Kinetics of electrophysiologic changes during oral loading of amiodarone and after withdrawal of amiodarone in the unsedated dog

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ABSTRACT We examined the temporal kinetics of onset and offset of the cardiac electrophysiologic effects of orally administered amiodarone in chronically instrumented, unsedated adult dogs (n = 8). Right atrial (RA), atrioventricular nodal (AVN), and right ventricular (RV) effective refractory period (ERP), and AVN functional refractory period (FRP), were determined daily for 21 days during amiodarone loading (24 mg/kg/day) and for 21 days after cessation of amiodarone. Left ventricular (LV) ERP was assessed in four of eight animals. Group mean RA-ERP peaked and plateaued early during amiodarone loading (time to reach one-half observed peak change \( t_{1/2} \) onset = 1.2 ± 0.5 days) and rapidly returned toward baseline after cessation of drug (decay time to one-half peak value \( t_{1/2} \) offset = 2.0 ± 1.7 days). Group mean RV-ERP rose in a linear manner throughout the loading period \( t_{1/2} \) onset = 9.3 ± 2.1 days) and remained elevated after cessation of drug \( t_{1/2} \) offset > 21.0 days). Group mean AVN-ERP and FRP exhibited temporal kinetics intermediate between those of the RA-ERP and RV-ERP, both during amiodarone loading and after cessation of the drug. Group mean LV-ERP onset kinetics (assessed in a limited number of animals, \( n = 4 \)) appeared to differ from RV-ERP onset kinetics \( t_{1/2} \) onset = 2.5 ± 2.5 days), whereas LV-ERP and RV-ERP offset kinetics appeared similar \( t_{1/2} \) offset > 21 days). In summary, our findings demonstrate that during oral loading, the temporal sequence of onset of amiodarone-induced electrophysiologic effects is site dependent. Similarly, after cessation of amiodarone, the persistence of drug-induced electrophysiologic effects is both variable and site dependent.

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AMIODARONE is an investigational antiarrhythmic drug, undergoing evaluation for treatment of both ventricular and supraventricular tachyarrhythmias.1–7 Clinical studies have revealed that amiodarone possesses many novel properties, the foremost being a delayed onset of antiarrhythmic activity and a variable but prolonged half-life of antiarrhythmic activity after oral loading; the latter is estimated to be from 10 to 40 days.1, 4, 5, 8, 9 To understand the onset and offset characteristics of amiodarone’s cardiac electrophysiologic effects more fully, we sought to quantify the time course and magnitude of changes in atrial, atrioventricular nodal and ventricular refractory periods, His-ventricular conduction intervals, and pacing thresholds, during oral loading of amiodarone in an unsedated, chronically instrumented canine preparation. We further sought to determine the time course and magnitude of cardiac electrophysiologic changes after cessation of amiodarone loading. Finally, we wished to determine whether the onset and offset characteristics (i.e., temporal kinetics) of amiodarone-induced cardiac electrophysiologic changes differed among the cardiac tissues evaluated.

Methods

Experimental preparation. Adult mongrel dogs under inhalational anesthesia (\( n = 8 \)) and weighing 21 to 26 kg (mean 24)
were instrumented with pairs of bipolar epicardial electrodes for pacing/sensing the right atrium, right ventricle, and in four of eight animals, the left ventricle. A custom-manufactured bipolar epicardial His bundle electrode was additionally implanted in all animals, adjacent to the noncoronary sinus of Valsalva (figure 1).10 Animals were allowed 3 weeks to recuperate from surgery and conditioned to lie quietly in an unsedated state for subsequent electrophysiologic studies. This preparation yielded stable atrial, ventricular, and His bundle electrograms in all animals throughout the duration of the study.

**Experimental protocol.** Baseline determinations of atrial, atroventricular (AV) nodal, and ventricular refractory periods, His-ventricular (HV) conduction intervals, and pacing thresholds were obtained in all animals before administration of amiodarone (Cordarone, LABAZ). Amiodarone (24 mg/kg/day) was administered in a single daily oral dose for 21 days. Electrophysiologic measurements were obtained before each oral dose during the 21 day loading period. Daily electrophysiologic studies were continued for 21 days after cessation of amiodarone. The duration of the loading period (arbitrarily selected) was based on a desire to encompass the conventional 2 to 3 week loading periods typically used clinically.

**Electrophysiologic studies.** Electrophysiologic studies were carried out in awake unsedated animals conditioned to lie quietly. Right atrial effective refractory period (RA-ERP), AV nodal effective refractory period (AVN-ERP), AV nodal functional refractory period (AVN-FRP), and right and left ventricular effective refractory periods (RV-ERP and LV-ERP) were determined during bipolar pacing at cycle lengths of 450, 400, and 350 msec by means of an 8 beat drive train followed by a single extrastimulus.11 HV conduction intervals were measured during right atrial pacing at a cycle length of 450 msec.

Pacing and extrastimulus studies were performed at twice diastolic pacing threshold of the tissue being studied (Medtronic 5325 Programmable Stimulator). Electrograms were bandpass filtered (50 to 500 Hz) and amplified (Hewlett-Packard bioelectric amplifier, model 8811A) before being recorded on a multichannel recorder (Hewlett-Packard model 7404A) at a paper speed of 100 mm/sec. A digitizing tablet and interactive computer system (Complot Series 7000 digitizer, DEC, PDP 11/34 digital computer) were used to measure interstimulus and interelectrogram intervals.

**Data analysis.** Measurements of refractory period were normalized with respect to predrug baseline values and expressed as percent of baseline value. Normalized group mean values (with 95% confidence intervals) were plotted as a function of the day of drug administration (day 0 to day 21) or discontinuance (day 0 to day 21), with day 21 of drug administration corresponding to day 0 of drug discontinuance. Times to reach one-half peak observed change in refractory period during amiodarone loading (t½ onset) and time to decay to one-half peak observed change in refractory period after cessation of amiodarone (t½ offset) were determined for each animal at each site evaluated. Student’s t test was used to compare group mean t½ onset values and t½ offset data. Group mean HV intervals and right atrial, right ventricular, and left ventricular pacing thresholds during amiodarone administration (day 0 vs day 21) and after cessation of amiodarone (day 0 vs day 21) were similarly evaluated.

**Results**

Changes in measured variables from comparable sites were qualitatively and quantitatively similar among all animals. Group mean values at each site evaluated are therefore presented.

**Right atrial refractory periods.** Group mean RA-ERP (cycle length [CL] = 450 msec) peaked by approximately day 3 after initiation of oral amiodarone loading and appeared to remain relatively constant for the duration of the 21 day loading period (figure 2, A). Mean RA-ERP (CL = 450 msec) plateaued at 18 ± 5% above baseline, with a t½ onset of 1.2 ± 0.5 days.

After cessation of amiodarone loading, group mean RA-ERP (CL = 450 msec) returned toward baseline with a t½ offset of 2.0 ± 1.7 days (figure 2, B). Findings were comparable at other cycle lengths tested (table 1).

**AV nodal refractory periods.** Group mean AVN-ERP (CL = 450 msec) increased more slowly and variably than did RA-ERP, reaching an apparent plateau approximately 12 days after initiation of amiodarone loading (figure 3, A). Mean AVN-ERP (CL = 450 msec) plateaued at 54 ± 31% above baseline, with a t½ onset of 5.8 ± 5.2 days. With cessation of amiodarone, group mean AVN-ERP (CL = 450 msec) varied in a complex, biphasic manner (figure 3, B), precluding calculation of t½ offset. AVN-ERP demonstrated a primary return toward baseline occurring within 2 days after cessation of amiodarone, followed by rebound elevation and a secondary decay at 16 days after withdrawal of drug. Group mean AVN-FRP changes paralleled AVN-ERP changes both during and after cessation of oral amiodarone loading. Mean AVN-FRP (CL = 450 msec) plateaued at 36 ± 15% above baseline,

[FIGURE 1. Representation of epicardial His bundle electrode implantation. The right atrial appendage (RAA) is retracted to show the aortoatrial groove, developed through dissection of the base of the right atrial appendage (asterisk) off the aorta (AO). The site of electrode implantation (arrow), typically at the junction of the right and noncoronary sinuses of Valsalva, in the aortoatrial groove, is determined via intraoperative His bundle mapping. SVC = superior vena cava; RA = right atrium; RCA = right coronary artery; RV = right ventricle.]
with a $t_{1/2}$ onset of 4.3 ± 3.7 days. AVN-FRP (CL = 450 msec) values, like those of AVN-ERP, decayed in a complex manner after cessation of amiodarone loading. Findings at shorter cycle lengths (400 or 350 msec) could not be evaluated because drug-induced increases in AVN-ERP and AVN-FRP precluded assessment at these cycle lengths.

Right ventricular refractory periods. Group mean RV-ERP (CL = 450 msec) increased in a linear manner throughout the entire 21 day loading period (figure 4, A). RV-ERP (CL = 450 msec) rose 21 ± 5% above baseline, with a $t_{1/2}$ onset of 9.3 ± 2.1 days. After cessation of amiodarone, group mean RV-ERP (CL = 450 msec) remained elevated above baseline for the duration of the study, with a $t_{1/2}$ offset of greater than 21 days (figure 4, B). Findings at other cycle lengths were similar (table 1).

Left ventricular refractory periods. Group mean LV-ERP (CL = 450 msec) (based on observations in four animals) appeared to peak early, then plateaued at 15 ± 5% above baseline, with a $t_{1/2}$ onset of 2.5 ± 2.5 days (figure 5, A). After cessation of amiodarone, group mean LV-ERP (CL = 450 msec) remained elevated above baseline (figure 5, B), with a $t_{1/2}$ offset of greater than 21 days. Findings at other cycle lengths were comparable (table 1).

**FIGURE 2.** Graph depicting the temporal effect of orally administered amiodarone (A), or cessation of amiodarone (B) on group mean RA-ERP (CL = 450 msec) measured in dogs (n = 8). The ordinate indicates RA-ERP expressed as a percentage of predrug baseline value. The abscissa indicates day of amiodarone administration or withdrawal. Panels A and B depict measurements of RA-ERP over 42 consecutive days, with day 21 in panel A corresponding to day 0 in panel B. 95% confidence intervals are indicated for each data point (± 2 SEM).
temporal onset of amiodarone’s electrophysiologic actions progressed at variable, site-dependent rates. Specifically, the maximal effect of amiodarone on right atrial refractoriness occurred before its maximal effect on AV nodal refractoriness, which in turn occurred before its maximal effect on right ventricular refractoriness. (2) Offset kinetics of electrophysiologic effects after cessation of amiodarone demonstrated similar site-dependent characteristics, with right atrial effects regressing before AV nodal effects, while regression of right and left ventricular effects were minimal during this time. (3) Amiodarone-induced changes in the electrophysiologic properties of the right atrium, AV node, right ventricle and left ventricle regressed in a complex, biphasic manner after withdrawal of drug. (4) Amiodarone had no effect on conduction through the His-Purkinje system, as assessed by HV interval measurements.

Changes in refractory period during administration of amiodarone. Clinical studies have attempted to assess the electrophysiologic effects of amiodarone serially during oral loading. Wells et al. assessed RA-ERP, AVN-ERP, and RV-ERP in 15 patients before and after 14 days of oral amiodarone loading (6.3 g total loading dose); RA-ERP and AVN-ERP rose 20% and 39% above predrug levels, respectively, whereas RV-

**FIGURE 4.** Graph depicting the temporal effect of orally administered amiodarone (A) or cessation of amiodarone (B) on group mean RV-ERP (CL = 450 msec) measured in dogs (n = 8). The ordinate indicates RV-ERP expressed as a percentage of predrug baseline value. The abscissa indicates day of amiodarone administration or withdrawal. The format of the figure is otherwise the same as figure 2. 95% confidence intervals are indicated for each data point (± 2 SEM).

**FIGURE 5.** Graph depicting the temporal effect of orally administered amiodarone (A) or cessation of amiodarone (B) on group mean LV-ERP (CL = 450 msec) measured in dogs (n = 4). The ordinate indicates LV-ERP expressed as a percentage of predrug baseline value. The abscissa indicates day of amiodarone administration or withdrawal. The format of the figure is otherwise the same as figure 2. 95% confidence intervals are indicated for each data point (± 2 SEM).

**HV intervals.** Group mean HV intervals (CL = 450 msec) were not significantly altered by amiodarone loading (day 0, 29.1 ± 2.7 msec; day 21, 30.0 ± 2.5 msec, p = NS) or by cessation of amiodarone (day 0, 30.0 ± 2.5 msec; day 21, 29.5 ± 2.9 msec, p = NS).

**Pacing thresholds.** Although group mean right atrial pacing threshold appeared to rise minimally during oral amiodarone loading, the difference was not statistically significant (day 0, 1.6 ± 0.5 mA; day 21, 1.8 ± 0.8 mA, p = NS), and reversal did not occur after cessation of amiodarone (day 0, 1.8 ± 0.8 mA; day 21, 1.9 ± 0.7 mA, p = NS). Group mean right ventricular pacing threshold behaved similarly during amiodarone loading (day 0, 1.7 ± 0.9 mA; day 21, 1.9 ± 0.9 mA, p = NS) and after cessation of amiodarone (day 0, 1.9 ± 0.9 mA; day 21, 2.0 ± 0.9 mA, p = NS), as did group mean left ventricular pacing threshold (amiodarone loading: day 0, 0.8 ± 0.4 mA, day 21, 3.0 ± 2.7 mA, p = NS; cessation of amiodarone administration: day 0, 3.0 ± 2.7 mA, day 21, 3.2 ± 2.6 mA, p = NS).

**Discussion**

Four principal observations regarding the temporal sequence of electrophysiologic effects of orally administered amiodarone were made in this study: (1) The

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ERP rose only 10%. The magnitude of RA-ERP and AVN-ERP changes are comparable to our findings, while smaller RV-ERP changes may be interpreted as indicating that maximal effect had not yet occurred. This interpretation is supported by the results of clinical studies, which indicate that RV-ERP may be expected to rise 15% to 20% above baseline after 2 to 4 months of amiodarone administration.12-19 Mitchell et al.13 evaluated seven patients at 2, 6, and 10 weeks after onset of amiodarone loading (22.4 g total loading dose over 21 days, 400 mg/day maintenance dose) and noted that Wenckebach cycle lengths maximized within 2 weeks of therapy, whereas RV-ERP required 6 weeks to maximize at 18% above control. In a similar study, Kennedy et al.14 evaluated 25 patients with electrophysiologic studies at 8 and 69 days after onset of oral amiodarone loading (9.6 g total loading dose over 8 days, 660 mg/day maintenance dose). RA-ERP and Wenckebach cycle length changes (20% and 38% above baseline, respectively) plateaued by day 8, while RV-ERP rose 15% above baseline by day 69. In summary, the temporal sequence of onset of amiodarone’s cardiac electrophysiologic actions in these clinical studies appears consistent with site-specific differences in the temporal onset of amiodarone’s electrophysiologic actions identified in this study.

Changes in refractory period after withdrawal of amiodarone. Studies serially evaluating the regression of amiodarone-induced electrophysiologic changes after drug withdrawal have not been performed in humans. In the present study, electrophysiologic changes regressed in a complex, site-dependent manner after the cessation of amiodarone. A primary decay in refractory periods occurring 2 to 4 days after cessation of amiodarone, followed by rebound elevation and a secondary decay at 15 to 18 days after withdrawal of drug, is qualitatively present in measurements from all sites (figure 2, B, and 5, B), but is most apparent in AVN-ERP measurements (figure 5, B). These electrophysiologic findings mimic the biphasic plasma amiodarone elimination profile reported by Holt et al.9 in humans after withdrawal of long-term amiodarone therapy (200 to 600 mg/day, administered for longer than 30 days). In the latter study, plasma amiodarone levels fell to half steady-state levels by day 2.5, demonstrated rebound elevation, and fell again at 12 to 21 days after cessation of therapy.

Effect of amiodarone on intraventricular conduction. The reported effects of oral amiodarone on conduction through the His-Purkinje system have been variable. Zipes et al.20 noted a 10% to 20% prolongation in HV intervals in patients treated with a variety of oral amiodarone regimens (dosages typically lower than those in the present study). Reports on the effects of amiodarone on HV conduction intervals have ranged from infra-Hisian block to lack of a measurable effect.1, 4, 15, 18, 19, 21-23 In the present study, mean HV conduction intervals varied less than 2% throughout the loading and withdrawal periods and demonstrated no significant deviation from control values.

Clinical implications. Our findings are consistent with the observations of Rosenbaum et al.24 on latency and duration of amiodarone’s antiarrhythmic effects. Among 2000 patients undergoing treatment for a variety of arrhythmias, supraventricular tachyarrhythmias (including atrial fibrillation/flutter) were reported to respond maximally to amiodarone within 5 to 20 days of initiation of therapy, whereas ventricular arrhythmias (in the setting of ischemic heart disease) required 20 to 30 days of therapy before maximal response was achieved. Similarly, atrial arrhythmias were reported to recur as soon as 15 days after drug withdrawal, whereas ventricular arrhythmias typically recurred after drug had been withheld for 30 to 40 days. Our observations suggest that underlying these site-specific differences in latency and duration of amiodarone’s antiarrhythmic effects may be site-specific differences in drug-induced electrophysiologic effects on the atria, AV node, and ventricles.

The basis for site-dependence in the electrophysiologic effects of amiodarone is not clearly understood. Whether differential binding and storage of amiodarone and its metabolites (already demonstrated among various noncardiac tissues25) exists between atrial, AV nodal, and ventricular tissues, contributing to site-specific differences in local tissue amiodarone levels, remains to be determined but may be a potential mechanism underlying these observations. Indeed, our findings of qualitatively similar biphasic changes in refractory period measurements at all cardiac sites after amiodarone withdrawal (mimicking regression of plasma amiodarone levels after cessation of amiodarone in humans)25 in the presence of significant quantitative electrophysiologic differences between cardiac sites suggests that factors in addition to plasma drug concentration may be involved in local tissue response to amiodarone.

In summary, our findings indicate that the time course of amiodarone’s electrophysiologic effects differs among various cardiac tissues, both during amiodarone loading and after withdrawal of drug. Although the basis for this site dependence is not clearly understood, these observations provide insight into previously reported temporal differences in onset and du-
ration of maximal antiarrhythmic effect during oral amiodarone therapy for supraventricular and ventricular arrhythmias.

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