two right ventricular pacing sites during at least two paced cycle lengths (usually 600 and 400 msec). The remaining four patients did not undergo programmed stimulation after they received procainamide because of a history of an allergic reaction to procainamide (three patients) or development of marked hypotension while receiving intravenous procainamide (one patient). Procainamide was administered as a loading dose of 15 mg/kg at a rate of 50 mg/min followed by a continuous infusion of 8 mg/min. Stimulation was begun after 5 min of continuous procainamide infusion at 8 mg/min. The mean serum concentration at the time of repeat programmed stimulation was 7.2 ± 2.0 µg/ml. Serum for procainamide concentration was routinely measured at the time of initiation of the arrhythmia or at the time of completion of the stimulation protocol.

The following variables were assessed at the time of study after 14 days of amiodarone therapy alone and after the intravenous administration of procainamide: (1) the inducibility of a sustained ventricular arrhythmia, (2) the morphology of induced ventricular tachycardia, (3) the hemodynamic tolerance of the ventricular arrhythmia, and (4) the cycle length of tachycardia. Sustained ventricular arrhythmia was defined as a tachyarrhythmia lasting more than 30 sec or requiring termination before that time because of the development of symptoms consistent with hemodynamic collapse. Morphologies of ventricular tachycardia were considered distinct if they displayed a contralateral bundle branch block morphology or if their frontal plane QRS axes were more than 90 degrees divergent. Hemodynamic tolerance of the ventricular tachycardia was determined by systolic cuff blood pressure recordings obtained while the patient was in the supine position. An arrhythmia that resulted in a systolic blood pressure of more than 70 mm Hg in the absence of symptoms was considered to be tolerated hemodynamically. Patients with prompt loss of consciousness had their arrhythmias terminated either by pacing or external cardioversion before systolic cuff blood pressure recordings could be obtained. These patients were also considered to have poorly tolerated ventricular arrhythmias.

**Long-term therapy.** After electrophysiologic studies with amiodarone alone and with amiodarone and procainamide, patients were randomly assigned to therapy with amiodarone alone (20 patients) or that with amiodarone and a type IA agent (17 patients). Procainamide was the preferred type IA agent and was used in 13 patients; however, in four patients, because of a previous history of acute drug allergy or a history of procainamide-induced lupus erythematosus, quinidine was used. The dosage of procainamide was adjusted to maintain serum concentrations achieved during short-term drug testing. The dosage of quinidine, when this drug was used, was adjusted to maintain serum concentrations between 3 and 5 µg/ml.

**Follow-up.** All patients were discharged from the hospital while receiving 400 mg amiodarone daily. In three patients, the dose of amiodarone was subsequently reduced because of persistent nausea on the 400 mg/day regimen, and in three patients treated with amiodarone for more than 1 year, the dose was decreased to 200 or 300 mg/day in the absence of adverse effects. Patients were followed in the Arrhythmia Evaluation Center and were seen 1 month after discharge from the hospital and then every 2 to 3 months. At the time of these visits, serum concentrations of procainamide were assessed and the dosage of procainamide was adjusted so that serum concentrations were maintained at the level obtained during electrophysiologic testing. In patients who lived a distance from the medical center, patients and referring physicians were contacted at the same time intervals by phone to assess the development of symptoms and to obtain the results of measurements of serum procainamide. The duration of follow-up was calculated from the date amiodarone was started to the time of sudden cardiac death, documented occurrence of arrhythmia, development of syncope attributable to arrhythmias, or the development of side effects necessitating discontinuation of antiarrhythmic medication.

**Statistical analysis.** The Fisher exact test or Student’s t tests was used to test for intergroup differences. A p value < .05 was considered indicative of a significant difference. Survival was assessed by standard Kaplan-Meier life table analysis techniques. Results were analyzed with respect to the development of sudden cardiac death or syncope, recurrence of arrhythmia, or side effects necessitating discontinuation of medication. Likelihood ratio statistics were used to test the equality of survival curves.

**Results**

**Electrophysiologic study with amiodarone alone.** Thirty-five patients had inducible rapid ventricular tachycardia and two had inducible ventricular fibrillation on amiodarone alone. The mean cycle length of inducible ventricular tachycardia was 283 ± 30 msec. Twenty-seven of the 37 patients had a ventricular tachycardia that was not tolerated hemodynamically while they were in the supine position. Patients with ventricular tachycardia that was tolerated hemodynamically had a higher ejection fraction (39 ± 11% vs 29 ± 10%, p < .05) and a longer cycle length of tachycardia (306 ± 14 vs 274 ± 30 msec, p < .01) than those patients whose arrhythmias were not tolerated.

**Effects of procainamide.** The mean serum procainamide concentration achieved was 7.2 ± 2.0 µg/ml (range 4.4 to 11.1 µg/ml). Two of the 33 patients who underwent programmed stimulation after receiving intravenous procainamide had no inducible sustained ventricular arrhythmia after procainamide (figure 1).
THERAPY AND PREVENTION—VENTRICULAR TACHYCARDIA

FIGURE 1. Inducibility of sustained ventricular tachycardia (VT) or fibrillation after the addition of intravenous procainamide to amiodarone therapy. In only two of the 33 patients did sustained arrhythmia become noninducible.

Of the remaining 31 patients, 29 had inducible ventricular tachycardia, and two had inducible ventricular fibrillation. In both of the latter patients ventricular fibrillation was induced during therapy with amiodarone alone. After procainamide, the cycle length of induced ventricular tachycardia increased in 28 of 29 patients. The mean cycle length of ventricular tachycardia increased from 283 ± 30 to 352 ± 46 msec (p < .001) after procainamide. In 23 of the 29 patients, at least one induced ventricular tachycardia had the same morphology before and after procainamide.

Procainamide prolonged the cycle length of ventricular tachycardia of the same morphology by 15 to 110 msec (figure 2) from 286 ± 27 to 341 ± 40 msec (p < .001). Eighteen of 33 patients who received intravenous procainamide had either no inducible ventricular tachycardia or fibrillation (two patients) or hemodynamically tolerated ventricular tachycardia (16 patients) after procainamide, whereas only eight of these 33 patients had hemodynamically tolerated ventricular tachycardia while on amiodarone alone (figure 3). Those patients with hemodynamically tolerated ventricular tachycardia after procainamide had a higher ejection fraction (37 ± 12% vs 27 ± 9%, p < .05) and had ventricular tachycardia of a longer cycle length on the combination therapy (379 ± 34 vs 319 ± 37 msec, p < .001). Hemodynamic tolerance of ventricular tachycardia after intravenous procainamide was not related to the cycle length of ventricular tachycardia on amiodarone alone (286 ± 25 vs 276 ± 32 msec, p = NS) or serum concentration of procainamide (7.4 ± 2.0 vs 6.8 ± 2.2 µg/ml, p = NS).

Results of long-term therapy. The 20 patients were...
randomly assigned to therapy with amiodarone alone did not differ from the 17 patients who were treated with amiodarone and a type IA agent with respect to patient or arrhythmia characteristics or duration of follow-up (table 1). The mean follow-up for all patients was 14 ± 10 months. All patients were followed for at least 8 months (range 8 to 40). Outcome in patients, by life table analysis, did not differ between those treated with amiodarone and those receiving amiodarone and a type IA agent with respect to either the development of sudden death or syncope or the development of any arrhythmia event or side effect that required withdrawal of antiarrhythmic therapy (figure 4). Notably, four patients treated with amiodarone alone vs five patients treated with combination therapy developed sudden death or syncope during the follow-up period. Two of these four patients treated with amiodarone alone had an arrhythmia that was not tolerated hemodynamically during electrophysiologic testing on amiodarone alone. Also, three of the five patients who developed sudden death or syncope on amiodarone and a type IA agent had an inducible arrhythmia that was not tolerated hemodynamically at the time of electrophysiologic study with amiodarone and a type IA agent.

There was a trend for the development of more side effects on the combination antiarrhythmic therapy: 40% of that group developed adverse effects warranting withdrawal of therapy. Side effects included intractable anorexia and nausea, neutropenia, pulmonary toxicity, skin rash, and severe disequilibrium.

Discussion

Initial clinical studies reported an excellent survival rate and good control of ventricular arrhythmia during therapy with amiodarone.2-5 Most studies have found that despite good clinical control of arrhythmia most patients treated with amiodarone still have inducible sustained ventricular arrhythmias while receiving therapy.4-6 A limited role for electrophysiologic testing during amiodarone therapy has been suggested. Not all studies have found that long-term outcome is dramatically improved by amiodarone.6,10 Complete control of arrhythmias at 1 to 2 years has ranged between 28% and 50% in subsequent reports.5,10 Additionally, other studies have found that results of electrophysiologic testing of patients on amiodarone may help predict clinical outcome.1,11 Horowitz et al.1 found that only one of 20 patients whose arrhythmias were no longer inducible during therapy with amiodarone had recurrence of arrhythmia during a mean follow-up of 18 months. These 20 patients represented 20% of the study population. Just as importantly, these investigators found that 12 (50%) of the 24 patients in whom ventricular arrhythmia was not only inducible but also resulted in severe symptoms such as cardiovascular collapse died suddenly during follow-up. The mean cycle length of these induced rapid arrhythmias was 304 msec (range 250 to 320). No sudden deaths were noted in 56 patients in whom a well-tolerated ventricular tachycardia was induced during amiodarone therapy, although recurrence of a well-tolerated clinical arrhythmia occurred in 46% of these patients. Not only have the results of electrophysiologic testing been demonstrated to predict outcome, but DiCarlo et al.12 also determined that a history of cardiac arrest in association with a depressed ejection fraction predicted an increased incidence of sudden death during therapy with amiodarone.

Based on these previous reports, our study population consisted primarily of those at high risk for subsequent sudden cardiac death during continued amiodarone therapy. Thirty-one (84%) presented with a cardiac arrest, and 27 (73%) had evidence of hemodynamic embarrassment in association with the induced arrhythmia during amiodarone therapy alone. Only seven (19%) patients had an ejection fraction of greater than 40%. We arbitrarily selected a tachycardia cycle length of 350 msec as the cutoff for inclusion in the study. We selected this cycle length to include nearly all patients likely to develop hemodynamic collapse with induction of their ventricular arrhythmia.13,14 We recognized that we would be including some patients who would be likely to tolerate their arrhythmia in the supine position, particularly the few who had preserved left ventricular function. Notably, the 10 patients who tolerated their ventricular tachycardia while on amiodarone therapy alone had higher ejection frac-

| TABLE 1 |
| Characteristics of patients randomly assigned to drug therapy |
|---------------------------------|----------------|----------------|
|                                  | Amiodarone    | Amiodarone and type IA agent |
|                                  | (n = 20)      | (n = 17)        |
| Age (years)                     | 61 ± 9        | 60 ± 9          |
| Ejection fraction (%)           | 32 ± 9        | 31 ± 13         |
| VTCL-amiodarone (msec)          | 285 ± 31      | 281 ± 30        |
| VTCL-amiodarone and type IA agent| 351 ± 47     | 354 ± 47        |
| Procaainamide concentration (μg/ml) | 7.5 ± 2.0  | 7.0 ± 2.3       |
| No. with tolerated VT or no inducible VT at discharge | 7             | 9               |
| Mean follow-up (months)         | 14 ± 10       | 13 ± 12         |
| No. sudden death/syncope        | 4             | 5               |
| No. tolerated spontaneous VT    | 2             | 0               |

CL = cycle length; VT = ventricular tachycardia.
THERAPY AND PREVENTION—VENTRICULAR TACHYCARDIA

FIGURE 4. Life table analysis of outcome with respect to sudden cardiac death or syncope (A) and any arrhythmia event or side effect necessitating a change in therapy (B) in patients with rapid ventricular tachycardia treated with amiodarone alone and those receiving amiodarone and a type IA agent. The addition of type IA agent did not improve outcome in this patient population.

However, a significant slowing of cycle length of ventricular tachycardia was almost uniformly observed. The cycle length of ventricular tachycardia that was morphologically the same increased by a mean of 55 msec. The increase in cycle length resulted in hemodynamic tolerance of the ventricular arrhythmia in an additional 25% of the study population compared with the results on amiodarone therapy alone.

Despite the slower rate and improved hemodynamic tolerance of ventricular tachycardia after administration of procainamide, long-term clinical outcome was not improved by the combination therapy. The incidence of suspected life-threatening arrhythmia events during a mean follow-up of 14 months was 20% to 25% in both treatment groups. This incidence is less than the 50% rate of sudden cardiac death noted by Horowitz et al.\(^1\) in patients in whom rapid ventricular tachycardia was induced after amiodarone loading.
Notably, all the patients in their study population developed severe symptoms with induction of arrhythmia. This contrasts with the 27% incidence of tolerance of the induced arrhythmia in patients receiving amiodarone alone and the 52% incidence in patients receiving combination therapy in our study. This difference in arrhythmia tolerance may account for at least some of the difference in the incidence of sudden cardiac death in the two studies. This is also suggested by the fact that two patients in the present study, both treated with amiodarone alone, developed spontaneous ventricular tachycardia that was well tolerated hemodynamically. Both patients had a well-tolerated arrhythmia initiated during electrophysiologic testing while on amiodarone.

Not only was the incidence of suspected life-threatening arrhythmia events similar for the two groups of patients, but also the chance for successful therapy on the combination of antiarrhythmic agents was markedly limited by the development of side effects necessitating drug withdrawal. These side effects, which occurred in 40% of patients randomly assigned to therapy with amiodarone and a type IA agent, occurred despite maintenance of type IA serum concentrations at nontoxic levels. In addition, only one of five patients on combination therapy in whom serum amiodarone concentrations were assessed at the time of toxicity was the concentration above 2.5 \( \mu \)g/ml. This observation suggests that side effects were not merely due to a marked increase in serum concentration of amiodarone associated with administration of a type IA agent.

Our results suggest that alternative forms of therapy in patients with rapid ventricular tachycardia induced during therapy with amiodarone must be considered. Drug combinations that result in fewer side effects and better arrhythmia control should be sought and the use of the automatic implantable defibrillator or surgical therapy should be strongly considered.

**Limitations of study.** Because of the number of patients studied and a conservative estimate of 20% 1 year mortality during treatment with amiodarone alone, only a 100% reduction in the incidence of sudden death and syncope would have provided evidence sufficiently strong to suggest a definite beneficial effect of the combination therapy in preventing life-threatening arrhythmias. Nevertheless, estimates of probability of failure (by group) in our study indicate that there is a less than 1% chance that, even after studying an additional 100 patients, the combination therapy would be found to result in even a 50% better overall outcome. Even if we ignore side effects and the development of a tolerated ventricular tachycardia, the chance of the combination therapy inducing a 50% reduction in the incidence of sudden death or syncope is less than 5%. Thus, even with the relatively small number of patients, at this time we have strong evidence suggesting that the combination of amiodarone plus a type IA agent is unlikely to improve survival in this high-risk population, and its overall success will be frequently limited by the development of intolerable side effects.

Patients were randomly assigned to long-term therapy with amiodarone alone or amiodarone and a type IA agent regardless of the results of electrophysiologic testing with respect to inducibility and/or hemodynamic tolerance of induced ventricular tachycardia after institution of therapy with procainamide. Notably, three of the five patients who developed sudden cardiac death or syncope during the combination therapy had a poorly tolerated arrhythmia at time of electrophysiologic study while on their discharge regimen. It is possible that if combination therapy had been chosen only when the ventricular tachycardia was well tolerated or noninducible on that regimen, outcome with respect to sudden death or syncope would have been improved.

In addition, we studied the effect of procainamide concentration given in single dosing regimen resulting in a mean procainamide concentration of 7.2 ± 2.0 \( \mu \)g/ml (range 4.4 to 11.1 \( \mu \)g/ml). We then attempted to maintain serum concentrations during long-term oral administration of procainamide that approximated that during intravenous administration. The results of our study thus represents the effects of procainamide over a relatively narrow range of serum concentrations. It is possible that greater or lesser serum concentrations may have proven either more effective with respect to arrhythmia control (greater concentration) or as effective and less likely to produce side effects (lesser concentration).

Finally, the patients studied represent a selected population whose arrhythmias proved refractory to standard antiarrhythmic agents. It is therefore impossible to comment on the applicability of the results of our study to the therapy of the general population of patients with ventricular tachycardia.

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THERAPY AND PREVENTION-VENTRICULAR TACHYCARDIA

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