Electrophysiologic Effects of Quinidine

STUDIES USING CHRONICALLY IMPLANTED ELECTRODES IN AWAKE DOGS WITH AND WITHOUT CARDIAC DENERVATION

By Andrew G. Wallace, M.D., Robert E. Cline, M.D., Will C. Sealy, M.D., W. Glenn Young, Jr., M.D., and William G. Troyer, Jr., M.D.

ABSTRACT

Experiments were performed on awake dogs with chronic recording electrodes implanted on the SA node, His bundle, and right bundle branch. Quinidine at serum concentrations of 5 to 10 mg/liter had little effect on AV conduction, but slowed conduction in Purkinje tissue, prolonged ventricular activation, decreased the excitability of atrium and ventricle, and prolonged the atrial refractory period without a consistent effect on the ventricular refractory period. In awake dogs that had previously undergone cardiac denervation, quinidine decreased the excitability and prolonged the refractory period of atrium and ventricle. The effects of quinidine on excitability were dependent on the duration of the stimulus used to test excitability. The actions of quinidine on intraventricular conduction and excitability were enhanced at rapid rates of stimulation. These data indicate that slowing of intraventricular conduction is observed consistently at serum quinidine concentrations that are generally considered to be within the therapeutic range, but changes of the refractory period of the ventricle are not observed consistently. Although the vagolytic properties of quinidine may contribute to changes of heart rate, they do not appear to influence significantly the effects of quinidine on atrial refractoriness and AV conduction.

ADDITIONAL KEY WORDS arrhythmias sinoatrial node atrioventricular node specialized conduction system excitability refractory period sympathetic nervous system conscious dogs

Although quinidine has been used widely in the treatment of patients with heart disease, there is still much to be learned about the mechanism of its antiarrhythmic properties. In recent years electrophysiologic studies have shed new light on the possible mechanisms involved in disturbances of cardiac rhythm (1), and they have provided us with a broader view of the pharmacologic actions of quinidine on the myocardial cell (2). The purpose of this investigation was to use chronically implanted recording electrodes in awake dogs (3) to examine more precisely the electrophysiologic effects of quinidine on the specialized tissues of the intact heart. Awake dogs were used because previous studies (3) have demonstrated that anesthesia modifies the electrophysiologic properties of the heart and its response to certain antiarrhythmic agents. The data reported below demonstrate that many of the actions of quinidine recently shown in vitro also operate in the intact heart and, furthermore, that certain of these actions are not reflected accurately by the routine electrocardiographic trace.

Methods

Studies were done on 12 mongrel dogs weighing 12 to 17 kg. Prior to the studies, each dog was anesthetized and chronic recording electrodes were implanted on the His bundle and right bundle branch during separate periods of temporary occlusion of the venae cavae (4). A recording electrode also was implanted over the region of the sinoatrial node, and pacing electrodes were
ELECTROPHYSIOLOGIC EFFECTS OF QUINIDINE

sutured to the right atrium and right ventricle. Four of the 12 dogs were again anesthetized and underwent a second operation, at which total cardiac denervation (confirmed when the dogs were killed) was accomplished by mediastinal neural ablation (5). The dogs were studied 4 to 16 weeks after they had recovered from the operative procedures. During the interval between the operative procedures and the studies, the dogs were exercised regularly and were trained to sit quietly on a table in the laboratory.

Signals from each of the electrodes were amplified with Tektronix 122 preamplifiers, displayed on a Tektronix 561-A four-channel oscilloscope and recorded on a Hewlett-Packard 3917-A instrumentation tape recorder. Frequencies below 80 cycles/sec and above 1,000 cycles/sec were filtered out. The desired signals, lead II of the electrocardiogram also was recorded. After completion of a study, representative segments were selected from the tape and reproduced on a Brush photographic oscillograph at a paper speed of 10 inches/sec (report in preparation).

The refractory period of atrial muscle was determined by pacing the atrium at a basic frequency of 150 beats/min and then scanning the interval after each sixth basic response with a second pulse of 8 msec to obtain strength-interval curves. The effective refractory period was defined as the shortest interval after the basic beat at which a pulse of twice the end-diastolic threshold produced a propagated atrial response. A similar method was used to determine the effective refractory period of the ventricle.

The excitability of the atrium or ventricle was determined by pacing at a basic frequency of 150 beats/min and measuring the amount of current necessary to produce a propagated response after each sixth beat. One of the heart electrodes was used as the cathode, and a large skin electrode was used as the anode. Duration of the test pulse was 10 msec. Excitability was defined as the least amount of current required to elicit a propagated response at end-diastole. Complete strength-duration curves were obtained in 4 normal dogs and in 2 denervated dogs.

The following protocol was observed in each study. Control data were recorded on tape at the spontaneous heart rate and at a paced atrial rate of 150 beats/min. The effective refractory period and excitability of the atrium and of the ventricle were measured at a heart rate of 150 beats/min and the sample was then obtained and used as a control for subsequent measurements of the serum quinidine level. Quinidine hydrochloride, 10 mg/kg, was administered intravenously over a 30-min period, and the effects were recorded continuously on tape. Thirty minutes after completing the infusion of quinidine, records were taken at the spontaneous heart rate and at a paced rate of 150 beats/min. Measurements of the effective refractory period and excitability were made again and blood was obtained for determination of the serum quinidine level. In several of the studies, samples of blood for quinidine levels were obtained at intervals throughout the infusion period.

The dogs were considered to be denervated if there was no change of heart rate during electrical stimulation of the vagus nerves or stellate ganglia and if subsequent analyses of the catecholamine content of the atria and ventricles revealed levels of less than .05 μg/g of muscle.

Results

Except where otherwise noted, the observations reported below were made between 30 and 45 min after the total dose of quinidine had been administered. Serum quinidine levels varied from 5.4 to 10.6 mg/liter at that time, with a mean value of 8.2 mg/liter. During infusion of quinidine, the heart rate increased (Fig. 1) but usually returned to near control levels within 30 min. The average spontaneous heart rate was 110 beats/min before quinidine infusion and 118 beats/min 30 min after the infusion.

At a paced heart rate of 150 beats/min, quinidine had little or no effect on the interval between complexes recorded from the atrial septum and His bundle (A-H interval, Fig. 2). Before quinidine infusion, conduction times across the AV node averaged 76 msec, and the average change after quinidine was a decrease of 5 msec (Table 1). This change was within the range of spontaneous beat-to-beat variation.

The interval between complexes recorded from the His bundle and the right bundle branch (H-P interval) was used as an index of changes of conduction velocity in Purkinje tissue. The H-P interval was prolonged in every dog after infusion of quinidine. The average increase of the H-P interval was 4 msec, or 23%. These data are summarized in Table 1, and tracings from one such study are shown in Figure 2.

The influence of quinidine on the total time required for ventricular activation was evaluated by two separate measurements.
Early tachycardia after intravenous administration of quinidine. RA = right atrium; His = bundle of His; PPJ = Purkinje papillary junction; L-II = lead II of ECG; A = atrial septum; H = His bundle; S = ventricular septum; P = Purkinje spike; PM = papillary muscle.

**Table 1**

<table>
<thead>
<tr>
<th>Intervals</th>
<th>A-H (msec)</th>
<th>H-P (msec)</th>
<th>H-S (msec)</th>
<th>PM-S (msec)</th>
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<tbody>
<tr>
<td>Control</td>
<td>76 ± 7</td>
<td>17 ± 1</td>
<td>68 ± 3</td>
<td>35 ± 2</td>
</tr>
<tr>
<td>Quinidine</td>
<td>71 ± 7</td>
<td>21 ± 2</td>
<td>82 ± 4</td>
<td>43 ± 4</td>
</tr>
<tr>
<td>% Change</td>
<td>-5 ± 2</td>
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<td>+14 ± 3</td>
<td>+8 ± 3</td>
</tr>
<tr>
<td>P value</td>
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<td>&lt;0.005</td>
<td>&lt;0.005</td>
<td>&lt;0.025</td>
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<table>
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<th>Refractory period</th>
<th>Atrium (msec)</th>
<th>Ventricle (msec)</th>
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<tr>
<td>Control</td>
<td>120 ± 12</td>
<td>130 ± 9</td>
</tr>
<tr>
<td>Quinidine</td>
<td>145 ± 11</td>
<td>132 ± 15</td>
</tr>
<tr>
<td>% Change</td>
<td>+25 ± 12</td>
<td>-4 ± 10</td>
</tr>
<tr>
<td>P value</td>
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<td>&lt;0.25</td>
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<table>
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<th>Excitability threshold</th>
<th>Atrium (ma)</th>
<th>Ventricle (ma)</th>
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<tbody>
<tr>
<td>Control</td>
<td>0.8 ± 0.1</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>Quinidine</td>
<td>0.9 ± 0.2</td>
<td>+0.3 ± 0.1</td>
</tr>
<tr>
<td>% Change</td>
<td>+0.2 ± 0.6</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.01</td>
<td>&lt;0.005</td>
</tr>
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</table>

Mean serum quinidine level = 8.2 mg/liter; observations at paced heart rate of 150 beats/min; data analyzed statistically by paired observations in which each dog was used as his own control. A-H = interval from atrial septum to His bundle; H-P = interval from His bundle to Purkinje spike; H-S = interval from His bundle to ventricular septum; PM-S = interval from papillary muscle to ventricular septum.

*Mean and standard error.

of the interval between the His bundle and the base of the ventricular septum (H-S interval) were considered indicative of changes in total ventricular activation time, including the Purkinje network; changes of the interval between the right anterior papillary muscle and the ventricular septum (PM-S interval) paralleled alterations of QRS duration. Measurements of the H-S interval averaged 68 msec during control periods and increased in every dog after quinidine. The average increase was 14 msec, or 21%. The PM-S interval averaged 35 msec before infusion of quinidine and lengthened in every dog after it. The average change was an increase of 8 msec, or 23%. These data are summarized in Table 1 and illustrated by the example shown in Figure 2.

The effective refractory periods of atrial and ventricular muscle were determined before and after infusion of quinidine. The atrial refractory period averaged 120 msec during control periods and lengthened in every dog after infusion of quinidine; the average increase was 25 msec, or 21%. Changes of the ventricular refractory period were variable. In some dogs the refractory period increased; in others it decreased. The average of measurements during the control period
Effects of quinidine on conduction in a normal awake dog. The heart was paced (ST) from the right atrium at 150 beats/min. For explanation of symbols, see Figure 1. Quinidine level at the time of the tracings shown in the right panel was 8.2 mg/liter.

**FIGURE 2**

Effects of quinidine on refractoriness (panel A = strength-interval curve) and excitability (panel B = strength-duration curve) of the right ventricle in an awake normal dog. Current in milliamperes is plotted on the vertical axis. In panel A, the test pulse was 8 msec in duration, and its timing is plotted on the horizontal axis as the interval in msec after the basic response. In panel B, the test pulse was placed 300 msec after the basic response and its duration in msec was varied as shown on the horizontal axis. Control observations are shown by the solid lines and observations after the dog received quinidine are shown by the dashed line. See text for further details.

Circulation Research, Vol. XIX, November 1966
was 135 msec. The average change after quinidine was a decrease of 3 msec. These observations are summarized in Table 1, and strength-interval curves obtained from 1 dog are shown in Figure 3 (panel A).

The excitability of atrial and ventricular muscle was decreased in every dog after quinidine. The average value for control observations of atrial threshold was 0.8 ma with a mean increase after quinidine or 0.2 ma, or 25%. The average of control values for ventricular threshold was 0.6 ma, with an increase of 0.2 ma, or 33%, after quinidine. These data are summarized in Table 1.

Changes of the end-diastolic threshold after quinidine were more striking when test pulses of short duration were used. The strength-duration plot shown in Figure 3 (panel B) illustrates this finding. With pulses of 6 msec or longer, quinidine resulted in an 0.4-ma increase in ventricular threshold. However, with a pulse of 2 msec, the change was an increase of 1.4 ma, and with a pulse of 0.5 msec, an increase of 3.5 ma.

To assess the possible role of autonomic factors in modifying the direct effects of quinidine on the heart, studies were done on 4 dogs after complete cardiac denervation. In these dogs, quinidine produced essentially no change of heart rate and no major change in AV conduction. Conduction in Purkinje tissue was slowed, and ventricular activation was prolonged by quinidine in the denervated dogs. These changes were directionally similar and comparable in magnitude to those observed in normal dogs. In denervated dogs, quinidine prolonged the effective refractory periods and increased the diastolic thresholds of atrium and ventricle. Data from the 4 dogs are presented in Table 2, and tracings from 1 animal which illustrate the effects of quinidine on a denervated heart are presented in Figure 4.

During the first few days after cardiac denervation, spontaneous ventricular extrasystoles were observed frequently. On several occasions we took this opportunity to examine the effectiveness of quinidine as an antiarrhythmic agent. The tracings shown in Figure 5 demonstrate the ability of quinidine to abolish coupled extrasystoles. In this and one other experiment, a therapeutic effect of quinidine was achieved at a blood level of 3 mg/liter. At this blood level there was slowing of intraventricular conduction without a change in either the absolute or relative refractory period of the ventricle.

The influence of changes of heart rate on the electrophysiologic effects of quinidine was examined in denervated dogs to avoid alterations that might be ascribed to reflex adjustments. The data from 1 dog are presented in Table 3 and Figure 6. The heart was paced at selected rates from 100 beats/min to 300 beats/min. Before quinidine these alterations of rate produced no change of conduction velocity in Purkinje tissue (H-P interval), no significant change of ventricular activation time and had no effect on the end-diastolic threshold of the atrium. After quinidine, con-

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<tbody>
<tr>
<td></td>
<td>Atrium (msec)</td>
<td>Ventricle (msec)</td>
<td>Atrium (ma)</td>
<td>Ventricle (ma)</td>
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<tr>
<td>1,B</td>
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<td>A</td>
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<td>A</td>
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<td>A</td>
<td>52</td>
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<tr>
<td>A</td>
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<td>80</td>
<td>30</td>
<td>130</td>
<td>150</td>
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</tbody>
</table>

Mean serum quinidine level = 8.0 mg/liter; observations at paced heart rate of 150 beats/min; B = before quinidine; A = after quinidine. For explanation of symbols, see Table 1.
ELECTROPHYSIOLOGIC EFFECTS OF QUINIDINE

FIGURE 4
Effects of quinidine on conduction in an awake dog with total cardiac denervation. For explanation of symbols, see Figure 1. Serum quinidine level at the time of the tracings shown in the right panel was 8.0 mg/liter.

FIGURE 5
Effect of quinidine to abolish coupled extrasystoles in a dog with denervated heart. For explanation of symbols, see Figure 1. VPC = ventricular premature contraction which occurred after each sinus beat. Left panel shows tracings before quinidine and right panel, tracings after quinidine. Serum quinidine level at the time the tracings in the right panel were obtained was 3 mg/liter.

Quinidine has been used extensively in the treatment of patients with disturbances of cardiac rhythm, and during recent years there has been a surge of interest in the fundamental actions of the drug on myocardial cells. Despite this broad clinical experience and

beats/min, and were of even greater magnitude at a heart rate of 300 beats/min.

Discussion
Quinidine has been used extensively in the treatment of patients with disturbances of cardiac rhythm, and during recent years there has been a surge of interest in the fundamental actions of the drug on myocardial cells. Despite this broad clinical experience and
TABLE 3
Intervals before and after Quinidine at Several Heart Rates in an Awake Dog with Denervated Heart

<table>
<thead>
<tr>
<th>Heart Rate (per min)</th>
<th>A-H (msec)</th>
<th>H-P (msec)</th>
<th>H-S (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>100</td>
<td>65</td>
<td>65</td>
<td>18</td>
</tr>
<tr>
<td>120</td>
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</tr>
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<td>180</td>
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</tr>
<tr>
<td>300</td>
<td>100</td>
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</table>

Mean serum quinidine level 4.8 mg/liter. For explanation of symbols, see Table 1.

Mean serum quinidine level 4.8 mg/liter. For explanation of symbols, see Table 1.

Effects of quinidine on atrial excitability in an awake dog with denervated heart at heart rates varying from 100 to 300 beats/min. Excitability threshold was measured at end-diastole and is plotted on the vertical axis in milliamperes. Heart rate is plotted on the horizontal axis in beats per minute. The test pulse used was of 8 msec duration and at each heart rate, before and after quinidine, it was determined that the test pulse occurred when the strength-interval curve for that rate was flat.

Effects of quinidine on atrial excitability in an awake dog with denervated heart at heart rates varying from 100 to 300 beats/min. Excitability threshold was measured at end-diastole and is plotted on the vertical axis in milliamperes. Heart rate is plotted on the horizontal axis in beats per minute. The test pulse used was of 8 msec duration and at each heart rate, before and after quinidine, it was determined that the test pulse occurred when the strength-interval curve for that rate was flat.

Research effort, there is relatively little electrophysiologic data on the effects of quinidine on the intact heart of awake animals. Indeed, many of the assumed actions of the drug continue to reflect an early and probably incorrect view about the nature of fibrillation. The "circus movement" hypothesis (6) would suggest that any agent that prolongs refractoriness will close the gap between activation fronts and thereby abolish fibrillation. Slowing of conduction, on the other hand, would keep this gap open and thus tend to perpetuate the arrhythmia. Based on these propositions, prolongation of the Q-T interval is frequently regarded as the therapeutic effect of quinidine while prolongation of the QRS complex is considered a potentially toxic effect (7). Although these correlations between electrocardiographic changes and observed clinical results are useful, it seemed reasonable to examine more carefully the fundamental actions of quinidine on the intact heart and the extent to which the electrocardiogram accurately reflects these changes.

In vitro studies indicate that pacemaker function of the normal sinus node is relatively insensitive to the effects of quinidine (9). Quinidine possesses a potent vagolytic action, however, which is believed to account for certain of the changes in heart rate and AV conduction seen in intact animals (9). It was not surprising to find that quinidine produced a consistent although transient tachycardia in normal dogs, and that in dogs with chronically denervated hearts the drug failed to alter sinus rate. From these observations we have concluded that the early tachycardia observed in normal dogs was indeed an indirect effect of quinidine.

It was not possible in any of our awake dogs to induce a premature atrial beat that spread to the ventricles with either the same or a longer R-R interval than a slightly less premature stimulus. This finding indicates that under the conditions of our experiments the absolute refractory period of atrial muscle exceeded the functional refractory period of the AV node (10). At a constant heart rate, quinidine failed to change conduction time across the AV node in either normal or denervated dogs. Furthermore, in denervated dogs, quinidine failed to alter AV conduction time significantly, even at heart rates of 300 beats/min. These acute studies in awake dogs fail, therefore, to support the view that quinidine affects conductivity of the AV node either directly or as a consequence of its vagolytic actions (11). In this regard, it is possible to
offer an alternative explanation for the fact that quinidine may increase the ventricular rate in the presence of atrial fibrillation (12). It is generally believed that the irregularity of ventricular responses during atrial fibrillation results from penetration of the upper AV node by atrial impulses that are eventually blocked. These "concealed" nodal responses in turn influence propagation during subsequent beats (13, 14). It follows that any agent that enhances the atrial rate may lead to more concealed responses (15). Conversely, any agent such as quinidine (16) that slows the atrial rate could lead to fewer concealed responses and thus enhance ventricular rate.

Transmembrane action potentials recorded from Purkinje fibers and from ventricular muscle have shown that quinidine produces a substantial decrease in the rate of rise of the action potential before there are any major changes in duration of action potential (17, 18). Since the rate of rise of the action potential is a major determinant of conduction velocity (19), a decrease of intraventricular conduction would be expected to be an early consequence of quinidine's action (20). In normal dogs, quinidine slowed conduction in the Purkinje system and prolonged the total activation time of the ventricles. Changes of a comparable magnitude were observed in dogs with denervated hearts. In those animals in which quinidine was administered slowly and in which blood was obtained at intervals throughout the infusion, slowing of conduction was evident at blood levels of 2 to 3 mg/liter. These observations are consonant with the view that one of the earliest effects of quinidine is to suppress intraventricular conduction. This conclusion would appear to be valid, even though prolongation of ventricular activation is not generally considered to be one of the early electrocardiographic manifestations of quinidine's action (21). In all likelihood, failure to recognize this effect on the electrocardiogram is a consequence of the fact that measurements of QRS duration from the usual clinical records are not sufficiently precise to detect changes of less than 10 msec.

Quinidine consistently produced a lengthening of the effective refractory period of atrial muscle. This effect also was noted in dogs with denervated hearts. These data appear to indicate that the vagolytic properties of quinidine contribute little, if any, to changes in atrial refractoriness. It might be argued that failure of denervation to alter the effects of the drug does not exclude a vagolytic action of quinidine on refractoriness since postganglionic parasympathetic fibers persist after neural ablation (22). This possibility seems unlikely, however, since atropine fails to alter either sinus rate or the atrial refractory period in cardiac denervated dogs (Wallace, unpublished observations).

In contrast to the effects of quinidine on atrial refractoriness, the drug did not produce consistent alterations of the refractory period of ventricular muscle in normal dogs. In denervated dogs, however, quinidine prolonged the ventricular refractory period. The difference between the responses of normal and denervated dogs suggests that quinidine does indeed have the direct effect of prolonging the effective refractory period but that this action can be offset in the intact dog by reflex adjustments of cardiac sympathetic nerve discharge (23). An alternative explanation for the changes of refractoriness might be that a heart depleted of its catecholamine stores as a consequence of denervation responds differently to the effects of quinidine. In our studies, changes of the Q-T interval, were variable. Regardless of the directional changes of the Q-T interval quinidine failed to produce parallel changes of the effective refractory period when heart rate was held constant.

Thresholds for electrical stimulation of atrium and ventricle were increased by quinidine. This was a consistent observation at blood levels above 2 mg/liter in all animals. Previous reports have presented conflicting views concerning the effects of quinidine on excitability. In vitro studies by West and Amory (24) have shown that diastolic threshold may be increased by as much as 25% at quinidine concentrations of 6 mg/liter.
Moe and Abildskov (11) have reported that doses of 10 mg/kg (those used in this study) did not have a major influence on the thresholds of atrial or ventricular muscle in vivo. When excitability was measured with pulses of long duration, quinidine produced relatively small changes in diastolic threshold. However, with pulses of shorter duration the influence of quinidine became more apparent (Fig. 3). In comparing reports concerning the influence of quinidine on excitability, it is important to recognize that the duration of the test pulse can be a major determinant of the results obtained.

Johnson and McKinnon (25) reported that the effects of quinidine on myocardial action potentials and excitability were rate dependent. At relatively rapid rates of stimulation, therapeutic concentrations produced a decrease in rate of rise of the action potential and a decrease of excitability. At the same concentrations, slowing the rate of stimulation abolished the evidence of a quinidine effect. These in vitro observations were supported in our studies of intact awake dogs. It was demonstrated that the degree of intraventricular conduction delay as well as the magnitude of changes of end-diastolic threshold consequent to the action of quinidine were substantially greater at rapid rates of stimulation than at slower rates. One interpretation of the above observations is that tachycardia might render the heart more sensitive to the electrophysiologic effects of quinidine. Such a possibility might account for the frequent success in converting atrial fibrillation to normal rhythm with quinidine (26), while quinidine therapy is less effective in terminating slower atrial arrhythmias such as flutter of paroxysmal tachycardia (11). It also seems reasonable to speculate that if the effects of quinidine are related fundamentally to cycle length, then such a relation might account for the observation that quinidine is most useful in abolishing ventricular extrasystoles when the coupling interval is short (27).

Although the precise mechanisms which underlie specific clinical disturbances of cardiac rhythm remain unclear, certain of the general mechanisms which might be operative have been elucidated. For example, many of the specialized cells within the His-Purkinje system are latent pacemakers. Under appropriate conditions these cells can become automatic and initiate a propagated impulse. Undoubtedly, one of the important antiarrhythmic effects of quinidine is its ability to suppress automatic firing in the His-Purkinje system (8). In addition to automatic mechanisms, many disturbances of cardiac rhythm are probably a consequence of changes of conduction. For example, loss of membrane potential from any cause can lead to marked slowing of propagation and unidirectional block (28). The coexistence of slow propagation and unidirectional block create the necessary conditions for local reentry. The studies described in this report emphasize that a decrease of excitability and slowing of propagation are consistent electrophysiologic effects of quinidine at serum concentrations generally considered within the therapeutic range. Since the conditions which permit reentry must also greatly reduce the safety factor for conduction within the reentry path, any agent which further suppresses conduction and excitability could lead to complete decrement, and this would represent one mechanism of extinguishing the reentrant impulse (Fig. 5). Although the above analysis is purely conjectural, the data presented in this paper demonstrate that slowing of propagation is a consistent and early effect of quinidine, while alterations of refractoriness, at least in the ventricle, are not observed at therapeutic levels of the drug. Future experiments should be designed to examine the possibility that changes of excitability or conduction, or both, rather than alterations of refractoriness, are the primary antiarrhythmic properties of quinidine.

Acknowledgment

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ELECTROPHYSIOLOGIC EFFECTS OF QUINIDINE

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