Effect of Amiodarone on Conduction and Refractoriness of the His-Purkinje System in the Human Heart

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Although the antiarhythmic aspect of amiodarone has been extensively studied, its effects on His-Purkinje system conduction and refractoriness have not been systematically investigated in human beings. In 24 patients, anterograde His-Purkinje system conduction (HV intervals) and variables of His-Purkinje system refractoriness using the ventricular extrastimulus (V2) technique were analyzed before and after long-term therapy with amiodarone. The mean duration of amiodarone therapy at the time of repeat study was 16.2 ± 7.7 weeks (range 11 to 42). The anterograde His-Purkinje system conduction time (HV interval) measured 49.6 ± 9.5 ms (range 40 to 80) before and 60.6 ± 10.7 ms (range 45 to 90) after amiodarone (p < 0.005). During retrograde refractory period studies, the longest V1V2 interval at which a retrograde His bundle potential (H2) emerged from the V2 electrogram (relative refractory period of the His-Purkinje system) was consistently longer after amiodarone as compared with the control period (376.4 ± 46.6 versus 318.8 ± 33.1 ms, p < 0.005). Similarly, the shortest and longest His-Purkinje system conduction times (V2H2 interval) at comparable V1V2 intervals were uniformly and significantly prolonged after administration of the drug. Amiodarone also abolished macroreentry in the His-Purkinje system in six of the nine patients who showed such reentry during the control period. The effective refractory period of the ventricular myocardium was also increased from a mean of 227.1 ± 13.9 to 259.2 ± 20.2 ms (p < 0.005) in this series of patients.

The results indicate that long-term amiodarone administration uniformly produces prolongation of His-Purkinje system conduction time and refractoriness in the human heart.

Amiodarone is a potent antiarrhythmic agent, particularly in its oral form (1-10). Studies of electrophysiologic effects of amiodarone during long-term oral therapy (4,6,10) have shown the drug to prolong refractoriness of the atrium, ventricular myocardium, accessory pathway and the atrioventricular (AV) node. Although this agent is effective in controlling ventricular tachycardia, its electrophysiologic actions on refractoriness of the human His-Purkinje system have not been systematically evaluated. Paucity of data in this regard is partly related to the drug’s significant prolongation of AV nodal refractoriness, which makes His-Purkinje system refractoriness difficult to assess during anterograde propagation of impulses. Because the ventricular extrastimulus method circumvents these problems, this technique was employed to systematically study the refractoriness of the His-Purkinje system in 24 patients receiving long-term amiodarone therapy. The present electrophysiologic findings and their clinical implications are discussed in this report.

Methods

Patients. The study group consisted of 24 consecutive patients (16 men and 8 women) aged 31 to 75 years (mean 58.9 ± 11.4) who underwent complete electrophysiologic studies before and 11 to 42 weeks (mean 16.2 ± 7.7) after oral administration of amiodarone. Eighteen patients had atherosclerotic heart disease, three had congestive cardiomyopathy, two had mitral valve prolapse and the remaining patient had no clinically detectable structural heart disease.

Electrophysiologic studies. These studies were conducted with the patient in a postabsorptive nonsedated state. The nature of the procedure was explained to all patients and signed consent was obtained. During the control study, no patient was taking cardioactive medication. Under local anesthesia, multipolar electrode catheters were introduced percutaneously into peripheral veins, and under fluoroscopic monitoring...
guidance were positioned into the regions of high right atrium, AV junction and right ventricle for pacing or recording, or both, with techniques previously described (11). Surface electrocardiographic leads I, II and V2, intracardiac electrograms and time lines were simultaneously displayed on a multichannel oscilloscope and recorded on a magnetic tape for later reproduction.

Electrical stimulation was performed using a digital stimulator capable of delivering rectangular impulses with adjustable voltage and duration. During these studies, patients were isolated and all equipment was grounded at equipotential. In all patients, atrial and ventricular incremental pacing and premature stimulation were completed according to the protocols previously described. Retrograde refractory period studies were performed using the ventricular extra-stimulus method. At predetermined ventricular basic cycle lengths (S1S1 or V1V1), progressively shorter S1S2 (or V1V2) intervals were introduced until the effective refractory period of ventricular myocardium was reached. In patients who had AV dissociation during the basic drive, the right atrium and ventricle were paced simultaneously to avoid interruption of basic cycle length from ventricular capture by the sinus beats.

**Definition of terms.** Complete lists of definitions for anterograde and retrograde conduction and refractory period studies have been described previously (11,12). Only pertinent definitions related to this study are described here.

**Anterograde studies.** The HV interval was measured from the onset of His bundle potential to the earliest detectable ventricular activity measured on the surface electrocardiograms or any of the intracardiac electrograms.

**Retrograde studies.** During basic ventricular cycle length, the retrograde His bundle deflections were not identifiable, but during S1S2 (or V1V2) at closer coupling intervals, His deflection emerged from the V2 electrogram. During ventricular premature stimulation, the site of retrograde conduction delay or block, or both, (that is, the AV node versus the His-Purkinje system) was determined by identifying the retrograde His (H2) deflection by morphology and electrophysiologic behavior (13). When doubt existed, the site of retrograde block was confirmed by programming an atrial extrastimulus after V2 and assessing the site of retrograde concealed conduction (that is, the AV node versus His-Purkinje system). The S2H2 (or V2H2) intervals were measured from the stimulus artifact to the onset of H2 deflection. It should be pointed out that in this report, the terms S2H2 and V2H2 are used interchangeably.

**Effective refractory period of the His-Purkinje system.** This was defined as the longest V1V2 interval where V2 blocks below the His bundle recording site.

**Functional refractory period of the His-Purkinje system.** This was defined as the shortest S1H2 (or V1H2) interval in response to a full range of S1S2 intervals. S1H2 (or V1H2) was taken in lieu of retrograde H1H2 because retrograde H1 is generally not visible during basic drive but maintains a constant relation with S1 (11,14).

**Effective refractory period of ventricular myocardium.** This was defined as the longest S1S2 interval at which S2 fails to depolarize the ventricle.

**Reentry His-Purkinje system.** The definition for reentry His-Purkinje system has been published previously. Zone of reentry His-Purkinje system was the range of V1V2 intervals where V2 produced reentry His-Purkinje system (11,15).

**Oral amiodarone therapy.** After control studies, all patients received a loading dose of 1,200 to 1,600 mg/day for 1 to 2 weeks and then continued on a maintenance dose of 400 to 800 mg/day until the time of repeat electrophysiologic study (Table 1). The duration of therapy at time of study ranged from 11 to 42 weeks (mean 16.2 ± 7.7) (Table 1) and the patients were not receiving any other antiarrhythmic agent at the time of repeat study.

**Statistical analysis.** Statistical significance of changes in electrophysiologic variables after amiodarone was assessed using Student’s paired t test. Data are expressed as mean values ± standard error of the mean.

**Results**

Relevant clinical data are summarized in Table 1. All patients were in sinus rhythm during both the control and postamiodarone studies. Atrioventricular (AV) conduction was intact in all but one patient (Case 15) who had congenital third degree AV nodal block with a junctional escape mechanism. Complete data concerning anterograde and retrograde conduction and refractory periods are available for all of these cases. However, only data pertaining to His-Purkinje system conduction and refractoriness will be reviewed in detail here.

The effect of amiodarone on sinus cycle length, anterograde AV nodal conduction and refractoriness and atrial refractoriness was similar to that described previously (4,6,10). In virtually all instances, these variables were prolonged.

**Anterograde His-Purkinje system conduction (HV intervals)** (Table 2). In all but three patients (Cases 3,16 and 19), the HV interval showed a prolongation after administration of amiodarone. The mean value for the HV intervals during the control period was 49.6 ± 9.5 ms (range 40 to 80) and increased to 60.6 ± 10.7 ms (range 45 to 90) after amiodarone. The mean increase in the HV interval was 11.0 ± 5.6 ms (p < 0.005). In 21 of 24 patients, the HV intervals were within the normal range (35 to 55 ms) during the control period; in the remaining 3 patients (Cases 6, 12 and 19), these intervals were prolonged (60, 80 and 70 ms, respectively). The magnitude of change after amiodarone was the same regardless of the duration of the HV interval during the control period.
Table 1. Clinical Data

<table>
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<th>Case</th>
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<th>Surface Electrogram</th>
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<th>Dosage (mg/day) at Repeat Study</th>
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ant = anterior; ASHD = arteriosclerotic heart disease; F = female; inf = inferior; LBBB = left bundle branch block; LV = left ventricle; LVA = left ventricular aneurysm; MVP = mitral valve prolapse; M = male; RBBB = right bundle branch block; sept = septal; SR = sinus rhythm; VF = ventricular fibrillation; VPC’s = ventricular premature complex; VT = ventricular tachycardia.

Retrograde His-Purkinje system conduction and refactoriness (Table 2). The introduction of $V_2$ was started at a $V_1V_2$ interval generally 100 to 150 ms shorter than the basic ventricular cycle length ($S_1S_2$). The longest $V_1V_2$ interval that produced emergence of retrograde $H_2$ from $V_2$ was longer after amiodarone in 18 patients (Cases 1 to 16, 19 and 24, Table 1, Fig. 1 and 2A); in the remaining 6 patients $V_2$ encountered bilateral block below the His bundle, that is, within the His-Purkinje system. In the 18 patients in whom $V_2$ produced an $H_2$ response during both studies, the mean value of the longest $V_1V_2$ intervals at $H_2$ emergence was 318.8 ± 33.1 ms before and 376.4 ± 46.6 ms after amiodarone ($p < 0.005$). The mean increase in $V_1V_2$ at the point of $H_2$ emergence ranged from 10 to 130 ms at the basic ventricular cycle length tested. At the longest $V_1V_2$ interval, no significant stimulus to ventricular response latency was observed after $S_2$ as compared with $S_1$ on any intracardiac electrogram recorded before or after drug administration.

The $V_2H_2$ delays were also compared in all patients in whom the two values were available before and after amiodarone. Table 2 shows that at the same $V_1V_2$ intervals, the shortest and the longest $V_2H_2$ delays were consistently longer in virtually all patients. At the longest $V_2H_2$ delays, the corresponding coupling intervals were short and generally accompanied by stimulus to ventricular response latency both before and after drug administration. However, at these short (and long) $V_1V_2$ intervals, the $V_2H_2$ interval after amiodarone consistently exceeded control values when this interval was measured from the end of the local $V_2$ electrogram (or QRS complex) (compare Fig. 1 and 2). This observation suggests that intramyocardial delay did not sig-
sificantly contribute to prolongation of V\textsubscript{2}H\textsubscript{2} intervals after administration of amiodarone. The shortest available V\textsubscript{1}H\textsubscript{2} intervals were also consistently longer after amiodarone administration.

Nine patients (Cases 12 to 20, Table 2) demonstrated the phenomenon of macroreentry in the His-Purkinje system during the control study. In four of these nine (Cases 17 to 20), reentry in the His-Purkinje system did not occur after amiodarone administration because of persistent retrograde block in the His-Purkinje system, whereas in two of nine (Cases 12 and 13), reentry in the His-Purkinje system was abolished even though the V\textsubscript{2}H\textsubscript{2} delays were longer after amiodarone than in the control period. In only three of the nine (Cases 14 to 16) was reentry in the His-Purkinje system noted during the repeat study. Reentry in the His-Purkinje system in two of the latter three cases appeared at longer V\textsubscript{1}V\textsubscript{2} intervals after amiodarone administration as compared with that in the control period. In the zone of reentry in the His-Purkinje system, the V\textsubscript{2}H\textsubscript{2} and H\textsubscript{2}V\textsubscript{1} intervals were also longer during the repeat study on amiodarone. In all instances, the reentry in the His-Purkinje system was in the form of a single beat (V\textsubscript{2}) which terminated with retrograde block in the His-Purkinje system (that is, no H\textsubscript{2}).

**Refractoriness of the ventricular myocardium.** The effective refractory period of the ventricular myocardium was prolonged in all patients (mean 227.1 \pm 13.9 ms [range 200 to 260] before and 259.2 \pm 20.2 ms [range 240 to 290] after amiodarone).

**Discussion**

**Effect of amiodarone on His-Purkinje system.** Our results show that amiodarone prolongs the conduction time and refractoriness of the His-Purkinje system in the human heart. Even the three patients without prolongation of the HV interval manifested lengthening of other variables of His-Purkinje system refractoriness. It is not completely clear why the HV interval was not prolonged in these cases. It may, in part, be related to the possibility that the recordings during the repeat study were obtained from a more distal location. This could have counterbalanced a small degree of prolongation in the His-Purkinje system conduction time.
AMIODARONE AND HIS-PURKINJE SYSTEM

Figure 1. Case 14. His-Purkinje system conduction refractoriness in the control period before amiodarone. A, The atria (closed arrows) and ventricles (open arrows) are being paced simultaneously during the basic drive. At a basic cycle length (BCL) of 600 ms and an S1S2 interval of 300 ms, the S2H2 interval (retrograde His-Purkinje system conduction time) measures 150 ms. B, The longest S2H2 intervals obtained in this patient before the effective refractory period of ventricular myocardium was encountered at an S1S2 interval of 220 ms. The duration of sinus cycle length, AH and HV intervals during the control period are labeled in A. HB = His bundle electrogram; RA = right atrial electrogram; 2 = surface electrocardiographic lead II.

after amiodarone administration. Published data (4,6,10) concerning the effect of amiodarone on the His-Purkinje system are rather limited and have not shown a consistent prolongation in His-Purkinje system conduction time of the magnitude seen here. Some of the discrepancy between our results and previous data suggesting insignificant effects on His-Purkinje system conduction may be due to the longer duration of treatment and higher average dose used in our study compared with those in earlier reports. To date, a systematic appraisal of the effect of amiodarone on His-Purkinje system refractoriness in the human heart has not been reported.

Effect of amiodarone on ventricular myocardium. Amiodarone lengthened the effective refractory period of ventricular myocardium in our study as in those of others (4,6,10). Because refractoriness of the ventricular myocardium was increased after administration of the drug, one can argue whether the prolongation of V2H2 intervals was

Figure 2. Case 14. His-Purkinje system conduction and refractoriness after amiodarone. At the same basic cycle length as in Figure 1, the S2H2 interval is significantly longer than in panel A of Figure 1 (250 versus 150 ms) despite a much longer S1S2 interval (420 versus 300 ms). The longest available S2H2 delays seen in panel B of both figures were also significantly longer after amiodarone. Even though the QRS complex of paced V2 is wider after amiodarone (as compared with the control study in Figure 1), the V2H2 intervals are significantly longer after amiodarone therapy even when the measurement is made from the end of the V2 electrogram. Panel A also shows the sinus cycle length, AH and HV intervals, which are prolonged after amiodarone as compared with the control period (panel A of Fig. 1).
secondary to intramyocardial rather than His-Purkinje system conduction delays. This possibility cannot be excluded at shorter coupling intervals associated with stimulus to ventricular myocardium response latency. However, a uniform increase in $V_2H_2$ delays at the longest coupling intervals where no such intramyocardial delays were noted after amiodarone suggests a direct depressant effect of this study on the His-Purkinje system. The occurrence of persistent bilateral block within the His-Purkinje system (that is, $V_2$ but no $H_2$) in 6 of 24 patients also supports the drug's depressant effect on the His-Purkinje system.

Effect of amiodarone on reentry in the His-Purkinje system. Macrobeentry in the His-Purkinje system was abolished in six of nine patients in whom the phenomenon was noted during the control period. In four of the six, persistent retrograde bilateral block in the His-Purkinje system accounted for this effect, whereas in two patients (Cases 12 and 13), abolition of reentry in the His-Purkinje system despite longer available $V_2H_2$ delays suggests that prolongation of the refractoriness in the right bundle branch produced this effect. In the three cases where reentry in the His-Purkinje system was noted before and after amiodarone administration, the $V_3$ was associated with significantly longer $V_2H_2$ and $H_2V_3$ intervals during repeat study. These findings indicate that after $V_2$, a prolonged recovery time was needed for the right bundle branch to allow propagation of the $H_2$ impulse in the presence of amiodarone.

Implications. The exact role of the peripheral Purkinje system in the reentrant circuit of ventricular tachycardia in human beings is not completely known at the present time. For example, it is not clear whether ventricular tachycardia circuits are entirely localized within ventricular myocardium or whether the adjacent Purkinje fibers are an essential part of the circuit (16–18). Because amiodarone exerts a depressant effect on the normal and abnormal His-Purkinje system and on ventricular myocardium, the drug will be expected to be efficacious in a wide variety of ventricular tachyarrhythmias. The clinical experience with amiodarone thus far attests to its potency in controlling ventricular tachyarrhythmias (5–8, 10). Even though amiodarone efficacy in controlling ventricular tachyarrhythmias may not necessarily be due to drug-induced prolongation of conduction and refractoriness of the His-Purkinje system or ventricular myocardium, or both, the latter remains a likely mechanism.

We thank Ann Edwards and Brian Miller for their assistance in the preparation of this manuscript.

References