Amiodarone Therapy: Role of Early and Late Electrophysiologic Studies

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Electrophysiologic testing has been useful in guiding therapy in patients with sustained ventricular tachycardia treated with conventional antiarrhythmic drugs (1,2). This is based on the premise that drugs that suppress the induction of ventricular tachycardia in the laboratory are effective, whereas drugs that fail to prevent induction of ventricular tachycardia are associated with recurrent arrhythmia. These drugs are usually evaluated after the patient has been treated for at least five half-lives (that is, when serum drug concentrations are at steady state).

The role of programmed electrical stimulation in the management of patients treated with amiodarone remains controversial (3-16). Most patients with inducible ventricular arrhythmia who are studied with programmed electrical stimulation within a few weeks of starting amiodarone therapy continue to have inducible arrhythmia. However, many of these patients continue to do well despite their inducible state. In addition, previous studies (17,18) have shown that the electrophysiologic effects of amiodarone after a single intravenous dose differ from those observed after high dose oral loading. This suggests that the electrophysiologic effects of amiodarone may change over time. However, the changes

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in electrophysiologic effects between oral loading and steady state are less well characterized (13-15).

The purposes of this study were 1) to explain the disparity between amiodarone and conventional drug response to programmed electrical stimulation; 2) to compare the electrophysiologic effects of oral amiodarone after oral loading and at steady state; and 3) to determine whether the response to programmed electrical stimulation is helpful in predicting clinical outcome.

Methods

Study patients. This prospective study consisted of 42 patients with a history of one or more episodes of symptomatic ventricular tachycardia or ventricular fibrillation. In each case, the arrhythmic episode was not associated with myocardial ischemia or infarction, metabolic disturbance or proarrhythmic drug effect. All patients had ventricular tachycardia induced by programmed electrical stimulation in the drug-free state. The patients ranged in age from 41 to 74 years (mean age 62); there were 34 men and 8 women. Thirty-four patients had coronary artery disease, seven had cardiomyopathy and one had valvular heart disease. Of those patients with coronary artery disease, 33 (97%) of 34 had a history of transmural myocardial infarction; in each, it had occurred at least 6 weeks before initial evaluation. The mean ejection fraction for the entire group was 30 ± 13%.

Before initiation of amiodarone therapy, 20 patients had documented sustained ventricular tachycardia, and 10 had a cardiac arrest during which ventricular tachycardia or fibrillation was recorded. Four patients had presyncope during a spontaneous episode of nonsustained ventricular tachycardia, and eight additional patients experienced syncope after an episode that strongly suggested the presence of a tachyarrhythmia. All 20 patients with sustained ventricular tachycardia had a monomorphic arrhythmia documented by either 12 lead electrocardiogram (ECG) or ambulatory monitoring. All patients had had at least one unsuccessful drug trial before starting amiodarone.

Electrophysiologic study protocol. Patients were brought to the electrophysiology laboratory in the postabsorptive nonsedated state after all antiarrhythmic drugs had been discontinued for at least five half-lives. All patients who received digoxin, beta-receptor blockers or calcium channel blockers at the time of the control study continued to receive them at the time of all subsequent studies. Two quadripolar pacing catheters were inserted percutaneously into a femoral vein and advanced to the right atrium and right ventricular apex. A tripolar catheter was inserted into the opposite femoral vein and advanced across the tricuspid valve for recording of the His potential. Surface ECG leads I, aVF and V, were recorded along with intracardiac electrograms filtered at 30 to 500 Hz. Cardiac stimulation was performed using a programmed digital stimulator (Bloom Associates), delivering impulses of 2 ms duration at twice diastolic threshold. Data were displayed on an oscilloscope (Electronics for Medicine VR-12) and recorded at a paper speed of 50 to 100 mm/s. Conduction intervals were measured in standard fashion. The maximal sinus node recovery time was calculated as previously described (19). Sinus atrial conduction time was calculated by the method of Strauss et al. (20). Incremental atrial pacing was performed until atrioventricular (AV) block developed. Atrial refractory periods were determined at a paced cycle length of 600 ms.

Programmed ventricular stimulation was then performed using single, double and triple extrastimuli at three ventricular paced cycle lengths (600, 500 and 400 ms). Stimulation was repeated at the right ventricular outflow tract if sustained ventricular tachycardia was not induced at the right ventricular apex. The end point of the protocol was the induction of sustained monomorphic ventricular tachycardia. If nonsustained ventricular tachycardia or polymorphic ventricular tachycardia was induced, the stimulation protocol was continued until sustained ventricular tachycardia or ventricular fibrillation was initiated or completion of the protocol.

Amiodarone administration. After the control electrophysiologic study, patients began the amiodarone loading regimen. The loading dose of amiodarone consisted of 1,200 mg/day for a mean of 12 ± 2 days. Forty patients received the loading dose orally in divided doses, and two patients received half the dose intravenously and half orally. After the loading dose, electrophysiologic testing was repeated as during the initial electrophysiologic study, and is designated as early electrophysiologic testing. At this time, standard electrophysiologic variables were measured and attempts to reinude ventricular tachycardia were made using programmed stimulation. The ventricular stimulation protocol was the same as in the control study (that is, up to three extrastimuli at three ventricular paced cycle lengths from the right ventricular apex and outflow tract, regardless of the initial mode of induction). The induction of ventricular fibrillation was considered an end point only if it was induced at the initial study. The stimulation protocol was continued until monomorphic tachycardia was induced or the protocol was completed. Induced polymorphic ventricular tachycardias were not considered as an end point or included in the analysis of arrhythmia inducibility during amiodarone therapy.

Patients were then discharged from the hospital on a maintenance dose of 400 mg/day of amiodarone. Three patients received concomitant oral procainamide because rapid ventricular tachycardia was induced at early electrophysiologic testing. All other patients were treated with oral amiodarone alone. After a minimum of 3 months of therapy, consenting patients returned at a mean of 17 ± 4 weeks for late electrophysiologic testing. Nineteen patients did not return for late electrophysiologic testing: four pa-
patients did not have inducible arrhythmias at early electrophysiologic testing, four had a recurrence before 3 months, two died a nonsudden death (one from acute myocardial infarction and one from congestive heart failure) and nine refused further study. Electrophysiologic variables were measured again, and programmed stimulation was repeated. Patients were then followed up clinically while receiving oral amiodarone (400 mg daily), regardless of the results of late electrophysiologic testing and were seen every 2 to 3 months in the arrhythmia clinic.

**Definitions.** Sustained ventricular tachycardia was defined as a tachycardia lasting 30 s or requiring termination before 30 s because of hemodynamic compromise. Non-sustained ventricular tachycardia was defined as a tachycardia lasting for six complexes to 30 s in duration. In this study, only induced monomorphic tachycardias were used as an end point for therapy. After amiodarone therapy, a tachycardia was considered inducible if >15 beats of ventricular tachycardia were induced by any portion of the protocol, regardless of the initial mode or site of stimulation. During amiodarone therapy, the tachycardia was considered nonsustained if it lasted >15 complexes but <30 s, and sustained if it lasted >30 s or required termination. The tachycardia was considered noninducible if ≤15 complexes of ventricular tachycardia were initiated by the complete stimulation protocol at both the right ventricular apex and outflow tract.

The clinical response to the induced ventricular tachycardia was considered tolerated if the induced arrhythmia did not cause cardiovascular collapse, angina, near syncope or systolic arterial pressure <80 mm Hg.

**Statistical analysis.** The data are presented as mean ± standard deviation. Electrophysiologic data were tested for significance by paired t tests (Systat). Clinical response was tested using chi-square analysis. A p value <0.05 was considered significant.

**Amiodarone levels.** Serum concentrations of amiodarone and desethylamiodarone were determined at early and late electrophysiologic testing in the first 11 patients using previously described methods (21).

**Results**

**Electrophysiologic effects of amiodarone.** In the 42 patients assessed at early electrophysiologic testing, amiodarone prolonged the paced cycle length to AV Wenckebach block from 406 ± 82 to 493 ± 88 ms and the AH interval from 85 ± 24 to 107 ± 31 ms. In addition, the HV interval increased from 52 ± 11 to 59 ± 13 ms. The atrial effective refractory period increased from 256 ± 36 to 292 ± 44 ms, the ventricular effective refractory period increased from 258 ± 30 to 295 ± 27 ms and the corrected QT interval increased from 418 ± 37 to 461 ± 49 ms. Therefore, on the basis of results from early electrophysiology testing, amiodarone significantly prolonged atrial and ventricular refractoriness while slowing AV node and His-Purkinje conduction (p = 0.001). Paced cycle length to AV Wenckebach block was the only variable that significantly changed from early to late electrophysiologic testing (501 ± 86 to 547 ± 89 ms, p < 0.05).

**Effect of amiodarone on inducibility of ventricular tachycardia.** All 42 patients had inducible ventricular tachycardia or fibrillation at the control study. In 35 patients, the induced ventricular tachycardia was sustained, and in 4 patients, it was nonsustained; two of the latter four patients had a history of prior cardiac arrest. Ventricular fibrillation was induced in the remaining three patients.

The results of programmed stimulation after oral amiodarone loading are summarized in Figure 1. Among the 35 patients with inducible sustained ventricular tachycardia at control study, the arrhythmia remained inducible at early electrophysiologic testing in 30, became nonsustained in two and became noninducible in 3. Of the three patients with ventricular fibrillation, one had inducible sustained ventricular tachycardia, one had no change, and in one the arrhythmia became noninducible. Of the four patients with inducible nonsustained ventricular tachycardia, the arrhythmia became sustained in three and remained nonsustained in one. Therefore, of 42 patients studied with programmed stimulation after amiodarone loading, a total of 4 (10.5%) had no inducible arrhythmia.

Twenty-three of the patients with inducible ventricular tachycardia returned for late electrophysiologic testing (Fig. 2). Of 22 patients who had inducible sustained ventricular tachycardia at early study, the arrhythmia remained inducible...
ible in 15, was inducible but nonsustained in 2 and became noninducible in 5. The remaining patient with nonsustained ventricular tachycardia induced at early study who was restudied developed noninducible ventricular tachycardia. Therefore, at late electrophysiologic testing, an additional 6 (26%) of 23 patients had noninducible ventricular tachycardia.

At control study, ventricular tachycardia was inducible in 5 patients with single, 19 patients with double and 18 patients with triple extrastimuli. At early electrophysiologic testing, ventricular tachycardia was inducible in 3 patients with single, 21 patients with double and 14 patients with triple extrastimuli. At late electrophysiologic testing, ventricular tachycardia was inducible in one patient with single, nine patients with double and seven patients with triple extrastimuli. Only 5 of the 24 patients whose tachycardia was induced with single or double extrastimuli at the control study required a third extrastimulus for induction at subsequent studies.

Cycle length of induced ventricular tachycardia. The mean cycle length of induced ventricular tachycardia increased from 275 ± 61 ms at control study to 340 ± 58 ms at early electrophysiologic testing (p = 0.001). Ventricular tachycardia cycle length continued to increase from 341 ± 38 ms at early electrophysiologic testing to 375 ± 63 ms at late electrophysiologic testing in the 17 patients who still had inducible arrhythmias at the late study (p < 0.05).

Clinical follow-up. The relation of outcome to the results of early and late programmed stimulation was evaluated (Fig. 3). Of the 42 patients studied with early electrophysiologic testing 4 had no inducible arrhythmias (1 with ventricular fibrillation and 3 with sustained ventricular tachycardia induced at control study); all 4 have had no recurrences. Among the 23 patients who underwent late electrophysiologic testing and were followed up for a mean of 21.7 months (range 4 to 47), there were no recurrences among the 6 patients with noninducible arrhythmias, but there were five recurrences among the 17 patients with persistently inducible arrhythmias. Of these five patients with recurrences, four died suddenly and one had tolerated sustained ventricular tachycardia.

Fifteen of the 38 patients who had inducible ventricular

Figure 2. Changes in ventricular tachycardia inducibility between early and late electrophysiologic testing in 23 patients. Abbreviations as in Figure 1.

Figure 3. Relation of outcome to results of early and late programmed stimulation in 42 patients.
tachycardia at early electrophysiologic testing did not return for late study. Of these 15 patients, 4 had recurrent ventricular tachycardia before 3 months (1 had sudden death and 3 had tolerated sustained ventricular tachycardia). The 11 remaining patients have been followed up for a mean of 16.3 months. There have been four recurrences; two patients died suddenly and two had tolerated sustained ventricular tachycardia. Therefore, recurrent ventricular tachycardia or sudden death has occurred in 13 (31%) of 42 in the original study group treated with oral amiodarone. No clinical or electrophysiologic variable other than inducibility status was useful in predicting which patients would have clinical recurrences. The mean ejection fraction was 27 ± 11% for the patients with noninducible arrhythmias and 32 ± 14% for the patients with persistently inducible arrhythmias (p = NS).

Clinical response to the induced ventricular tachycardia. This was evaluated in the 23 patients who had both early and late electrophysiologic testing (Fig. 4). At control study, 5 (22%) of 23 patients had tolerated tachycardia induced, and at early study 8 (34%) of 23 patients had tolerated tachycardia (p = NS). At late study, 6 (26%) of 23 patients had noninducible arrhythmias, and 9 (39%) of 17 patients with inducible tachycardia had inducible tolerated tachycardia. Therefore, as patients were treated longer with amiodarone, more tachycardias became either tolerated or noninducible (p < 0.001). Of note are two patients who had nontolerated tachycardia induced at early electrophysiologic testing. Both patients were treated with concomitant oral procainamide after it was demonstrated that the addition of intravenous procainamide produced further slowing and improved tolerance of the induced tachycardia. Both patients were studied at late electrophysiologic testing while receiving amiodarone only and had tolerated tachycardia induced. During follow-up study, two of nine patients with tolerated tachycardia had recurrences; one had tolerated sustained ventricular tachycardia and one died suddenly 1 month after lowering the dose of amiodarone on his own. Three of the eight patients with nontolerated tachycardia at late electrophysiologic testing had recurrences; all three patients died suddenly. As previously stated, there were no recurrences in the six patients with noninducible tachycardia.

Amiodarone serum concentrations. These were analyzed in the first 11 patients that had both early and late electrophysiologic testing. At early electrophysiologic testing, serum amiodarone concentration was 2.11 ± 0.91 versus 2.38 ± 1.16 μg/mL at late study (p = NS). The level of desethylamiodarone was 1.02 ± 0.65 μg/mL at early study and 1.36 ± 0.53 μg/mL at late study (p = NS).

Discussion

The major findings of this study are that: 1) The timing of programmed electrical stimulation will affect the results of the study in patients treated with oral amiodarone. At steady state as compared with early electrophysiologic testing, the percent of patients who do not have inducible arrhythmias is higher and more patients have better tolerated tachycardias. 2) Patients who do not have inducible arrhythmias while receiving amiodarone appear to be at low risk for recurrent arrhythmias and sudden death. 3) Serial programmed electrical stimulation may be useful in stratifying patients with life-threatening ventricular arrhythmias treated with oral amiodarone.

Changes in ventricular tachycardia inducibility and cycle length. Several studies (3-16) have examined the response to programmed stimulation after amiodarone therapy. The majority of patients were free of clinical recurrences despite continued inducibility. This has led some to suggest that programmed stimulation is of little value and that empiric therapy is indicated (4-6). In previous studies, arrhythmia became noninducible in 5-53% of patients after administration of amiodarone. In comparing the results of programmed electrical stimulation, it is important to note differences in the groups of patients studied, as well as the timing of the follow-up electrophysiologic study. Such differences may help explain the diverse results of programmed stimulation.

In previous studies, there was great variability and inconsistency in the timing of programmed stimulation, which was performed by some investigators (4,11) as early as 2 days after starting amiodarone, while others (5,7,9,16) waited 3 to 4 weeks. Our data suggest that the timing of the study will influence the results. Our patients were systematically studied after oral loading doses (12 ± 2 days) and after 4 months of therapy (mean 17 ± 4 weeks). Although arrhythmia was noninducible in only 10.5% of patients after the initial loading dose, it became noninducible in an additional 26% at late electrophysiologic testing. In addition, induced tachycardia cycle length was prolonged from 275 ± 61 ms at control to 340 ± 58 ms at early study (p = 0.001). At late
study, there was evidence of further prolongation of tachycardia cycle length from $341 \pm 38$ to $375 \pm 63$ ms ($p < 0.05$).

These changes in inducibility and tachycardia cycle length demonstrate a temporal dependence of the electrophysiologic effects of amiodarone. The cause of this time dependence is unknown. Proposed mechanisms include a change in the ratio of desethylamiodarone to amiodarone. Although we did not demonstrate such a change, two previous studies (13,17) have shown an increase in the desethylamiodarone/amiodarone ratio with time. Talajic et al. (23) demonstrated that desethylamiodarone produces greater sodium channel blockade than does its parent compound. This may account for the further prolongation of tachycardia cycle length observed at late electrophysiologic testing. Other mechanisms that might account for the temporal changes seen include intracellular effects of amiodarone, which might take time to develop, or the secondary effects of amiodarone on thyroid metabolism as suggested by Morady et al. (17).

The effects of long-term amiodarone therapy on ventricular tachycardia inducibility and prolongation of the tachycardia cycle length were observed without significant changes in the right ventricular effective refractory period or HV interval. In addition, serum concentrations of amiodarone and desethylamiodarone were unchanged from early to late study. These measures of refractoriness and conduction reflect changes in noninfarcted myocardial tissue. The determinants of conduction and refractoriness within the diseased reentrant circuit may be quite different from those localized to the right ventricular apex. The absence of correlation between these measured variables and the results of late electrophysiologic testing suggest that this may be possible.

Clinical follow-up. In our patients, there were no recurrences of ventricular tachycardia in the 10 noninducible patients with arrhythmia, while 5 of 17 with arrhythmia that was still inducible at late electrophysiologic testing had recurrences. In addition, the clinical outcome was similar to the clinical response to the induced tachycardia. Three of eight patients with nontolerated tachycardia at late electrophysiologic testing died suddenly, whereas only one of nine who had a tolerated tachycardia died suddenly. This patient had decreased his dose of amiodarone and presumably no longer had adequate serum levels of amiodarone. Another finding is that some patients have tolerated tachycardia at late electrophysiologic testing even if the arrhythmia is poorly tolerated initially. It seems appropriate to provide an alternative or additive (that is, a combined) drug regimen for these patients until amiodarone reaches its steady state effect.

Comparison with previous studies. Several other studies have evaluated patients early and late in the course of amiodarone therapy. Kadin et al. (13) evaluated 29 patients with recurrent sustained ventricular tachycardia or cardiac arrest with early (2 weeks) and late (after mean of 5 months) electrophysiologic testing. Twenty-one of 22 patients studied early had inducible arrhythmia, whereas 26 of 29 had inducible arrhythmia at late study. The predictive value of their early and late study is difficult to assess because many of their patients were taking a concomitant type 1 antiarrhythmic drug. None of our patients received an antiarrhythmic drug in addition to amiodarone after late electrophysiologic testing. Wyndham et al. (24) observed that the percent of patients whose arrhythmia becomes noninducible during amiodarone therapy increases over time. Ferrick et al. (25) also observed that the percent of patients with noninducible arrhythmia changed after 2 weeks and 3 months of therapy. The optimal timing of late electrophysiologic testing was not addressed by these studies.

Clinical implications. Patients with life-threatening ventricular arrhythmia treated with amiodarone may be risk stratified with serial electrophysiologic testing. Those without inducible arrhythmia appear to be at low risk for recurrent arrhythmia, whereas those with continued induction of ventricular tachycardia are at high risk. Although we could not find any clinical or electrophysiologic variable that predicted recurrence, those patients with inducible poorly tolerated tachycardias were at relative risk for sudden death. Whereas the percent of patients with no inducible arrhythmia while receiving amiodarone appears to change over time, it is not clinically feasible to wait several months before electrophysiologic testing. Therefore, electrophysiologic testing has generally been performed after oral loading. If a poorly tolerated tachycardia is induced at early electrophysiologic testing, the addition of a type I antiarrhythmic agent may sufficiently slow the tachycardia rate to produce hemodynamic benefit. If rapid tachycardia is still inducible at either early or late study, an alternative therapy such as implantation of an internal defibrillator or arrhythmia surgery should be explored. In patients with an automatic implantable defibrillator that uses the rate of ventricular tachycardia for detection, late electrophysiologic testing is indicated because ventricular tachycardia cycle length prolongs between the loading dose period and steady state.

Amiodarone is an extremely effective drug for the treatment of life-threatening arrhythmias. However, in our study group, 13 (31%) of 42 patients still had recurrent arrhythmia, and 7 of the 13 died suddenly. Serial electrophysiologic studies may be useful in developing treatment strategies in patients with life-threatening ventricular arrhythmias treated with amiodarone.

References


