Electropharmacology of Amiodarone Therapy Initiation

Time Courses of Onset of Electrophysiologic and Antiarrhythmic Effects

L. Brent Mitchell, MD, D. George Wyse, MD, PhD,
Anne M. Gillis, MD, and Henry J. Duff, MD

The time courses of onset of the electrophysiologic and antiarrhythmic effects of amiodarone were determined with serial electrophysiologic studies in 34 patients with inducible ventricular tachycardia. A standardized oral loading dosage was used for all patients (1,200 mg/day for 14 days; 800 mg/day for 7 days; and 400 mg/day thereafter). Eleven patients had the studies performed at baseline and after 2, 6, 10, and 20 weeks. Subsequently, 23 patients had studies at baseline and after 2 and 10 weeks. Changes in atrial, sinus, and atrioventricular nodal properties and in conduction intervals were maximal within 2 weeks (early effects). For example, atrioventricular nodal Wenckebach cycle length increased between baseline (369±80 msec) and 2 weeks (498±78 msec) (p<0.001) but did not change further after 10 weeks (500±89 msec). However, ventricular Class III effects required 10 weeks to become maximal (late effects). For example, the QT interval during atrial pacing increased between baseline (355±36 msec) and 2 weeks (406±37 msec) (p<0.001) and increased further after 10 weeks (436±45 msec) (p<0.001). Antiarrhythmic effects also followed different time courses of onset. Suppression of ventricular premature beats was maximal within 2 weeks. However, suppression of ventricular tachycardia inducibility and slowing of ventricular tachycardia rate was not maximal for 10 weeks. Correlations between serum desethylamiodarone concentrations and some late effects suggest that the mechanism of the time delay to maximal ventricular Class III effects may involve desethylamiodarone. In conclusion, the time courses of onset of the electrophysiologic and antiarrhythmic effects of amiodarone are dependent on the site and type of effect. (Circulation 1989;80:34–42)

Amiodarone was first introduced as an antiarrhythmic agent 20 years ago. Since that time, it has been recognized as very effective therapy for a broad spectrum of tachyarrhythmias. However, widespread acceptance of this agent has been slowed by the potential severity of its many adverse effects and by its unusual pharmacokinetics. The adverse effect profile of amiodarone has limited its use to circumstances where the need for effective therapy outweighs the potential risks. Thus, amiodarone therapy is usually reserved for patients with drug-resistant, life-threatening tachyarrhythmias. The unusual pharmacokinetic features of amiodarone include a very long elimination half-life (approximately 25–60 days), an active metabolite that may have an even longer elimination half-life, and a long time delay between therapy initiation and maximum pharmacologic effects. These characteristics have resulted in the routine use of loading regimens to shorten the time delay between therapy initiation and maximal effects.

The purpose of the present study was to examine the pharmacology of amiodarone therapy initiation with serial studies of patients with symptomatic ventricular tachycardia or ventricular fibrillation. We evaluated specific questions: How long after therapy initiation do the electrophysiologic effects of amiodarone become maximal? Are the time delays...
TABLE 1. Characteristics of Study Patients

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Group 1</th>
<th>Group 2</th>
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</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>41</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Age (yr, mean±SD)</td>
<td>61±11</td>
<td>60±9</td>
<td>64±10</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>36 (88%)</td>
<td>11 (100)</td>
<td>19 (83)</td>
</tr>
<tr>
<td>LVEF, documented ventricular fibrillation</td>
<td>0.36±0.14</td>
<td>0.38±0.11</td>
<td>0.38±0.15</td>
</tr>
</tbody>
</table>

Values are mean±SD or number of subjects (%). LVEF, radionuclide left ventricular ejection fraction; VF, documented ventricular fibrillation; sustained VT, documented, symptomatic sustained ventricular tachycardia; nonsustained VT, documented, symptomatic nonsustained ventricular tachycardia; SUO, syncope of unknown origin with inducible, sustained ventricular tachycardia; EP trials, number of failed electropharmacologic trials.

...to maximal electrophysiologic effects of amiodarone the same for all effects? How long after therapy initiation do the ventricular arrhythmic effects of amiodarone become maximal? Are the time delays to maximal effects related to serum concentrations of amiodarone or its major metabolite, desethylamiodarone?

**Methods**

**Study Patients**

Patients presenting with symptomatic ventricular tachycardia or ventricular fibrillation or syncope of unknown etiology were candidates for participation in this study if ventricular tachycardia or ventricular fibrillation was reproducibly induced during a baseline electrophysiologic study. If no effective therapy could be found by subsequent serial electropharmacological testing, the patients were considered for implanted antitachycardia device therapy, electrosurgical therapy, or long-term empiric amiodarone therapy. Patients who were to be treated with long-term amiodarone therapy were invited to participate in the present study. Forty-one consecutive consenting patients were enrolled. The group consisted of 36 men and 5 women with a mean age of 61±11 years. The clinical features of these patients are presented in Table 1. Forty of these patients (98%) had atherosclerotic heart disease, and 38 (93%) had experienced a remote myocardial infarction. One patient had hypertensive heart disease. These patients had undergone a mean of 6.6±1.7 unsuccessful drug trials before being considered for amiodarone therapy.

**Study Protocol**

Each patient received amiodarone in a standardized dosage. The initial daily dosage was 1,200 mg for 14 days. The daily dosage was then reduced to 800 mg for the next 7 days. Thereafter, the daily maintenance dosage was 400 mg. To examine in detail the onset of the electrophysiologic and arrhythmic effects of amiodarone, the first 11 patients completing the protocol (group 1) had serum amiodarone and desethylamiodarone concentration determinations, a 24-hour ambulatory electrocardiogram (ECG), and an electrophysiologic study performed at baseline and after 2, 6, 10, and 20 weeks of amiodarone therapy. The data from group 1 patients identified the optimal timing of follow-up studies and indicated that the remaining aims of the study could be achieved by repeating these measurements at less-frequent intervals. Accordingly, the remaining 23 patients presenting the protocol (group 2) had these investigations performed at baseline and after 2 and 10 weeks of amiodarone therapy.

The present study was approved by the Conjoint Medical Ethics Committee of the University of Calgary and Foothills Provincial General Hospital.

**Electrophysiologic Studies**

Electrophysiologic studies were performed with dilute (0.33%) lidocaine local anesthesia. Surface ECG leads I, aVF, and V₁ were recorded simultaneously with intracardiac electrograms from the high right atrium, His bundle recording site, and right ventricular apex at a paper speed of 100 mm/sec (Electronics for Medicine VR 16, Siemens Mingograf). Cardiac pacing was performed with a programmable stimulator (Bloom Associates) with stimuli 2 msec in duration and of tenfold diastolic threshold intensity.

Electrophysiologic intervals were determined from the mean of five successive cycles during both sinus rhythm and constant rate atrial pacing using standard definitions. The maximum corrected sinus node recovery time (CSNRT) was the longest recovery cycle length minus the spontaneous sinus cycle length observed after 30 seconds of atrial pacing at cycle lengths of 700, 600, 500, and 400 msec. The atrioventricular (AV) node Wenckebach cycle length (WCL) was the cycle length that first conducted with Type I second-degree AV block during decremental atrial pacing. The atrial effective refractory period (AERP), atrial functional refractory period (AFRP), AV nodal effective refractory period (AVERP), AV nodal functional refractory period (AVFRP), ventricular effective refractory period (VERP), and ventricular functional refractory period (VFRP) were determined by the extrastimulus technique using standard definitions.

Ventricular tachycardia was defined as 5 or more consecutive ventricular beats at a cycle length of 500 or less msec and was considered sustained when it persisted for 30 or more seconds or required termination because of hemodynamic collapse. The rationale of our ventricular tachycardia induction protocol has been described previously. Single, double, and triple extrastimuli were applied to the right ventricular apex after 8-beat trains of 600, 500, and 400 msec. Thereafter, 4- and 15-beat trains of
rapid ventricular pacing at cycle lengths of 300–240 msec (in 10-msec decrements) were applied. In all study patients, ventricular tachycardia was reproducibly induced by this protocol. The end-point of ventricular stimulation during amiodarone treatment was completion of the protocol or induction of sustained ventricular tachycardia. The electrophysiologist had the option of stopping programmed stimulation after induction of nonsustained runs of rapid ventricular tachycardia in patients who had previously required transthoracic cardioversion. Effective antiarrhythmic therapy was defined as the inability to induce ventricular tachycardia. Ventricular tachycardia induced during amiodarone treatment was considered to be the same as that induced at baseline if the bundle branch patterns were the same (right bundle branch block pattern, left bundle branch block pattern) and the frontal plane QRS axes were in the same quadrant.

As this investigation was nearing completion, Waller et al.\textsuperscript{51} reported that a beneficial response to antiarrhythmic drug therapy could be predicted by electrophysiologic study despite continued ventricular tachycardia inducibility if the ventricular tachycardia cycle length was prolonged by more than 100 msec compared with baseline, if the ventricular tachycardia could be terminated by pacing techniques, and if the ventricular tachycardia did not produce symptoms of hemodynamic compromise. Data relevant to the last of these criteria were not collected prospectively during the present investigation. Nevertheless, we report the time dependence of the first two criteria of a beneficial antiarrhythmic effect.

**Ambulatory Electrocardiographic Monitoring**

Ambulatory ECG recordings were analyzed with commercially available systems (Instrument for Cardiac Research, Cardiodata). Tapes not suitable for automated analysis were printed in their entirety and were counted by hand. We have previously reported the mean±SD reproducibility (92±8%) and accuracy (86±8%) of hourly ventricular prematurity beat (VPB) frequency determinations with this analysis system.\textsuperscript{52}

**Drug Concentration Determination**

Serum amiodarone and desethylamiodarone concentrations were determined by high-performance liquid chromatography.\textsuperscript{53} The observed day-to-day variability with a 1 μg/ml test sample was 4% with a mean±SD of 0.96±0.08 μg/ml.

**Statistical Analysis**

Continuous data are presented as mean±SD and were compared with unpaired or paired t tests. Proportional data were compared with χ² techniques. The time dependence of changes in electrophysiologic measurements were examined with two-way analysis of variance with Duncan's multiple range test. The relations between changes in electrophysiologic measurements and serum amiodarone and desethylamiodarone concentrations were examined by linear regression. VPB frequency was transformed to ln(VPB+1) to create a normally distributed variable before analysis. The null hypothesis was rejected when the two-tailed p value was <0.05.

**Results**

**Study Patients**

Forty-one consecutive consenting patients were enrolled in this study. The first 11 patients to complete the protocol had serum drug determinations, ambulatory ECG recordings, and electrophysiologic studies performed at baseline and after 2, 6, 10, and 20 weeks of amiodarone therapy (group 1). The next 23 patients completing the protocol had these investigations performed at baseline and after 2 and 10 weeks of amiodarone therapy (group 2). There were no significant differences in clinical characteristics between group 1 and group 2 patients (Table 1). The remaining seven patients did not complete the protocol—one patient died suddenly after 3 weeks of amiodarone therapy, one patient developed unstable angina precluding follow-up electrophysiologic testing, and five patients withdrew consent. Patients who were unable to complete the protocol had a lower mean left ventricular ejection fraction (0.26±0.12) than patients who completed the protocol (0.38±0.14) (p=0.04), but there were no other significant differences in clinical characteristics between these two groups.

**Time-Electrophysiologic Effect Relations**

The data collected from group 1 patients demonstrated two distinct time courses of electrophysiologic changes after amiodarone therapy initiation. Changes in conduction intervals and measures of the electrophysiology of the atrium and of the sinus and AV nodes occurred within 2 weeks of amiodarone therapy without further changes thereafter (Figure 1, upper panel). In contrast, changes in measures of ventricular repolarization and refractoriness were not completed until after 10 weeks of amiodarone therapy (Figure 1, lower panel). There were no changes in any electrophysiologic measurement between the 10-week and the 20-week electrophysiologic studies. Based on these initial observations, group 2 patients were assessed at baseline and after 2 and 10 weeks of therapy. These data and the data from group 1 patients were combined and are presented in Table 2.

The majority of the electrophysiologic effects of amiodarone demonstrated an “early” time course of onset with no significant change after 2 weeks of therapy (Table 2). However, two measurements demonstrated additional significant changes after the 2-week study. The QT interval during fixed rate atrial pacing increased from baseline (355±36 msec) to the 2-week study (406±37 msec) (p<0.001) and then increased further after 10 weeks of therapy.
(436±45 msec) \( (p<0.001) \). Similarly, the VFRP increased from baseline (274±30 msec) to the 2-week study (310±27 msec) \( (p<0.001) \) and then further increased after 10 weeks of therapy (325±30 msec) \( (p<0.001) \). Although VERP increased from baseline (238±28 msec) to the 2-week study (277±24 msec) \( (p<0.001) \), the further increase after 10 weeks of therapy (282±30 msec) did not reach statistical significance \( (p=0.17) \).

**Time-Antiarrhythmic Effect Relations**

Three measures of antiarrhythmic efficacy were examined in these patients—suppression of spontaneous VPB, suppression of inducible ventricular tachycardia, and slowing of inducible ventricular tachycardia. The drug-free 24-hour ambulatory ECG examination demonstrated a mean VPB frequency of 160±249/hr. As shown in Figure 2, there was a significant decrease in VPB frequency after 2 weeks of amiodarone therapy (37±118/hr; average reduction, 77%) \( (p<0.01) \) that did not change further after 10 weeks of therapy (32±84/hr; average reduction, 80%). Of the 25 patients with a baseline VPB frequency of 10/hr or more, 18 patients (72%) had at least 80% VPB suppression after 2 weeks of therapy. In contrast, a cumulative antiarrhythmic effect as assessed by inducible ventricular tachycardia was noted between the 2- and 10-week electrophysiologic studies. All patients had inducible ventricular tachycardia before amiodarone administration and after 2 weeks of amiodarone therapy. However, three patients did not have inducible ventricular tachycardia at the time of the 10-week electrophysiologic study \( (p=0.07) \). Of the 31 remaining patients with inducible ventricular tachycardia at each of the electrophysiologic studies, 22 patients had the same ventricular tachycardia induced at each study. As shown in Figure 2, the ventricular tachycardia cycle length increased from baseline (248±60 msec) to the 2-week study (313±69 msec) \( (p<0.001) \) and then increased further after 10 weeks of therapy (341±79 msec) \( (p<0.05) \).

The time course of a beneficial antiarrhythmic response to amiodarone was assessed in the 11 group 1 patients. A beneficial antiarrhythmic response included treatment studies during which ventricular tachycardia was no longer inducible and studies during which the induced ventricular tachycardia satisfied the first two criteria of a beneficial drug response (see “Methods”) of Waller et al.\(^{51}\)
TABLE 2. Time Course of Electrophysiologic Effects of Amiodarone

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 wk</th>
<th>10 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSCL</td>
<td>754±127</td>
<td>891±177*</td>
<td>913±165</td>
</tr>
<tr>
<td>CSNRT</td>
<td>308±92</td>
<td>430±298*</td>
<td>357±149</td>
</tr>
<tr>
<td>AERP</td>
<td>230±26</td>
<td>301±49*</td>
<td>305±49</td>
</tr>
<tr>
<td>AFRP</td>
<td>264±24</td>
<td>338±45*</td>
<td>342±46</td>
</tr>
<tr>
<td>Paced AH</td>
<td>114±42</td>
<td>179±68*</td>
<td>178±62</td>
</tr>
<tr>
<td>WCL</td>
<td>369±80</td>
<td>498±78*</td>
<td>500±89</td>
</tr>
<tr>
<td>AVERP</td>
<td>238±28</td>
<td>277±24*</td>
<td>325±30t</td>
</tr>
<tr>
<td>VERP</td>
<td>353±86</td>
<td>417±75</td>
<td>423±78</td>
</tr>
<tr>
<td>AVFRP</td>
<td>417±72</td>
<td>519±95*</td>
<td>514±101</td>
</tr>
<tr>
<td>Paced HV</td>
<td>49±13</td>
<td>58±22*</td>
<td>57±15</td>
</tr>
<tr>
<td>Paced QRS</td>
<td>113±28</td>
<td>136±32*</td>
<td>130±33</td>
</tr>
<tr>
<td>VFRP</td>
<td>355±36</td>
<td>406±37*</td>
<td>436±45$</td>
</tr>
<tr>
<td>VFRP</td>
<td>274±30</td>
<td>310±27*</td>
<td>325±30$</td>
</tr>
</tbody>
</table>

Values are mean±SD (msec).
*p<0.001 comparing 2 weeks with baseline; tp<0.01 comparing 2 weeks with baseline; $p<0.001 comparing 10 weeks with 2 weeks.

SSCL, spontaneous sinus cycle length; CSNRT, maximal corrected sinus nodal recovery time; AERP, atrial effective refractory period; AFPR, atrial functional refractory period; paced, interval determined during fixed-rate atrial pacing; WCL, atrial pacing cycle length producing Wenckebach atrioventricular (AV) nodal block; AVERP, AV nodal effective refractory period; AVFRP, AV nodal functional refractory period; VERP, ventricular effective refractory period; VFRP, ventricular functional refractory period.

After 2 weeks of amiodarone therapy, three of the 11 patients (27%) demonstrated a beneficial response; after 6 weeks of therapy, four patients (36%) had a beneficial response; and after 10 weeks of therapy, six patients (55%) had a beneficial response. No further increase in the proportion of patients demonstrating a beneficial response occurred between the 10- and 20-week electrophysiologic studies.

Time-Concentration Relations

The time dependence of amiodarone and desethylamiodarone serum concentrations are shown in

Figure 2. Plots of time dependence of onset of the antiarrhythmic effects of amiodarone in group 2 patients. Group mean±SD values are plotted against the number of weeks after amiodarone therapy initiation. *p<0.05 compared with the preceding point on the time course graph; ln(VPB+1), normalized mean hourly ventricular premature beat frequency; VT, induced ventricular tachycardia.

Figure 3. There was no significant difference between the mean serum amiodarone concentrations after 2 and 10 weeks of therapy (1.6±0.8 vs. 1.4±0.7 μg/ml, respectively). However, the mean serum desethylamiodarone concentration increased from the second week (0.8±0.3 μg/ml) to the tenth week of therapy (1.0±0.4 μg/ml) (p=0.03). Relations between changes in electrophysiologic measurements and serum concentrations of amiodarone and desethylamiodarone were examined by linear regression. The data points for this linear regression analysis were defined by a change in an electrophysiologic measurement (value at time t value at baseline) and by the serum drug concentrations at time t. Accordingly, data from group 1 patients included 2-, 6-, 10-, and 20-week samples while data from group 2 patients included 2- and 10-week samples. Changes in seven electrophysiologic measurements were significantly correlated with either amiodarone or desethylamiodarone concentrations (Table 3). Changes in five measurements (spontaneous sinus cycle length, paced AH interval, AVERP, AVFRP, and WCL) were significantly correlated with serum amiodarone concentration. The time course of change of each of these measurements was early (completed within 2 weeks; see Figure 1). The change in VFRP was significantly correlated with serum desethylamiodarone concentration. The time course of change of this measurement was late (not completed until 10 weeks of therapy; see Figure 1). The change in VERP was significantly correlated with both serum amiodarone and desethylamiodarone concentrations. The time course of change of this measurement was intermediate between the early and late patterns (see Figure 1).

Discussion

The present study assessed time courses of onset of electrophysiologic and antiarrhythmic effects of amiodarone using an oral loading dosage regimen representative of those in general use. Most of the electrophysiologic effects of amiodarone have
reached steady state 2 weeks after therapy initiation. These early effects are those of Class I (sodium channel blocking), Class IV (calcium channel blocking), and antiadrenergic activities. In contrast, the effects of amiodarone on QT interval and on VERP and VFRP are not maximal for 6–10 weeks. These late effects have a common dependence on prolongation of ventricular muscle action potential duration. Onset of the ventricular antiarrhythmic effects of amiodarone also follows two different time courses. Suppression of VPB frequency is maximal within 2 weeks. However, effects on inducibility of ventricular tachycardia and on the cycle length of ventricular tachycardia are not maximal for 10 weeks. Early effects tend to correlate with serum amiodarone concentrations, whereas late effects tend to correlate with serum desethylamiodarone concentrations.

### Time-Electrophysiologic Effect Relations

The acute electrophysiologic effects of amiodarone are dominated by increases in AH interval and AV nodal refractory periods. Sinus nodal recovery time is prolonged, and the sinus cycle length may lengthen. Thus, the immediate actions of amiodarone are nodal antiadrenergic or Class IV effects or both. With longer usage, changes compatible with Class I and Class III effects become manifest. However, considering the long half-life of amiodarone, these changes will not reach steady state until after many weeks of maintenance therapy. Consequently, step-down, oral, loading dosage regimens have been recommended. With such regimens, many investigators have demonstrated diffuse and marked electrophysiologic effects after 1–2 weeks of amiodarone therapy. Nevertheless, three groups have reported that the effects of several months of therapy exceed those of 1–2 weeks of therapy. The most consistent observations are that ventricular tachycardia is less often inducible and has a longer cycle length after several months of therapy. Kadow et al also noted a significant increase in VERP between an early and a late electrophysiologic study. The present study extends these observations by determining the time courses of onset of the effects of amiodarone using frequent, prospectively timed, serial electrophysiologic studies in humans.

Previous attempts to define these time courses with serial electrophysiologic studies have been limited to animal models. Tuna et al examined the effects of amiodarone loading using daily electrophysiologic studies in dogs. They found that increases in ERPs followed different time courses. Effects on right atrial ERP were maximal after 3 days and effects on VERP were maximal after 12 days. However, the right VERP increased throughout their 21-day experiment. Our results indicate similar site-dependent time courses of electrophysiologic change during oral amiodarone loading in humans.

### Time-Antiarrhythmic Effect Relations

The time courses of onset of the antiarrhythmic effects of amiodarone have been estimated previously with suppression of spontaneous ventricular arrhythmias. With constant (or increased) dosages, Naedeman et al noted VPB suppression beginning within 2–3 weeks and becoming maximal after 4–6 weeks. Similarly, with fixed dosages of 600 mg/day, Connolly et al noted VPB suppression after a mean of 13±12 days. Of relevance to site dependence, Rosenbaum et al have reported that antiarrhythmic effects are evident earlier when using the drug for supraventricular arrhythmias (5–20 days) than when using the drug for ventricular arrhythmias in patients with structural heart disease (20–60 days). Rakita and Sobol have reported that spontaneous ventricular arrhythmias are controlled in less time (mean, 16 days) when oral loading doses are used. With respect to suppression of VPB, our results are comparable to those of Rakita and Sobol. However, we noted further antiarrhythmic effect, as judged by inducibility of ventricular tachycardia and the cycle length of ventricular tachycardia, after 10 weeks of therapy. Furthermore, the proportion of patients with a beneficial antiarrhythmic response as assessed by programmed stimulation (see “Methods”) increased progressively from 27% after 2 weeks of therapy to 36% after 6 weeks of therapy to 55% after 10 weeks of therapy without further increases thereafter. These results indicate that the optimal time for electrophysiologic study assessment of amiodarone therapy for inducible ventricular tachycardia is 10 weeks after therapy initiation.

<table>
<thead>
<tr>
<th>TABLE 3. Concentration-Effect Relations</th>
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<tr>
<td></td>
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<tr>
<td>Amiodarone</td>
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<tr>
<td>r</td>
</tr>
<tr>
<td>AVERP</td>
</tr>
<tr>
<td>SSCL</td>
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<tr>
<td>Paced AH</td>
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<tr>
<td>AVFRP</td>
</tr>
<tr>
<td>WCL</td>
</tr>
<tr>
<td>Intermediate effects</td>
</tr>
<tr>
<td>Late effects</td>
</tr>
</tbody>
</table>

Linear regression r and p values for those electrophysiologic measurements with significant correlations with either amiodarone or desethylamiodarone serum concentrations.

AVERP, AV nodal effective refractory period; SSCL, spontaneous sinus cycle length; paced, interval determined during fixed-rate atrial pacing; AVFRP, AV nodal functional refractory period; WCL, atrial pacing cycle length producing Wenckebach atrioventricular (AV) nodal block; VERP, ventricular effective refractory period; VFRP, ventricular functional refractory period.
Mechanisms

Concentration-Effect Relations

The present study demonstrated significant correlations between serum drug concentrations and electrophysiologic effects. Amiodarone concentrations correlated with changes in sinus cycle length, atrial paced AH interval, AVERP, AVFRP, and WCL; desethylamiodarone concentrations correlated with changes in VFRP; both amiodarone and desethylamiodarone concentrations correlated with changes in VERP. Of note, the changes correlating with amiodarone concentration occurred with an early time course; the changes correlating with desethylamiodarone concentrations occurred with a late time course; changes correlating with both amiodarone and desethylamiodarone concentrations occurred with an intermediate time course. Consistent with these concentration-response relations, Talajic et al\textsuperscript{1} have reported that, in the dog, the dominant acute effect of intravenous amiodarone is depression of AV nodal refractoriness while the dominant effects of intravenous desethylamiodarone are prolongation of atrial and ventricular refractoriness. Although others have reported a correlation between serum drug concentrations and the rate-corrected QT interval,\textsuperscript{61} we did not observe a similar relation with the QT interval during fixed-rate atrial pacing.

The present study did not identify a relation between serum amiodarone or desethylamiodarone concentrations and antiarrhythmic efficacy (suppression of VPB or inducible ventricular tachycardia). The absence of a clear relation between these drug concentrations and efficacy has been reported by other investigators.\textsuperscript{19,25,28,29}

Potential Mechanisms

The common factor shared by the changes that occur late after amiodarone therapy initiation (increases in VERP, VFRP, QT interval, and VT cycle length and reduced VT inducibility) is their dependence on an increase in ventricular muscle action potential duration. Because there were no comparable time delays in the effects commonly considered to be Class I activity (e.g., QRS duration, HV interval), the late effects are most likely due to delayed expression of ventricular Class III effects rather than a selective, delayed expression of a component of Class IA activity.

With the loading dose regimen of the present study, amiodarone serum concentrations after 2 and 10 weeks of therapy are similar. Thus, late effects are not the result of differences in amiodarone concentrations in the central compartment. Potential mechanisms for the delay between therapy initiation and late steady-state ventricular effects include gradual formation of the metabolite desethylamiodarone,\textsuperscript{40,41,62} slow accumulation of amiodarone or desethylamiodarone in myocardium,\textsuperscript{63,64} and time-dependent metabolic phenomena required for expression of late ventricular effects such as changes in thyroid hormone homeostasis\textsuperscript{65,66} or cellular lipid metabolism.\textsuperscript{67,68} The present study cannot determine which, if any, of these potential mechanisms is operative. However, the tendency for late effects to correlate with desethylamiodarone concentrations indicates that the metabolite may be involved in the delay to late steady-state ventricular effects.

Conclusions

The present study demonstrates that the time courses of onset of the electrophysiologic and antiarrhythmic effects of amiodarone vary depending on the site and type of effect. Those effects with the latest course of onset include changes in ventricular effective and functional refractory periods, QT interval, ventricular tachycardia inducibility, and ventricular tachycardia cycle length. These changes require 10 weeks of therapy to become maximal despite the use of oral loading dosage regimens.

Acknowledgments

We appreciate the important contributions of Claire Miller, RN, and the staff of the Electrophysiology Laboratory and Unit 92 of the Foothills Provincial Hospital, Calgary.

References

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Key Words • desethylamiodarone • ventricular tachycardia • ventricular fibrillation • electrophysiologic testing
Electropharmacology of amiodarone therapy initiation. Time courses of onset of electrophysiologic and antiarrhythmic effects.
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Circulation. 1989;80:34-42
doi: 10.1161/01.CIR.80.1.34

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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