Mechanisms of Termination of Reentrant Atrial Arrhythmias by Class I and Class III Antiarrhythmic Agents

Walter Spinelli and Brian F. Hoffman

We studied atrial flutter due to circus movement in chronically instrumented conscious dogs to identify the mechanism by which class I and class III antiarrhythmic drugs terminate reentrant excitation. We used a crossover experimental design administering five class I agents and one class III agent, by intravenous bolus followed by intravenous infusion. The class I agents other than lidocaine were almost uniformly effective in terminating the arrhythmia (disopyramide in six of seven dogs, propafenone in six of six, flecainide in seven of seven, and SC-40230 in seven of seven). Termination was preceded by a marked increase in cycle length (ranging from +78% with propafenone to +55% with disopyramide), but with the exception of disopyramide, class I agents did not significantly shorten the excitable gap. With disopyramide the gap decreased from 49±3% to 28±3% of the cycle length. With no class I agent did the wavelength of effective refractoriness increase to approach the cycle length of the arrhythmia. Lidocaine, used as a negative control, terminated the reentry in one dog with modest prolongation of the cycle length. Terminations with class I agents correlated with depression of conduction rather than prolongation of refractoriness. In contrast with class I agents, D-sotalol prolonged the cycle length minimally (+10%) and terminated the arrhythmia in six of seven dogs. It decreased the excitable gap from 42±4% to 26±6% of the cycle, but it still did not cause the wavelength of effective refractoriness to equal the cycle length. Terminations by D-sotalol seemed to result from either failure of the lateral boundaries of the circus path or reflection within the path. (Circulation Research 1989;65:1565-1579)

Early studies on arrhythmias caused by circus movement recognized that reentry was possible only if the length of the circus path exceeded the wavelength of the impulse.1,2 Lewis3 subsequently postulated that an antiarrhythmic drug would terminate circus movement only if it prolonged refractoriness more than it slowed conduction, so that the wavelength of refractoriness exceeded the path length. Recent studies4,5 have emphasized the importance of the wavelength of refractoriness in relation to the initiation and persistence of reentrant atrial arrhythmias and also have suggested that the effect of an antiarrhythmic drug on that wavelength is important in determining its efficacy.

The importance of changes in the wavelength of refractoriness in relation to the drug-induced termination of circus movement is not clear.6,7 In the model of leading circle reentry in the atrium developed by Allessie and colleagues,8-10 a model in which the impulse circulates around a functional barrier, one would expect propagation to parallel the fiber axis at times and to cross it at times. Studies by Spach et al11 on dog atrial tissues have shown that the velocity of impulse propagation in the longitudinal direction is much greater than in the transverse direction. In leading circle reentry, conduction velocity and, consequently, the wavelength of refractoriness would twice vary by a large amount during one revolution of the impulse. Similar or perhaps greater differences in conduction velocity and local differences in the duration of refractoriness are presented by models in which the impulse circulates around an area damaged by ischemia.12-14 In models such as these, it is not clear what the average value of the wavelength of refractoriness might mean and how it would be related to drug action in terminating circus movement. We have tried to eliminate these problems by using a model...
of atrial flutter in the canine heart in which the circus path is provided by the supravalvular anulus of the tricuspid ring. In this model, the impulse circulates around an anatomic obstacle in a ring of parallel fibers that have reasonably uniform anatomic and electrophysiological properties. The impulse propagates at uniform velocity in either direction around the path in tissues that have not fully recovered from the prior cycle of activity. In different control trials in the seven dogs, the excitable gap ranged from 23% to 57% of the cycle length of the arrhythmia. This model of circus movement is consistent and reproducible in any animal and comparable among animals. The arrhythmia is persistent, and under control conditions its cycle length is very stable. Each animal can be studied repeatedly over a period of weeks or months in the conscious state.

We have used this model to study the effects of class I and class III antiarrhythmic agents on the persistence of the arrhythmia, on its cycle length, and on the duration of the excitable gap. Our purpose was to study drug-induced changes in the wavelength of refractoriness and to evaluate their importance in relation to the termination of reentrant rhythms caused by circus movement. We selected three standard agents from class I that are known to be effective in the treatment of human atrial flutter: disopyramide (class Ia), propafenone (class Ib), and flecainide (class Ic). We also studied a new class Ib drug, SC-40230, a monobasic disobutamide derivative reported to have marked rate-dependent effects on atrial conduction and refractoriness. In the study we included lidocaine, which is not effective in the treatment of human atrial arrhythmias, to provide a convenient negative control. We compared the class I agents, which prolong refractoriness and depress conduction, to D-sotalol, a class III agent that prolongs action potential duration and refractoriness, but has no significant direct effect on conduction.

Our results show that all drugs except lidocaine were effective in terminating the reentrant rhythm and that the class I and class III agents differed markedly in terms of the extent to which they slowed the rhythm before termination. However, terminations with both classes typically occurred without major prolongation of the calculated wavelength of refractoriness in the circus path or abolition of the excitable gap. The results emphasize the limited usefulness of measuring the spatial mean value of the wavelength of refractoriness as an index of drug action. Finally, we found some evidence that termination of reentry due to circus movement may result from either failure of the lateral boundaries of the circus path or reflection in the path.

Materials and Methods

Surgical Procedures

We studied mongrel dogs weighing 17-25 kg, anesthetized with pentobarbital (30 mg/kg i.v.) and ventilated with room air by a respirator (Harvard Apparatus, South Natick, Massachusetts). We used sterile techniques to open the chest via the right fourth intercostal space. The tissues of the intercaval area were clamped, incised, and sewn together. This incision extended from the superior to the inferior vena cava and was 5-7 cm long. A second incision was then made in the right atrium. This incision, 5-7 cm long, was contiguous with the intercaval lesion and ran parallel to the atrioventricular groove toward the base of the atrial appendage (Figure 1). Five bipolar silver electrodes embedded in polyurethane plaques were then sutured to the epicardium of the lower right atrium at approximately equidistant sites along the circus path (Figure 1). One was on the aortic wall of the atrium caudal to the origin of Bachmann's bundle; another was near the anterior aortic root; two were on the left and right sides of the free wall near the atrioventricular groove; and one was near the coronary sinus ostium. These electrodes were used for recording and stimulation. A Tygon catheter (Norton Performance Plastics, Akron, Ohio) was inserted into the right atrium through the azygos vein. Two more silver electrodes were implanted subcutaneously, one rostral and the other caudal to the thoracotomy, to record the electrocardiogram. The leads from all the electrodes were exteriorized through a plastic connector implanted in the inter-
scapular area. The atrial catheter was exteriorized in the same area.

On the day of the surgery, the dog received an intramuscular injection of trimethoprim (4 mg/kg) and sulfadiazine (20 mg/kg); this treatment was repeated daily for 1 week. During the postoperative period, the dog was visited daily by the veterinarian. Additional antibiotics or analgesics were administered according to need. Starting about 1 week after the surgery, the dog was taken daily to the laboratory to become familiar with the environment and with the sling in which it would stand during the experiment. After about 2 weeks, flutter was induced by burst pacing the atrium at cycle lengths from 95 to 115 msec. Inducibility, stability, and reproducibility of the arrhythmia were studied during several sessions over a few days. Only animals in good health and in which flutter was stable, was easily inducible, and lasted for hours were used for the drug studies.

**Experimental Protocol**

The dog was placed in a sling, and the leads of the bipolar electrodes were connected through the transcutaneous device to stimulation and recording units. At the same time, physiological saline was infused via the azygos catheter. The bipolar electrograms and the ECG were recorded on an Electronics for Medicine recorder (model VR-12) and on an eight-channel paper recorder (Gould, Cleveland, Ohio). The experiment was also recorded on an eight-channel Vetter analog tape recorder. Before recording, the electrograms were filtered at 10 or 30 Hz (high pass) and 100 Hz (low pass). Stimuli were rectangular suprathreshold pulses of variable voltage isolated from ground and 3–4 msec in duration. They were delivered through one of the recording electrode pairs via a switching device and were controlled by digital timers and counters.

Drugs were infused through the azygos catheter by a constant speed infusion pump. Blood samples were withdrawn from a second temporary catheter positioned in the cephalic or saphenous vein and transferred to a plastic tube containing heparin. The plasma was separated at the end of the experiment and stored at −70°C.

On the day of the experiment, after the animal had grown accustomed to the laboratory environment, control records of sinus rhythm were taken. The heart was then paced at a cycle length of 300 msec (stimulus S1, 2–3 times threshold), and the atrial effective refractory period (ERP) at 300 msec (ERP300) was determined by introducing, at 5-msec increments, a timed premature stimulus (S2) after every 10 beats. The strength of the stimulus used to elicit premature responses was increased progressively as the stimulus became more premature until an increase in stimulus failed to permit further shortening of the S1–S2 interval. ERP300 was defined as the shortest S1–S2 interval that consistently produced a propagated response. Conduction time was estimated as the interval between two electrograms recorded through two adjacent bipolar electrodes on the anterior portion of the tricuspid ring. The time of activation for bipolar electrograms with predominantly biphasic complexes was taken as the moment when the tracing crossed the zero reference line, and for triphasic complexes, as the peak of the major deflection. After these control measurements had been made, flutter was initiated by a train of stimuli (cycle length, 95–115 msec) lasting 2–3 seconds. After the arrhythmia had been stable for at least 20 minutes, the earliest premature stimulus that could reset the arrhythmia was determined. This extra stimulus, introduced during every 10 cycles of flutter, was timed in relation to an electrogram and was progressively delayed until the flutter cycle length was reset. This measurement provided an estimate of the effective refractory period during flutter (ERPfl). The difference between this measure of ERP and the cycle length of the flutter constituted the excitable gap. This determination sometimes interrupted the arrhythmia; in this case, the flutter was reintroduced and followed for 20 minutes before the drug infusion was started. In the course of one experiment, we always used the same stimulating electrode to pace and determine the ERP before and after drug. We also tried to use the same electrode in different experiments. This, however, was not always possible because, with time, the exteriorized leads might have been damaged.

Immediately before starting drug administration, a blood sample was obtained to be used as a blank in the determination of drug levels. The drug was administered as a loading dose injected during a 4–5-minute period, followed by a constant rate infusion. Every 15–20 minutes the rate of infusion was doubled. Usually the infusion was continued until the arrhythmia terminated or until significant side effects were observed. However, in a few cases we stopped drug administration before termination of the arrhythmia or before observing side effects if we judged that we had already infused an adequate dose. In any case, at the end of the infusion, a blood sample was immediately taken to determine the plasma drug concentration. The cycle length at termination of the arrhythmia is the average of the last five cycles of the flutter.

If the arrhythmia was terminated by drug infusion, the heart was immediately paced at a cycle length of 300 msec, and ERP300 and conduction time were again measured. Then, attempts were made to reinduce the flutter. If the attempts were successful, the flutter was observed for at least 2–3 minutes to determine its stability. At this point, the excitable gap was again measured. In two trials the arrhythmia was not terminated by drug infusion (Table 1), and in these cases the excitable gap was measured immediately after stopping the infusion. Then the flutter was interrupted by burst pacing for 2–3 seconds (cycle length, 115 msec), and ERP300 and
TABLE 1. Drug Doses and Plasma Concentrations at the End of the Infusion

<table>
<thead>
<tr>
<th>Drug</th>
<th>Termination/number of experiments</th>
<th>Dose (mg/kg)</th>
<th>Duration of infusion (min)</th>
<th>Plasma concentration (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disopyramide</td>
<td>6/7</td>
<td>7.8±2.1</td>
<td>32±6</td>
<td>2.8±0.4</td>
</tr>
<tr>
<td>Flecainide</td>
<td>6/6</td>
<td>4.1±0.5</td>
<td>32±4</td>
<td>2.4±0.5</td>
</tr>
<tr>
<td>SC-40230</td>
<td>7/7</td>
<td>4.7±1.0</td>
<td>28±4</td>
<td>2.9±0.2</td>
</tr>
<tr>
<td>Propafenone</td>
<td>7/7</td>
<td>12.6±2.7</td>
<td>29±5</td>
<td>9.6±1.4</td>
</tr>
<tr>
<td>Sotalol</td>
<td>6/7</td>
<td>3.9±1.1</td>
<td>30±6</td>
<td>2.7±0.5</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1/5</td>
<td>11.3±1.2</td>
<td>47±4</td>
<td>6.4±1.2</td>
</tr>
</tbody>
</table>

All values are mean±SEM.

cad in conduction time were measured during pacing at a cycle length of 300 msec. Finally, in all cases, attempts were made to reintroduce the flutter to see if the drug action, although not effective in terminating the arrhythmia, might nevertheless prevent its initiation. Attempts to reintroduce the arrhythmia were continued for 30 minutes after the end of the infusion.

These variations in protocol, required by the course of the experiments, did not provide a uniform set of measures of the duration of the excitable gap after drug administration because 1) in the majority of the animals a variable interval (5-15 minutes) elapsed between termination of the arrhythmia and determination of the excitable gap, 2) in some animals the arrhythmia could not be initiated after drug administration, and 3) in two trials the gap was measured at the end of drug infusion but in the absence of termination. Therefore, we relied most strongly on the measurement of ERP during pacing at a cycle length of 300 msec. This measurement was made in all animals promptly after the end of drug infusion. We calculated the percent change in ERP_{300} from control and used this factor and the control value of ERP_{i} at the time of termination. We recognize that determination of the ERP at a paced cycle length that might be different from the cycle length of the arrhythmia is not ideal. We adopted this procedure for two reasons. First, when we measured ERP in three of the animals during pacing at a cycle length of 250 and 200 msec, we observed in most cases only a minimal additional shortening of ERP, and in some instances, we did not observe any further shortening over the values measured during pacing at cycle length of 300 msec (data not shown). Second, in many animals at cycle lengths shorter than 300 msec, there is a cycle-to-cycle variation in atrial action potential and ERP duration such that determination of a single value of ERP is most difficult. For class I agents, the flutter cycle length at termination and the paced cycle length were quite comparable, but for d-sotalol the cycle length of the arrhythmia at termination was significantly shorter (see "Results").

For this study, we administered each drug to each animal in a randomized sequence to minimize variability among animals. To ensure a good washout between different drugs, we usually waited 3-7 days between tests.

After each animal had been killed, we measured the circumference of the tricuspid ring to provide the length of the circus path. This parameter ranged from 9.5 to 12.5 cm.

**Drug Dosage**

SC-40230 was dissolved in saline by dropwise addition of 1N HCl. The pH of the solution was usually near neutrality without addition of base. Solutions of SC-40230 and of the other drugs were prepared daily in dark glass containers.

After an intravenous bolus, the plasma concentrations of all the drugs used in this study are better described in terms of a two-compartment kinetic system, in which an early rapid decline of plasma concentrations (alpha phase) is followed by a slower decline (beta phase). We tried to minimize the rapid decline by administering the drug by intravenous bolus (infused over 3 minutes) followed by slow infusion. Pharmacokinetic studies have shown that this dosing schedule reduces the rapid fall of plasma levels at the end of the infusion. The parameters of drug administration were the following: disopyramide, 1.2 mg/kg loading dose, 0.2 mg/kg/min infusion rate; propafenone, 1.6 mg/kg loading dose, 0.09 mg/kg/min infusion rate; flecainide, 1.05 mg/kg loading dose, 0.17 mg/kg/min infusion rate; SC-40230, 2.25 mg/kg loading dose, 0.35 mg/kg/min infusion rate; d-sotalol, 1.0 mg/kg loading dose, 0.1 mg/kg/min infusion rate; and lidocaine, 2.2 mg/kg loading dose, 0.22 mg/kg/min infusion rate. Every 15-20 minutes, the infusion rate was doubled. All doses are expressed as free base.

**Plasma Concentration Analysis**

Plasma concentrations of SC-40230 and disopyramide were determined at Searle Research and Development, Chicago, Illinois, by high-performance liquid chromatography (HPLC). Concentrations of propafenone and d-sotalol were determined at Knoll AG, Ludwigshafen, FDR, by HPLC. Concentrations of lidocaine and flecainide were determined by Roche Biomedical Laboratories, Raritan, New Jersey, by use of enzymatic immunoassay and HPLC, respectively.
Data Analysis

Each animal served as its own control. Results are reported as mean±SEM. Comparisons between control and treatment data were performed using the paired t test. Statistical significance was set at p <0.05.

Results

In this study we planned to use a crossover experimental design, in which each animal would receive each of the drugs in a randomized sequence. However, we were unable to complete the drug sequence in two of the seven animals. In one case, the dog damaged the connector implanted in the intrascapular area before we could test propafenone and lidocaine, and in the other case, the animal developed a respiratory tract infection and was killed before we could test lidocaine.

Characteristics of the Flutter

After the surgical preparation, a stable atrial arrhythmia resembling atrial flutter could be induced by burst pacing in each dog through any one of the five epicardial electrodes. An example is shown in Figure 2. The impulse can be seen propagating from electrode 1 across the aortic and free walls to electrode 5, near the ostium of the coronary sinus and then back to electrode 1 (dashed lines). Time lines represent 50-msec intervals. Dots indicate activity in atrial electrograms that results from ventricular depolarization.

In each animal, during different trials, the reentrant impulse might propagate around the ring in either a clockwise (from electrode 1 to electrode 5) or counterclockwise direction (i.e., from electrode 5 toward electrode 1). In either case, regardless of the direction of propagation, the cycle length of the arrhythmia was identical. In different trials in all animals the control cycle length ranged from 125 to 180 msec. The conduction velocity of the reentrant impulse was calculated from the cycle length and the circumference of the tricuspid ring, measured post mortem in the empty heart. Velocity ranged from 0.64 to 0.82 m/sec with an average of 0.72 m/sec. These values are consistent with propagation of fast responses.

Figure 3 illustrates the method used to estimate the ERP and excitable gap during flutter. The electrogram from electrode 1 is used as a timing reference to trigger a delay interval, which is represented by the rectangular wave. At the end of the delay, an extrastimulus is delivered at electrode 2. The delay interval is progressively increased until the extrastimulus causes a premature response and resets the cycle of the flutter. When corrected for conduction time between the triggering and the stimulating electrode, this delay interval provides an estimate of the ERP, and, by difference with the cycle length, of the duration of the excitable gap. For the different drug trials the average value of the excitable gap under control conditions ranged from 41±5% to 49±3% of the cycle length.

In the animals selected for these studies the induced tachyarrhythmia was regular and stable.
TABLE 2. Drug Effects on Cycle Length and Excitable Gap During Flutter, and Effective Refractory Period and Conduction Time During Pacing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Flutter cycle length (msec)</th>
<th>Conduction time (msec)</th>
<th>ERP&lt;sub&gt;90&lt;/sub&gt; (msec)</th>
<th>Excitable gap (% of cycle length)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>151±5*</td>
<td>254±25</td>
<td>28±4*</td>
<td>38±5</td>
</tr>
<tr>
<td>Propafenone</td>
<td>147±7*</td>
<td>262±28</td>
<td>36±5*</td>
<td>59±12</td>
</tr>
<tr>
<td>Flecainide</td>
<td>151±6*</td>
<td>261±19</td>
<td>32±4*</td>
<td>60±11</td>
</tr>
<tr>
<td>SC-40230</td>
<td>152±4*</td>
<td>255±22</td>
<td>23±2*</td>
<td>39±3</td>
</tr>
<tr>
<td>D-Sotalol</td>
<td>149±5*</td>
<td>163±4</td>
<td>34±6</td>
<td>34±7</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>153±7*</td>
<td>185±8</td>
<td>42±11</td>
<td>42±11</td>
</tr>
</tbody>
</table>

All values are mean±SEM. C, control; D, after drug. Pacing was at basic cycle length of 300 msec.
*p<0.05 between C and D.

For the different drug trials the average cycle length ranged from 147±7 to 153±7 msec. Each episode of flutter that lasted more than a few seconds continued for several hours, and its cycle length did not vary by more than 10 msec during any episode. Characteristics and cycle length of the flutter were reproducible in the same animal in different trials over a period of 2–3 months. These observations are consistent with the results of previous studies.\(^{15}\)

**Drug Effects on Flutter Persistence**

Table 1 lists the drugs used in this study and summarizes the average doses infused and the duration of infusion, which was similar for all drugs except lidocaine. Every drug used, with the exception of lidocaine, was usually effective in terminating the arrhythmia. In six trials, we interrupted the infusion without terminating the flutter. In one case, after receiving 17 mg/kg disopyramide in 58 minutes, the dog showed significant adverse effects (signs of hypotension, vomiting, and a marked increase of QRS duration). In the second case, the same animal received 9.6 mg/kg D-sotalol in 57 minutes. Although the animal did not show obvious side effects, we judged that we had already injected a sufficient dose. With lidocaine, we interrupted the infusion in four trials: three of the dogs started showing central nervous system effects (tremors, muscle twitching, and agitation), and the fourth had already received 13 mg/kg lidocaine in 32 minutes. The plasma concentrations of the various drugs at the end of the infusion are also reported in Table 1. Most drug doses and plasma concentrations are comparable with levels previously reported to be arrhythmogenic in canine models of ventricular arrhythmias.\(^ {28-31}\) The only exception is lidocaine, for which the levels were in the toxic range. Despite the large doses infused and the high plasma levels attained (Table 1), lidocaine terminated the arrhythmia in only one animal. It should also be noted that this animal was particularly sensitive to all the drugs studied; its flutter was stopped by doses considerably lower than those required by the other animals. At the end of the infusion, the average plasma lidocaine level of the five dogs was 6.4±1.2 μg/ml. The individual values (range, 4.3–11.4 μg/ml) were within or, in some cases, well above the higher limit of the human therapeutic range.\(^ {32}\)

**Effects on the Cycle Length and Excitable Gap of the Flutter, and ERP and Conduction Time During Pacing**

Table 2 summarizes the average values of cycle length, excitable gap, conduction time during pacing, and ERP<sub>90</sub> for the various drug trials. There were no significant differences in cycle lengths across the various treatment groups. All effective class I agents prolonged cycle length progressively during the drug infusion. At termination, disopyramide had increased cycle length by 55%; propafenone, by 78%; flecainide, by 73%; and SC-40230, by 68%. In contrast, D-sotalol, the class III agent, increased cycle length only by 9% before termination. Even lidocaine, which was ineffective in all but one animal, prolonged cycle length to a larger extent (21%) than did D-sotalol. The changes in conduction time during pacing at a cycle length of 300 msec paralleled the changes in cycle length: all the effective class I agents increased conduction time (disopyramide by 36%, propafenone by 64%, flecainide by 87%, SC-40230 by 70%), but D-sotalol and lidocaine caused no change. Finally, all class I agents except lidocaine significantly increased the value of ERP<sub>90</sub>; D-sotalol also caused a significant increase in this parameter. The changes were: disopyramide, +47%; propafenone, +43%; flecainide, +34%; SC-40230, +28%; and D-sotalol, +16%. Class I agents, with the exception of disopyramide, did not significantly decrease the duration of the excitatory gap expressed as a percentage of the cycle length of the flutter. Only disopyramide and the class III agent D-sotalol significantly shortened the duration of the gap, from 49±3% to 28±3% with disopyramide and from 42±4% to 26±6% with D-sotalol.

**Effects on Conduction Velocity and Spatial Wavelength of Refractoriness**

Table 3 shows the drug-induced changes of ERP<sub>90</sub>, of conduction velocity, and of their product, the
TABLE 3. Drug-Induced Changes in the Effective Refractory Period During Flutter, Conduction Velocity During Flutter, and the Wavelength of Refractoriness Estimated By Two Methods

<table>
<thead>
<tr>
<th>Drug</th>
<th>Estimate 1</th>
<th>Estimate 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>ERPr (msec) CV La, ERP (cm/sec) (cm)</td>
<td>ERPR (msec) CV La, ERP (cm/sec) (cm)</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>57±7</td>
<td>7.2±0.2</td>
</tr>
<tr>
<td></td>
<td>57±7</td>
<td>7.2±0.2</td>
</tr>
<tr>
<td>D-Sotalol</td>
<td>5±81</td>
<td>7.2±0.3</td>
</tr>
<tr>
<td></td>
<td>5±81</td>
<td>7.2±0.3</td>
</tr>
<tr>
<td>Flecainide</td>
<td>48±18</td>
<td>7.0±0.2</td>
</tr>
<tr>
<td></td>
<td>48±18</td>
<td>7.0±0.2</td>
</tr>
<tr>
<td>SC-40230</td>
<td>2</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>85</td>
</tr>
</tbody>
</table>

All values are mean±SEM. C, control; D, after drug; ERPr, effective refractory period (ERP) during flutter; CV, conduction velocity during flutter; La, wavelength of refractoriness.

For estimate 1, ERPr was measured when the flutter had been reinitiated after drug-induced termination. Estimate 2 is based on the change in ERP at a cycle length of 300 msec measured after drug-induced termination. CV is derived from cycle length at termination and path length, which ranged from 9.5 to 12.5 cm with a mean of 10.7±0.4 cm.

ERSpp, wavelength of refractoriness (LERSP).

Only the data obtained from the six dogs in which we were able to administer each drug are used for this table. Two sets of values are shown: on the left (estimate 1), the values of ERPr and conduction velocity in presence of drug are those measured after reinduction of the arrhythmia. As described below, in several cases we were not able to start the arrhythmia after drug-induced termination. On the right (estimate 2), the values of ERPr and conduction velocity during control are similar to those in estimate 1. However, values of ERPr in presence of drug are estimated from the changes in ERPr estimated in "Materials and Methods." From both estimates of La, it is clear that none of the drugs caused the wavelength of the impulse to equal the length of the circus path. Similar results were obtained from the estimation of the wavelength at termination and by the actual measurement when the flutter had been restarted 5-15 minutes after termination. The latter method provided somewhat larger values of the average wavelength with the class I agents, but once again in no instance did La approach the path length.

Effects on ECG and Ventricular Rate

Drug-induced changes in the ECG were measured during sinus rhythm (PR interval) and during pacing at a cycle length of 300 msec (QRS and QT intervals) and are reported in Table 4. In general, the effects of the various drugs were modest. Only D-sotalol significantly prolonged the PR interval by 7%. All effective class I agents, by depressing conduction, increased the QRS duration: disopyramide by 21%, propafenone by 15%, flecainide by 20%, and SC-40230 by 19%. D-Sotalol did not alter the QRS duration. The QT interval was prolonged by 8% by D-sotalol and by 7% by disopyramide. Both molecules are known to prolong action potential duration, and in this study, both decreased the excitable gap during flutter. Lidocaine shortened the QT interval by 5%.

All class I agents increased the proportion of atrial beats transmitted to the ventricle during the tachyarrhythmia. At the time of termination, the ventricular rate was increased 14% over control with disopyramide, 43% with propafenone, 27% with flecainide, and 53% with SC-40230. Even

TABLE 4. Drug Effects on the ECG and Ventricular Rate

<table>
<thead>
<tr>
<th>Drug</th>
<th>PR interval (msec)</th>
<th>QRS interval (msec)</th>
<th>QT interval (msec)</th>
<th>Ventricular rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>117±7</td>
<td>109±7</td>
<td>61±4*</td>
<td>74±5</td>
</tr>
<tr>
<td>Propafenone</td>
<td>108±4</td>
<td>115±4</td>
<td>61±5*</td>
<td>70±6</td>
</tr>
<tr>
<td>Flecainide</td>
<td>115±7</td>
<td>117±8</td>
<td>65±3*</td>
<td>78±5</td>
</tr>
<tr>
<td>SC-40230</td>
<td>114±6</td>
<td>105±5</td>
<td>61±5*</td>
<td>73±5</td>
</tr>
<tr>
<td>D-Sotalol</td>
<td>109±6*</td>
<td>117±6</td>
<td>60±3*</td>
<td>60±4</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>110±7</td>
<td>116±7</td>
<td>62±5*</td>
<td>65±6</td>
</tr>
</tbody>
</table>

Values are mean±SEM. C, control; D, after drug. PR interval was measured during sinus rhythm; QRS and QT intervals were measured during pacing at basic cycle length of 300 msec. Ventricular rate was measured during flutter before infusion (C) and at the moment of termination (D).

*p<0.05 between C and D.
lidocaine, which caused only a modest increase in the cycle length of the flutter, increased ventricular rate by 47%. In contradistinction, d-sotalol did not increase but rather decreased the ventricular rate.

**Drug Effects on Flutter Reinduction**

After termination of the flutter, either caused by drug or by electrical stimulation, we routinely tried to reintroduce the arrhythmia. Each animal was challenged for 2–3 seconds at a rapid cycle length (115–145 msec) for up to 30 minutes after the termination. After SC-40230, a stable flutter lasting at least 5 minutes could be induced in three of the seven animals and after d-sotalol in five of the seven animals. After disopyramide, propafenone, and flecainide, we succeeded in reinducing the arrhythmia in all but one animal in each group. After treatment with class I agents, the cycle length of the reinduced arrhythmia was shorter than at the time of termination. With disopyramide, the cycle length was 19% shorter than at termination; with propafenone, 26%; with flecainide, 25%; and with SC-40230, 16%. After treatment with d-sotalol, the cycle length of the arrhythmia changed minimally.

**Characteristics of Drug-Induced Terminations**

Examination of the last few cycles of the flutter showed several characteristic patterns of termination induced by the class I drugs. In some cases, when termination occurred without a very great increase in cycle length, the electrograms recorded just before termination showed only a modest slurring and broadening, and there was a clear alternation in duration of the last few cycles. The sequence of events in Figure 4 showing the effects of flecainide is an example. During the cycle labeled A, the impulse accelerated as it moved from electrode 1 to electrode 5 so that cycle length decreased from 245 to 215 msec. Cycle B was short at electrodes 1–4, but conduction slowed markedly to give a cycle of 250 at electrode 5. During cycle C, the cycle length was 260–255 msec as the impulse moved from electrode 1 to electrode 4, but it shortened to 215 msec at electrode 5. The final cycle, D, was even shorter, 205 msec, and conduction was blocked as the impulse approached electrode 5. At this site, block occurred when a short-cycle impulse approached a site at which the prior cycle had been short.

A somewhat similar pattern is shown in Figure 5. Here propafenone had been administered to the same animal as in Figure 4. The cycle length is greatly prolonged, and the electrograms are slurred, broadened, and, at electrode 1, fragmented. Termination occurs when two long cycles (C,D; cycle length, 350 msec) are followed by a short cycle (E). Once again, block of propagation occurs when the short-cycle impulse approaches a site at which the prior cycle had been short.

In other cases, termination followed a modest prolongation (10–15 msec) of the last cycle in absence of alternations in cycle length or significant change in electrogram configuration, and at times the reentry ended without measurable change in cycle length. Finally, at times a modest decrease in cycle length of the last cycle (10–20 msec) led to quite delayed activation at one electrode, marked slurring and fragmentation of the record at that site, and no propagation to the next site.

The terminations with d-sotalol were more intriguing in many ways. As noted, the cycle length did not much increase before termination. Shortly before termination the cycle-to-cycle variation was minimal, usually no more than 5 msec. Then, as shown in Figure 6, an unusual sequence occurred. At electrode 1, there was an abrupt decrease in cycle length (C). As the impulse propagated from this site, it slowed, and electrograms broadened and developed altered morphology. By the time the impulse returned to the site of initial shortening (electrode 1),
the slowing of propagation had resulted in prolongation of the cycle to 160 msec (D). However, at electrode 3, there appeared a premature impulse of altered configuration. At electrode 3, the cycle length was only 115 msec, whereas that at electrode 1 was 160 msec. The records suggest that a new impulse had arisen at electrode 3, propagated back to electrode 2, and collided with impulse, spreading in the opposite direction from electrode 1. Similar sequences of activation before termination were frequently recorded after treatment with another experimental class III agent (data not shown).

Discussion

We judge that the preparation we used was suitable for the studies conducted because in most cases we were able to study each drug in each animal and because the behavior of the arrhythmia was quite consistent in any animal and comparable among animals. We found that all drugs with the exception of lidocaine were similarly effective in terminating the arrhythmia. The effective plasma concentrations for the standard agents were similar to the therapeutic plasma concentrations in humans (Table 1), with the exception of flecainide, for which concentrations would be considered toxic.

It may be worthwhile to comment briefly on the ways in which this model of flutter differs from others that have been used to evaluate the mechanism of action of antiarrhythmic drugs. Boyden and Hoffman have developed a model of atrial flutter caused by dilatation and hypertrophy of the right atrium. The flutter results from circus movement around a functional barrier or a combination of functional and anatomic barriers. The arrhythmia does not show entrainment or resetting by pacing.
behave similarly to the model described by Boyden and Hoffman. Recent studies by Dillon et al. indicate that the areas of block reported in earlier studies may in fact be areas of very slow conduction and that the factor crucial to establishing reentrant excitation is the anisotropic nature of the anatomy of the cardiac muscle and its effects on conduction.

The model we have used is much simpler than other models, and thus, data obtained from it are more susceptible to simple interpretation than in the case of complex paths. The impulse propagates in a known path composed of normal fibers with relatively uniform properties; throughout the path, conduction parallels the major axis of the fibers, and there is no area of unidirectional block.

The major problem in interpreting our data stems from our inability to directly measure the duration of ERP and excitable gap just before the termination of the arrhythmia. Obviously, we could not anticipate the moment of termination. We could not make repeated measurements of the duration of the excitable gap during drug infusion because, in contrast to control conditions, during drug administration, premature impulses induced even late in the cycle almost always terminated the arrhythmia. Moreover, frequently it was not possible to promptly start the flutter again. For these reasons, our direct measurements of the drug effects on the duration of the ERP and excitable gap during flutter were made when the arrhythmia had been reinitiated after completion of the pacing protocol. This was done some 5-15 minutes after the moment of termination. Undoubtedly at this time the plasma concentration and the intensity of drug effect had decreased from the peak values that were present at the moment of termination. Some indication of the magnitude of this change is provided by comparison of the cycle length of the reinduced arrhythmia with the cycle length at the moment of termination. For disopyramide, in the five dogs in which the flutter could be reinduced, the cycle length of the reinduced flutter was 19% less than at termination. A decrease of similar magnitude was found for the other class I agents at the time of direct measurement of ERP and excitable gap during reinduced flutter. With disopyramide, the cycle length changed minimally. Because of these limitations of direct measurement at the moment of termination, we estimated ERP and gap duration for the moment of termination from the measured changes in ERP during pacing at a cycle length of 300 msec. The validity of these estimates is based on the assumption that the change in ERP30 is proportional to the change in ERP. Thus, on this assumption, we were able to calculate both the duration of the excitable gap and LERP (Table 3). It seems reasonable to make this assumption for the class I agents since the cycle length of the flutter at termination was not markedly different from the paced cycle length of 300 msec.
just before the arrhythmia ended, it was possible for cycles as short as 130 msec. Our observations showed that after D-sotalol, the gap was abolished and that this was the mechanism responsible for terminating the arrhythmia.

In addition, the records of termination showed that, in some cases, the impulse to propagate at a cycle length considerably shorter than the average preceding cycle length would have been forced to the extent that it abolished the excitable gap. Our findings support this concept (Table 2); after D-sotalol, ERP had increased by 16% in the absence of any significant slowing of conduction. The calculated ERP at the moment of termination increased by 19%, and the fraction of the cycle occupied by the excitable gap had decreased as had the actual duration of the gap (from an average of 66 msec to 42 msec). However, in no case did D-sotalol increase ERP to the extent that it abolished the excitable gap. For example, the calculated LERP (Table 3) increased slightly (from 6.3±0.5 to 6.9±0.4 cm) but remained considerably shorter than the path length (9.5-12.5 cm).

Several other findings support the concept that at the moment of termination ERP had not grown to equal the path length. Had the prolongation of the action potential increased the ERP to equal the cycle length, the impulse would have been forced to arise in tissues that had not repolarized enough to permit propagation at a velocity of 0.60-0.72 msec. However, ERP varied minimally from control to termination, and ERP increased by 16% after D-sotalol, suggesting that this was the mechanism responsible for terminating the arrhythmia.

Typically, termination was associated with and appeared to result from early excitation at one site in the circus path. For example, in Figure 6, at electrode 3, a cycle lasting 130 msec is followed by a new electrogram complex after an interval of only 115 msec. This complex slightly precedes activity at electrode 1 and, at electrode 2, is followed by a small slurred complex. The record suggests a collision at or near electrode 2 of an impulse propagating in an antegrade direction from electrode 1 and in a retrograde direction from electrode 2. One might hypothesize that the premature activation at electrode 3 resulted from a reflected impulse generated within the circus path or from a failure of the lateral boundaries of the path that permitted the circulating impulse to leave the path at one site and return to preexcite it at another. A diagrammatic representation of this latter possibility is shown in Figure 7.

The basis for this figure is the concept of lateral boundaries of reentrant circuits as developed by Frame et al. Maintained circulation of the impulse in the circuit is possible only if there is no alternative path over which a wave front can leave and return to the path before the arrival at the same point of the primary reentrant impulse. In our model, there are alternative paths over which conduction time is not greatly different from the time required for the revolution of the reentrant impulse. Under control conditions, these alternative paths do not short-circuit the reentrant path because propagation in them is blocked by the collision of...
two wave fronts (see Figure 4 in Frame et al). Under the influence of an antiarrhythmic drug, one wave front responsible for the crucial collision might block. If this happened, the wave front in an alternate path might prematurely excite some part of the primary circuit and thus terminate the reentrant excitation.

Our findings here for d-sotalol are similar to earlier results with two other class I agents. In the same model, N-acetylprocainamide terminated the arrhythmia after prolonging the cycle length by only 36% with the ERP remaining a constant fraction of the cycle length (51% vs. 52%), and clofilium terminated the arrhythmia after increasing the cycle length by 18% and the ERP from 63% to 71% of the cycle length.

Unlike d-sotalol, the class I agents other than lidocaine caused a large increase in the flutter cycle length before termination and thus obviously had been quite effective in slowing conduction. The extent to which the cycle length was prolonged was not related to the length of the circuit path. The average slowing of conduction before termination of the flutter was 55% for disopyramide, 78% for propafenone, 73% for flecainide, and 68% for SC-40230 (Table 2). After the flutter had terminated, during pacing at a cycle length of 300 msec, the increases in ERP and conduction time were: ERP 47%, conduction time 36% for disopyramide; ERP 43%, conduction time 63% for propafenone; ERP 34%, conduction time 63% for flecainide; and ERP 28%, conduction time 69% for SC-40230. Thus, during pacing, disopyramide was the only agent to cause a greater change in refractoriness than in conduction. Disopyramide also was the only class I agent that decreased the fraction of the flutter cycle occupied by the excitable gap. Even for disopyramide, however, because of the increase in the cycle length, the actual duration of the gap only decreased from 74 to 66 msec. The difference between the effect of disopyramide and the other agents probably stems from the fact that, unlike most class I drugs, disopyramide increases the duration of the canine atrial action potential.

Like d-sotalol the class I agents terminated the arrhythmia without abolishing the excitable gap. Also, the calculated ERP (Table 3) did not increase to equal the length of the circus path. Finally, contrary to early predictions, drugs that slowed conduction more than they prolonged refractoriness were strikingly effective in terminating a reentrant rhythm due to circus movement. One might conclude that these agents interrupt reentry primarily by depressing conduction to a point at which propagation becomes impossible. A similar conclusion was reached by Moe on the basis of experiments with quinidine. Figure 5 contains records compatible with this surmise. The cycle length of the flutter lengthens progressively, and the electrograms become smaller and broader until propagation ceases. In this case the ERP increased by 70% while conduction slowed by 120%; the calculated value of LERP thus decreased from 4.5 to 3.5 cm.

Our findings are not in agreement with conclusions of others who have examined the relative importance of changes in refactoriness and conduction in relation to drug-induced termination of reentry. Feld et al, in comparing class I and III agents in the Rosenblueth and Garcia-Ramos model of atrial flutter, concluded that increased refactoriness was more closely correlated with conversion and prevention of reinduction of the arrhythmia than was depressed conduction. Okumura and Waldo compared quinidine with N-acetylprocainamide in a canine model of flutter caused by sterile pericarditis. They found N-acetylprocainamide to be more effective than quinidine and speculated that this increase in refractoriness played the most important role. Rensma et al used programmed electrical stimulation of normal dog atria to study the influence of refractoriness and conduction and their product, LERP, on the induction of arrhythmias. They found that alterations in conduction velocity alone or in refractory period alone were not good predictors for the induction of arrhythmias. They stressed the importance of LERP in evaluating the action of antiarrhythmic drugs.

Our findings for the changes in LERP do not appear to explain the manner by which the class I agents bring about the termination of reentrant excitation due to circus movement. The problem very likely is that we have calculated what can be thought of as the mean spatial value of the wavelength, that is, the product of the ERP duration times the conduction velocity derived from the cycle length. It is clear from our records (see Figures 4 and 5) that before termination there not only were cycle-to-cycle variations in cycle length but also considerable variations in local speed of conduction and thus in the cycle duration at any one recording site. This behavior has been emphasized by Frame and Simson. As we have noted, propagation of the circulating impulse often seemed to stop when a short-cycle impulse approached a site at which the prior cycle had been short. (We realize that it is incorrect to speak of more than "one impulse" in this type of arrhythmia, but to employ a more precise descriptor, such as short-cycle upstroke, seems unwieldy). Usually one expects a short cycle to be associated with a short refractory period and conversely a long cycle to be associated with a long refractory period. Thus, one would expect block to occur when a short cycle follows a long cycle. Under the effect of the class I antiarrhythmic drugs, this may not be the case. Since the impulse is propagating in incompletely repolarized tissue, the upstroke of the first short-cycle impulse arises from less fully repolarized membrane than prior upstrokes at that site. Because repolarization has been less complete, there probably has been less dissociation of drug from fast channels than for prior upstrokes. Thus, after the first short-cycle upstroke, there
would be a greater fraction of fast channels in the drug-associated and blocked state. This might be sufficient to prolong the local ERP.

Most of the drugs we have used are reported to have a long time constant for dissociation from fast channels,\textsuperscript{49} and thus, the effect we are describing may not be relevant; unfortunately, quantitative data are not available for atrium under the conditions of our study. In addition, when the propagating impulse arises during phase 3, it seems likely that current generated by the approaching upstroke will retard repolarization of tissues in advance of that upstroke. If the local cycle length is short, this electrotonic interaction may cause a more prominent delay of repolarization than when the cycle length is long. One can assume that, as a result of both of these factors, when the impulse returns to the same site to generate a second short cycle, the recovery of responsiveness may not be sufficient to permit continuing propagation. In terms of $L_{ERP}$, this longer than usual ERP, coupled with the relatively fast conduction of the second short-cycle impulse, might give as a product a significantly prolonged $L_{ERP}$. Our data, unfortunately, do not permit a test of this hypothesis. Our records show local variation of conduction velocity as great as 50%, but we have no measure of the cycle-to-cycle differences in duration of the local ERP. In conclusion, although our findings appear to disagree with the standard concept of the importance of $L_{ERP}$, this might result from the fact that we were only able to measure the average value of $L_{ERP}$.

In spite of this limitation, it is clear that, contrary to Lewis's view,\textsuperscript{3} even though an antiarrhythmic drug may under standard conditions of measurement slow conduction more than it prolongs refractoriness, that drug still can be effective in terminating reentry due to circus movement around an anatomic obstacle.

We included lidocaine to have a negative control in our tests and to verify the sensitivity of this model in identifying agents effective in terminating reentrant atrial arrhythmias. In agreement with the reported lack of efficacy in atrial arrhythmias in humans,\textsuperscript{48,49} lidocaine terminated flutter in only one dog. The flutter in this animal, although stable and reproducible, was particularly sensitive to all the drugs studied in that it was stopped by doses and at plasma concentrations considerably lower than those needed for all the other animals. Despite the considerable average plasma concentration reached at the end of the infusion (Table 1), neither atrial ERP\textsubscript{oo} nor conduction time was significantly increased. However, lidocaine did exert a modest but statistically significant action in prolonging the cycle length of the flutter.

The minimal effects of quite high plasma concentration of lidocaine on the cycle length of the arrhythmia in our model is somewhat surprising. Lidocaine is known to slow conduction more in damaged and partially depolarized than in normal myocardium.\textsuperscript{50} This model of arrhythmia does not contain an area of depressed or damaged tissue in the reentrant circuit; this characteristic of the model may explain the lack of efficacy of lidocaine. It is also stated that lidocaine will be effective only for very rapid arrhythmias because the drug dissociates rapidly from inactivated fast channels.\textsuperscript{49} The time constant of dissociation at normal resting potential has been reported to be close to 100 msec.\textsuperscript{51} The arrhythmia we have studied certainly is rapid. It might be that the minimal effect of lidocaine on conduction velocity in our model can be ascribed to the fact that lidocaine preferentially blocks inactivated channels and that the voltage-time course of the atrial transmembrane action potential is too brief to permit extensive drug binding. Records of monophasic action potential obtained during flutter in this model indicate that for approximately half of the cycle length of the arrhythmia the transmembrane potential is positive to $-55$ mV.\textsuperscript{7} Thus, there would be an interval of 70–80 msec for drug dissociation from channels recovering from inactivation.

Finally, lidocaine, unlike many other class I antiarrhythmic agents, shortens the transmembrane action potential. We do not know how much shortening occurs in canine fibers at the cycle length of the flutter, but one can postulate that a decrease in action potential duration negates the ability of lidocaine to delay recovery of fast channels from inactivation. Obviously, an explanation for the ineffectiveness of lidocaine awaits additional studies on its association with and dissociation from canine atrial fast channels at different cycle lengths and different values of membrane potential. At any rate, our results with lidocaine and the other molecules suggest that this animal model of atrial flutter can be useful in discriminating among clinically effective agents.

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