Comparative Mechanisms of Antiarrhythmic Drug Action in Experimental Atrial Fibrillation

Importance of Use-Dependent Effects on Refractoriness

Jinjun Wang, MD; Gerald W. Bourne, MD; Zhiguo Wang, MSc; Christine Villemaire, MScA;
Mario Talajic, MD; Stanley Nattel, MD

Background. Antiarrhythmic drugs are considered to terminate atrial fibrillation by prolonging refractoriness, but direct experimental evaluation of this concept has been limited. The atria are activated rapidly during atrial fibrillation, and antiarrhythmic drugs are known to have important rate-dependent actions. The potential role of such properties in determining drug effects during atrial fibrillation has not been evaluated.

Methods and Results. We evaluated the effects of representative class Ia (procainamide), Ic (propafenone), and III (sotalol) antiarrhythmic drugs on sustained cholinergic atrial fibrillation and atrial electrophysiological properties in anesthetized, open-chest dogs. Loading and maintenance doses were used to produce stable plasma concentrations, and computer-based 112-electrode epicardial mapping was used to study atrial conduction and activation during atrial fibrillation. Clinically used doses of procainamide and propafenone terminated atrial fibrillation in 13 of 13 (100%) and 7 of 10 (70%) dogs, respectively, but a dose of sotalol (2 mg/kg IV) in the clinical range terminated atrial fibrillation in only 2 of 8 (25%) dogs (P<.0005 vs procainamide, P=.08 vs propafenone). Procainamide and propafenone prevented atrial fibrillation induction in 13 of 13 (100%) and 7 of 10 (70%) dogs, respectively, compared with none of 8 dogs for 2 mg/kg sotalol (P<.0001 vs procainamide, P=.004 vs propafenone). A larger dose of sotalol (cumulative dose, 8 mg/kg) was uniformly effective in terminating atrial fibrillation and preventing its induction. All drugs significantly increased atrial refractory period, with effects that were use dependent for propafenone but reverse use dependent for sotalol. Effective doses of all drugs significantly increased the wavelength for reentry at rapid atrial rates in the presence of vagal stimulation into the range observed under drug-free conditions in the absence of vagal input. The inefficacy of clinical doses of sotalol was explained by the reverse use dependence of its effects on refractoriness, which resulted in reduced effects on wavelength at rapid rates. The effects of propafenone on refractoriness were significantly increased at rapid rates, contributing to its ability to increase wavelength and terminate atrial fibrillation. Activation mapping showed that drugs terminated atrial fibrillation by reducing the number and increasing the size of reentry circuits, leading to termination by mechanisms related to block in the remaining circuit(s).

Conclusions. We conclude that antiarrhythmic drugs terminate experimental atrial fibrillation by increasing the wavelength for reentry at rapid rates, leading to a reduction in the number of functional reentry circuits and, eventually, failure of reentrant excitation. Use-dependent effects on refractoriness can limit (in the case of the reverse use dependence of sotalol) or contribute (in the case of propafenone) to antiarrhythmic drug efficacy against atrial fibrillation by determining drug-induced changes in wavelength at rapid atrial rates. (Circulation. 1993;88:1030-1044.)

Key Words • propafenone • sotalol • procainamide • antiarrhythmia agents

Atrial fibrillation is the most common sustained cardiac arrhythmia in clinical practice and is likely to become more common with the aging of the population. Antiarrhythmic drugs have been used to convert atrial fibrillation since 'Thomas Lewis' work with quinidine in 1922. Drugs used to convert atrial fibrillation have included quinidine, procainamide, propafenone, sotalol, and amiodarone.

Experimental studies of antiarrhythmic drug action in atrial fibrillation have been limited. Rensma and colleagues showed that drug effects on the atrial rhythm response to premature stimulation are related to changes in the wavelength for reentry. A subsequent study showed that an experimental class Ic drug reduces the duration of atrial fibrillation induced by burst pacing in awake dogs. We found that clinically used doses of flecaïnide were highly effective in terminating sustained, vagotonic atrial fibrillation in the dog. The drug's efficacy appeared to be due to tachycardia-dependent increases in atrial effective refractory period, which outweighed conduction changes and increased the

Received January 5, 1993; revision accepted April 7, 1993.
From the Department of Medicine (J.W., G.W.B., C.V., M.T., S.N.), Montreal Heart Institute and University of Montreal, and Departments of Pharmacology and Therapeutics and Medicine (Z.W., S.N.), McGill University, Montreal, Canada.
Correspondence to Dr Stanley Nattel, Montreal Heart Institute, 5000 Belanger St E, Montreal, Quebec, Canada H3C.
wavelength. These actions are consistent with the ability of flecainide to produce rate-dependent increases in atrial action potential duration in vitro\textsuperscript{26} and in vivo.\textsuperscript{27}

It remains uncertain whether these properties are peculiar to flecainide or are common to class Ic compounds. Furthermore, the antiarrhythmic mechanisms of other drugs in atrial fibrillation remain poorly understood and have not been tested in experimental sustained atrial fibrillation. We designed the present work to study (1) the efficacy of representative class Ia, Ic, and III drugs in experimental atrial fibrillation; (2) their rate-dependent actions on atrial effective refractory period and conduction; and (3) the mechanisms whereby they terminate atrial fibrillation.

We studied procainamide as a class Ia drug because intravenous procainamide is often used to terminate acute atrial fibrillation in humans and the drug causes less hypotension than quinidine. We chose the class Ic compound propafenone because other than flecainide, it is the only Ic agent widely used to treat clinical atrial fibrillation. To evaluate class III action, we used d,l-sotalol. Because our dogs are β-blocked with nadolol, any effects observed with sotalol cannot be mediated by interactions with β-adrenergic receptors.

**Methods**

Adult mongrel dogs of either sex (weight, 21 to 31 kg) were anesthetized with morphine (2 mg/kg IM) and α-chloralose (100 mg/kg IV) and ventilated with room air supplemented with oxygen. Respiratory parameters were adjusted to maintain physiological arterial blood gases (Sa\textsubscript{O}, more than 90%; pH 7.38 to 7.44). Catheters were inserted into the left femoral artery and both femoral veins and kept patent with heparinized saline solution (0.9%). A median sternotomy was performed, and a pericardial cradle was created. Body temperature was maintained at 37 to 39°C with a homeothermic heating blanket. Two bipolar Teflon-coated stainless-steel electrodes were inserted into the right atrial appendage for recording and stimulation. A programmable stimulator (Digital Cardiovascular Instruments, Berkeley, Calif) was used to deliver 4-ms pulses at twice-threshold current. A demand pacemaker (GBM 5880, Medtronic Inc, Minneapolis, Minn) was used to pace the right ventricle when the ventricular rate was less than 90 min\textsuperscript{-1}. A P23 1D transducer (Statham Medical Instruments, Los Angeles, Calif), electrophysiological amplifiers (Bloom Ltd, Flying Hills, Pa), and a paper recorder (Astromed MT-9500, Toronto, Ontario) were used to record six standard surface ECG leads, an atrial electrogram, and stimulus artifacts.

**TABLE 1.** Doses of Antiarrhythmic Drugs and Resulting Plasma Concentrations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading dose (mg/kg)*</th>
<th>Maintenance dose (mg·kg\textsuperscript{-1}·h\textsuperscript{-1})</th>
<th>Plasma concentration (mg/L)</th>
<th>5 Min MD</th>
<th>40 Min MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaainamide</td>
<td>12.5</td>
<td>25</td>
<td>16.7±1.1</td>
<td>19.5±1.9</td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>2</td>
<td>4</td>
<td>3.0±0.6</td>
<td>2.8±0.3</td>
<td></td>
</tr>
<tr>
<td>Sotalol (dose 1)</td>
<td>2</td>
<td>1</td>
<td>4.0±0.5</td>
<td>3.0±0.3</td>
<td></td>
</tr>
<tr>
<td>Sotalol (dose 2)</td>
<td>6</td>
<td>3</td>
<td>12.3±1.9</td>
<td>9.9±1.6</td>
<td></td>
</tr>
</tbody>
</table>

5 Min MD and 40 Min MD indicate results obtained 5 and 40 minutes after starting the maintenance dose, respectively.

*The loading dose was administered over 15 minutes, and the maintenance infusion was begun immediately after the end of the loading dose.

Nadolol was administered as an initial dose of 0.5 mg/kg IV, followed by 0.25 mg/kg every 2 hours.\textsuperscript{28}

**Atrial Fibrillation Model**

The cervical vagal trunks were isolated and decentralized, and bipolar hook electrodes were inserted via a 21-gauge needle into the middle of each nerve, with the electrode running parallel to vagal fibers for several centimeters.\textsuperscript{29} The Teflon insulation was removed from the distal 1 cm of each electrode. Bilateral vagal nerve stimulation was delivered by a DS-9F stimulator (Grass Instruments, Inc, Quincy, Mass) with a pulse width of 0.1 ms and an applied voltage of 5 V. The stimulation frequency was adjusted in each dog to two thirds of the threshold for asystole under control conditions. In the presence of vagal stimulation, a short burst (1 to 3 seconds) of atrial pacing (10 Hz frequency, four times threshold current) induced atrial fibrillation. Atrial fibrillation persisted in the presence of vagal stimulation for more than 30 minutes and terminated within seconds after stopping vagal stimulation. Atrial fibrillation was defined as a rapid (more than 500 min\textsuperscript{-1} under control conditions), irregular atrial rhythm with varying atrial electrogram morphology. To control for time-dependent changes in vagal actions, the vagal frequency-response relation was assessed before each atrial
fibrillation induction, and the vagal stimulation frequency was adjusted to produce consistent sinus node slowing. A similar procedure was used to establish vagal stimulation parameters during maintenance drug infusion.

**Activation Mapping**

Five thin plastic sheets containing 112 bipolar electrodes with 1-mm interpolar and 6-mm interelectrode distances were sewn into position on the atrial epicardial surface (Fig 1). One sheet was placed under the root of the aorta to cover the anterior aspect of the atrial appendages and Bachman’s bundle. Three sheets were sewn to the posterior aspects of the atrial appendages and to the free walls. The parietal pericardium was gently separated, and a fifth plaque was placed between the pulmonary arteries and veins.

Each signal was filtered (30 to 400 Hz), digitized with 12-bit resolution and a 1-kHz sampling rate, and transmitted into a microcomputer (model 286, Compaq Computer, Houston, Tex). Software routines were used to amplify, display, and analyze each electrogram signal as well as to generate activation maps. Each electrogram was analyzed with computer-determined peak-amplitude criteria and was reviewed manually. The accuracy of activation time measurements was ±0.5 ms. The maps displayed in this manuscript were photographed directly from the monitor screen—artistic renditions and tracings were avoided to prevent distortion of the data.

**Assessment of Vagal Frequency-Response Relations**

To dissociate direct drug effects on atrial fibrillation from anti-vagal actions, vagal frequency-response curves were obtained before and after drug administration. Vagal stimulation voltage was kept constant, and the vagus nerves were stimulated for 30 seconds at frequencies ranging from 2 to 10 Hz, with a 30-second rest period between stimulations at each frequency. Heart rate was determined over the last 20 seconds of each stimulation period. Change in heart rate was plotted against vagal stimulation frequency, and stimulation frequency was adjusted during each maintenance infusion to produce the same effect on sinus rate as observed under control conditions.

**Experimental Design**

Conduction velocity and refractory period were assessed after at least 2 minutes of constant pacing at basic cycle lengths between 150 and 400 ms. The effective refractory period was measured with a train of 15 basic (S1) stimuli followed by a premature (S2) stimulus. The effective refractory period was defined as the longest S1S2 interval failing to produce a propagated response. Activation maps during steady-state pacing were generated offline after the experiment, and con-
Fig 4. Plots of effects of antiarrhythmic drugs on atrial effective refractory period (ERP) in the absence (left) and presence (right) of vagal stimulation respectively. Top, Values (mean±SEM) of atrial ERP under control (Cont.) conditions, in the presence of propafenone (PF) and procainamide (PA), and after 2 mg/kg (S 2mg) and 6 mg/kg (S 6mg) doses of sotalol, respectively. Where no error bar is visible, it falls within the symbol for the mean. *P<.05, **P<.01, ***P<.001 compared with control at same cycle length. Bottom, Percent change in ERP compared with control at the same frequency caused by each drug. *P<.05, **P<.01, ***P<.001 compared with the effect of same drug at a cycle length of 400 ms.

Conduction time was determined between a site adjacent to the stimulating electrode and another site in the direction of rapid propagation. Inter-electrode distance was divided by conduction time to calculate conduction velocity. The same sites were used for conduction velocity measurements during control and drug infusion periods, after ensuring a constant pattern of impulse propagation.

After conduction velocity and effective refractory period had been measured at all cycle lengths in the absence of vagal stimulation, atrial fibrillation was induced, and an 8-second window of electrogram data was obtained. Vagal stimulation was continued for 30 minutes to verify the stability of atrial fibrillation and then stopped to allow a return to sinus rhythm. Measurements of conduction velocity and effective refractory period then were obtained during vagal stimulation at all cycle lengths.

After the acquisition of baseline data, one of the drugs listed in Table 1 was selected. Vagal stimulationFig 5. Plots of effects of antiarrhythmic drugs on conduction velocity (CV) in the absence (left) and presence (right) of vagal stimulation, respectively. Top, Values (mean±SEM) of CV under control (Cont.) conditions, in the presence of propafenone (PF) and procainamide (PA), and after 2 mg/kg (S 2mg) and 6 mg/kg (S 6mg) doses of sotalol, respectively. *P<.05, **P<.01, ***P<.001 compared with control at same cycle length. Bottom, Percent change in CV compared with control at the same frequency caused by each drug. *P<.05, **P<.01, ***P<.001 compared with the effect of same drug at a cycle length of 400 ms.

Fig 6. Plots of effects of antiarrhythmic drugs on wavelength (WL) in the absence (left) and presence (right) of vagal stimulation, respectively. Top, Values (mean±SEM) of WL under control (Cont.) conditions, in the presence of propafenone (PF) and procainamide (PA), and after 2 mg/kg (S 2mg) and 6 mg/kg (S 6mg) doses of sotalol, respectively. *P<.05, **P<.01, ***P<.001 compared with control at same cycle length. Bottom, Percent change in WL compared with control at the same frequency caused by each drug. *P<.05, **P<.01, ***P<.001 compared with the effect of same drug at a cycle length of 400 ms.

Fig 7. Bottom, Mean (+SEM) atrial fibrillation cycle length (AFCL) under control conditions (C) and immediately before atrial fibrillation termination by propafenone (PF), procainamide (PA), and the higher dose of sotalol (S2) as well as the value at the end of the loading dose of low-dose sotalol (S1). ***P<.001 vs control. Top, Percent increase in AFCL caused by propafenone, procainamide, and either dose of sotalol relative to control. ***P<.001 vs effect of PF or PA.
was begun, and atrial fibrillation was initiated. When atrial fibrillation had persisted for 5 minutes, the drug was administered as a loading dose over 15 minutes, followed by the maintenance dose. If atrial fibrillation was terminated, an 8-second window of activation data was acquired, with the trigger for data acquisition set to obtain at least 2 seconds of data before termination. If atrial fibrillation was not terminated within 30 minutes,
vagal stimulation was stopped to restore sinus rhythm. Atrial fibrillation reinduction then was attempted. Atrial fibrillation was considered nonsustained if it persisted for less than 30 seconds and sustained if it persisted for more than 30 seconds. The measurements of effective refractory period, conduction velocity (with and without vagal stimulation), and responses to vagal stimulation were repeated in the presence of the drug. All dogs receiving sotalol had the above procedures performed after an initial dose of 2 mg/kg and again after an additional 6 mg/kg. Plasma drug concentrations were measured by previously described high-performance liquid chromatography approaches.30,33,34 A total of 10 dogs received propafenone, 13 received procainamide, and 8 received both doses of sotalol.

Data Analysis

Group values are presented as mean±SEM values. Comparisons between groups of data were performed by two-way ANOVA with Scheffe’s test, and comparisons between two means only were made by Student’s t test. A two-tailed P<.05 was taken to indicate statistical significance. Rate dependence of effects was evaluated by an F test for interaction. Wavelength (A) was calculated with the formulation of Wiener and Rosenblueth,35 according to the relation $\lambda$=effective refractory period×conduction velocity.

Results

Effects of Antiarrhythmic Drugs to Terminate Atrial Fibrillation and Prevent Its Reinduction

At loading doses similar to clinical doses,7,8,11 propafenone and procainamide terminated atrial fibrillation in a majority of dogs (70% and 100%, respectively; P=NS; Table 2). A loading dose of sotalol (2 mg/kg) similar to the clinical dose (1.5 mg/kg)36,37 terminated atrial fibrillation in only two dogs (25%), but an additional 6 mg/kg (cumulative dose, 8 mg/kg) terminated atrial fibrillation in all.

Sustained atrial fibrillation could be induced in only 3 of 10 dogs (30%) after propafenone (the dogs in whom propafenone failed to terminate atrial fibrillation) and in no dogs after procainamide or high-dose sotalol. After low-dose sotalol, however, sustained atrial fibrillation could be induced in all dogs (Table 2). The prevention of atrial fibrillation induction could not be due to antivagal actions because vagal frequency was readjusted during each maintenance dose to produce the same bradycardic effect as under control conditions (see “Methods”).

Neither propafenone nor sotalol showed significant antivagal actions (Fig 2). Procainamide, on the other hand, significantly reduced the bradycardic effects of vagal stimulation (Fig 2), consistent with its ability to block ganglionic transmission.38 The termination of atrial fibrillation by procainamide thus could have been due to antivagal actions. To control for antivagal actions, we studied five additional dogs in which vagal stimulation frequency was increased by 80% during atrial fibrillation before procainamide infusion. The adequacy of this adjustment was assessed by comparing the control vagal frequency-response curve to the curve in the presence of procainamide after atrial fibrillation termination (Fig 3) and by showing that the increase in vagal stimulation frequency caused a bradycardic effect in the presence of procainamide similar to the effect under control conditions of the lower vagal frequency. Procainamide terminated atrial fibrillation in all five dogs, despite this compensation for the drug’s antivagal actions.

Drug Effects on Effective Refractory Period, Conduction Velocity, and Wavelength

Atrial effective refractory period decreased with decreasing cycle length under control conditions in the absence of vagal stimulation (Fig 4). Propafenone reversed the rate dependence of atrial effective refractory period so that it increased with decreasing cycle length. Consequently, propafenone increased atrial effective refractory period more at faster rates. Sotalol showed an opposite profile of action, with effects being largest at long cycle lengths (slow rates). Vagal stimulation markedly abbreviated atrial effective refractory period, whereas all three drugs increased atrial effective refractory period.

To appreciate better the rate dependence of drug action, we calculated the drug-induced increase in effective refractory period relative to the corresponding control value at each cycle length in each experiment (Fig 4, bottom). Effects at a given cycle length that are significantly different from those at a basic cycle length of 400 ms are shown by the asterisks in the lower panels of Fig 4. A similar approach was taken to the analysis of rate-dependent changes in conduction velocity (Fig 5) and wavelength (Fig 6). The effects of sotalol were dose dependent and increased with increasing cycle length. Propafenone increased effective refractory period most at short cycle lengths, whereas procainamide’s actions did not change with cycle length. All drugs increased atrial effective refractory period more in the presence of vagal stimulation (right) than in its absence (left).

Changes in conduction velocity are illustrated in Fig 5. Neither vagal stimulation nor sotalol altered conduction velocity. Sotalol’s ability to increase effective refractory period without changing conduction velocity confirms its class III actions in the canine atrium. Propafenone and procainamide slowed atrial conduction, with their effects exaggerated by decreasing basic cycle length. Drug effects on conduction were not altered by vagal stimulation.

Vagal stimulation strongly reduced the wavelength for reentry (Fig 6), decreasing the value at a cycle length of 150 ms from a mean of 11.1±0.4 cm to 7.1±0.4 cm (P<.001). Sotalol’s effects on wavelength were reduced as cycle length decreased, paralleling its actions on
effective refractory period. In the presence of vagal stimulation, large changes in effective refractory period resulted in substantial prolongation of wavelength by propafenone. In the absence of vagal stimulation, propafenone had little effect on wavelength, with a greater tendency to increase wavelength at smaller, compared with larger, cycle lengths (Fig 6, bottom left). Procainamide increased wavelength in a rate-independent fashion.

During vagal stimulation, propafenone, procainamide, and high-dose sotalol increased wavelength (basic cycle length, 200 ms) from about 8 cm to 12 cm, similar to control values without vagal stimulation. Because of reverse use-dependent effects on effective
FIG 10. Maps of last three cycles before atrial fibrillation termination by propafenone. A, B, and C, Maps corresponding to cycles A, B, and C in panel D. Solid vertical lines delimit cycles, whereas dotted vertical lines indicate reference point (time 0) for cycle A (first line) and cycles B and C (second line). Yellow numbers at bottom of panel D indicate time in seconds. (For discussion, see text.)

The control data in Figs 4 through 6 are mean values for dogs receiving all drugs. To have shown control results for each individual drug would have so compli-

refractory period, 2 mg/kg sotalol did not significantly alter wavelength at a basic cycle length of 200 ms during vagal stimulation.
icated the figures that they would have become indi-cipherable. Because of small differences in control values among groups of dogs, the percent changes at the bottom of each figure do not correspond exactly to the values expected based on differences from overall control means shown at the top of each figure. Note also that the statistical significance shown at the top of each figure (Figs 4 through 6) is between drug and control values (raw data) at each basic cycle length, whereas the statistical significance at the bottom is for the comparison between percent change produced by a drug at a given basic cycle length and its effects at a basic cycle length of 400 ms.

Drug Effects on Activation During Atrial Fibrillation

All three agents slowed atrial activation during atrial fibrillation. Figure 7 shows the mean cycle length of atrial fibrillation under control conditions and immediately prior to atrial fibrillation termination. The mean atrial fibrillation cycle length was determined, as previously done,\textsuperscript{25} by counting the number of cycles over a 1-second period. The cycle length of atrial fibrillation was determined for at least 16 electrode sites widely dispersed over the atria, and the average at all sites was taken to represent the atrial fibrillation cycle length. Although all three agents increased the atrial fibrillation cycle length, the atrial fibrillation slowing effect of sotalol was significantly less than that of the other two drugs.

The mechanism of drug termination of atrial fibrilla-tion was further explored on the basis of activation mapping. Figure 8 shows activation data during atrial fibrillation under control conditions. Analog recordings from selected sites are at the left, and the solid vertical lines delimit the time interval over which the activation maps shown at the right were constructed. The reference point (time 0) for the maps is indicated by the dotted vertical lines. The map at the upper right (panel C) shows the activation map based on the first activation within the time window at each site. Seven zones of early activation (red or orange) are present, along with several zones of late activation (blue). The map at the lower right (D) is based on the second time of activation at each site and shows six zones of latest activation (darker blue). The latter correspond to zones activated early in panel C and likely to have been reactivated as a result of local reentry circuits.

Consider electrograms J1 through J8. J2 and J3 are initially activated just at the onset of the window. The impulse propagates through J6 and J7, passing close to J5 as shown by the low-amplitude potential at that site. Zones of crowded isochrones representing slow conduction or block are indicated by the stippled lines above and below the J2-J3 zone in panel C. The impulse travels superiorly around this region of functional block to activate I4, J1, and then J5. The latter is activated 52 ms after initial activation at J2, and J2 is reactivated 9 ms later, just before reactivation at J3 (panel B). The activation-reactivation interval at J2 is 61 ms, in the range of atrial effective refractory period during vagal stimulation. Similar reentry cycles occur at F2, N5, and K3-K6. The activation-reactivation intervals in each zone are similar to the mean atrial fibrillation cycle lengths at the bottom of Fig 7.

Figure 9 shows the change in activation caused by procainamide immediately before termination of atrial fibrillation in the same dog as Fig 8. Figure 9, A shows activation during the corresponding interval indicated on the electrogram recordings (panels D and E) at the right. A single macroreentry pattern is present, beginning at electrodes B1 and B2 and ending at site B4. A small second deflection at B1 (indicated by the arrow) suggests invasion of adjacent tissue by another wave front. Slow conduction from B4 to B1 initiates the next cycle (panel B), which has a conduction pattern similar to that shown in panel A. There is, however, a subtle difference, with B4 activated slightly earlier in cycle B, before activation at C2. In contrast to cycle A, in which the second deflection at B1 indicated by the arrow precedes activation at B4 by at least 30 ms, a similar deflection in cycle B occurs slightly after activation at B4. Perhaps as a result of this low-amplitude activation, block occurs between B4 and B1, and reentry is terminated. The next cycle is delayed and has initial activation in the sinus node region (DS) and Bachman's bundle (M1, L7), followed by rapid activation of both atria. Comparison between Figs 8 and 9 indicates that procainamide reduced the number of reentry circuits and increased their size until conduction failure in a critical zone led to arrhythmia termination.

Figure 10 shows an example of atrial fibrillation termination by propafenone. Activation begins near Bachman's bundle (sites L2-L4) and proceeds rapidly through both atria toward the atroventricular ring. A zone of relative refractoriness is present in the posterior left atrium, and activation in this region begins at sites K1 and K2, resulting in rather symmetrical activation in this zone. The mechanism by which the impulse reaches K1 and K2 is unclear, but it may involve conduction from C2 and C3 or H8 via the septum. The next activation (panel B) begins at sites activated early in the preceding cycle (A) adjacent to the zone activated late in cycle A. The posterior left atrium superior to (and including) sites K1 and K2 is activated with a substantial delay, indicating block in the conduction path by which K1 and K2 were previously excited. Because of this delay, the remaining portions of the atria recover excitability and are activated rapidly and symmetrically from the region around K1 and K2. This last activation is illustrated in panel C, in which activation times are referenced to the same time point as in cycle B. As in Fig 9, the drug resulted in a large macroreentry circuit. Block in a critical zone led to recovery of remaining atrial tissue, with consequent rapid, symmetrical activation precluding the possibility of further reentrant cycles.

Figures 11 and 12 illustrate the effects of low- and high-dose sotalol, respectively, on atrial activation during atrial fibrillation. Electrogram recordings from eight sites under control conditions are shown in Fig 11, panel A, and recordings from the same sites after the administration of 2 mg/kg sotalol are shown in panel D. Panels B and C show activation maps of one cycle of control atrial fibrillation, whereas E and F show corresponding maps for a cycle in the presence of sotalol. There are four zones of early activation (yellow) in panel B, with slow conduction around areas of functional block leading to delayed activation (green zones) adjacent to sites of early activity. Subsequent propagation to the early
Fig 11. Effects of 2 mg/kg sotalol on activation during atrial fibrillation. A, A 1-second recording of electrograms from sites B1-B8 during control atrial fibrillation. B, Activation map during a 75-ms cycle of atrial fibrillation under control conditions (shown by vertical lines in A) based on first activation at each electrode site. C, Map of activation during same 75-ms cycle of control atrial fibrillation, showing activation with second time of activation for sites activated twice during the cycle. D, A 1-second recording of electrograms from sites B1-B8 during atrial fibrillation after the administration of sotalol. E, Activation map during a 100-ms cycle of atrial fibrillation (delimited by vertical lines in D) in the presence of sotalol, based on first activation at each electrode site. F, Activation during same cycle as in E, with second activation time shown for sites activating twice during the cycle. The cycles selected for maps B, C, E, and F were defined by a distinct cycle in the anterior left atrium (H electrodes, not shown).
FIG 12. Termination of atrial fibrillation after the second dose (6 mg/kg) of sotalol. A and B, Second recording of electrograms from sites E1-E8 and K1-K8 at time of atrial fibrillation termination. Cycles mapped in C through F are delimited by vertical lines. C, Cycle of atrial fibrillation, with reentry occurring in the right atrial appendage and the anterior right atrium near the atrioventricular ring. D, Next activation cycle, with reentry in the right atrial appendage terminating by block in sites K3, K4, and K6, but reentry continuing in the anterior right atrium. Reactivation at D8 (indicated by hatched arrows) initiates the next cycle in the anterior right atrium, as illustrated in E. Arrowheads indicate direction of propagation for initiation of next cycle, as shown in F. This cycle terminates because of block at sites E3, E4, E7, and E8.
activating sites results in their reactivation, as shown (blue areas) in panel C. Sotalol (2 mg/kg) slows activation by about 25% (panel D). Four zones of early activation are present in panel E. Slow conduction around areas of functional block lead to the late reactivation of four atrial zones (panel F). Overall, although the duration of activation-reactivation cycles is slightly larger in the presence of the drug (panels D through F), there is little qualitative change in atrial activation compared with control (panels A through C).

Figure 12 shows an example of atrial fibrillation termination by high-dose sotalol. Electrograms from the right atrium near the atrioventricular ring (E1-E8) are shown in panel A and from the right atrial appendage (K3-K8) in panel B. Activation maps from the last four cycles of atrial fibrillation are illustrated in panels C through F. The cycle prior to that illustrated in C showed a single macroreentry circuit in the right atrial appendage. The same circuit is evident in panel C but is now accompanied by a second, figure-of-eight macroreentry circuit adjacent to the atrioventricular ring. During the next cycle, illustrated in panel D, reentry terminates in the right atrial appendage because of block at K3, K4, and K6 but continues in the lower right atrium. This is followed by two more cycles in the latter zone (panels E and F), with reentry terminating by block at sites E3, E4, E7, and E8. In contrast to atrial activation in the presence of low-dose sotalol (Fig 11), activation in the presence of high-dose sotalol is distinguished by a smaller number of reentry circuits, on which the persistence of atrial fibrillation depends. When reexcitation fails in a critical circuit, atrial fibrillation stops.

The detailed mode of atrial fibrillation termination varied from experiment to experiment for all drugs. However, in each case, the number of circuits immediately prior to termination was one or two, and termination occurred either via failure of reexcitation in a macroreentry circuit (as in Figs 9 and 12) or symmetrical spread from a single region (as in Fig 10). The former mechanism was involved in 6 of 12 terminations mapped for procainamide, 2 of 7 for propafenone, and 4 of 7 for sotalol, whereas variants of the latter mechanism were responsible for the remainder.

Discussion

We have shown that propafenone, procainamide, and sotalol are all capable of terminating atrial fibrillation and preventing its induction in a dog model of sustained atrial fibrillation. Effective doses of all three agents increase the wavelength at short cycle lengths, slow atrial activation during atrial fibrillation, and increase the size of reentry circuits.

Comparison With Previous Experimental Studies of Antiarrhythmic Drug Action During Atrial Fibrillation

Rensma and colleagues evaluated the effects of antiarrhythmic drugs on atrial arrhythmias induced by premature stimulation in dogs. Their study differs from ours in that they studied the inducibility of nonsustained arrhythmias in conscious dogs, mapping techniques were not used, and the details of drug and dose selection were different. Like them, we found that a cumulative dose of 8 mg/kg sotalol suppresses atrial fibrillation induction. In addition, however, we found that a dose of sotalol (2 mg/kg) slightly larger than the standard clinical intravenous dose of 1.5 mg/kg has limited ability to terminate atrial fibrillation in our model. This contrasts with the efficacy that we observed for clinical loading doses of procainamide7 and propafenone. Although Rensma and colleagues did not study procainamide, they found that the class Ia drug quinidine suppressed the induction of atrial arrhythmias. Rensma and colleagues did not report efficacy for propafenone, although Kirchhof and colleagues subsequently found another class Ic drug, ORG 7797, to be effective in the same model. Our results resemble those of Rensma and colleagues in that interventions that terminate or prevent atrial fibrillation in both models increase the wavelength for atrial reentry. Our results go beyond those of Rensma and colleagues by evaluating use-dependent drug action and by applying activation mapping to correlate electrophysiological effects with changes in activation during atrial fibrillation.

The effects of propafenone in the present experiments resemble those previously noted with flecainide and suggest a common mechanism of class Ic drug action in atrial fibrillation, with tachycardia-dependent increases in refractoriness counteracting the effects on wavelength of drug-induced conduction slowing. Kirchhof and colleagues also noted use-dependent atrial refractoriness prolongation by ORG 7797. The relative importance of changes in action potential duration and sodium channel blockade in the effective refractory period changes caused by Ic drugs remains to be established.

Implications Regarding Mechanisms of Antiarrhythmic Action Against Atrial Fibrillation

Our results support the role of wavelength in mediating antiarrhythmic action in atrial fibrillation. As previously suggested, increases in wavelength resulted in an increase in the size of functional reentry circuits in our animals. The number of circuits decreased, and the arrhythmia terminated when the remaining circuits failed to sustain themselves. These observations are consistent with the suggested importance of the number of reentrant impulses in sustaining atrial fibrillation. Termination tended to occur in two general ways—failure of reexcitation at a critical point (Figs 9 and 12) or a delay in activation allowing for recovery of the remaining portions of the atria (Fig 10). In the normal atrium, individual reentrant circuits tend to be unstable, so that in the presence of only one or two circuits functional perturbations readily lead to arrhythmia termination.

Although high-dose sotalol caused similar changes in wavelength (Fig 6) and activation patterns compared with the other two drugs, it caused less slowing in the atrial rate during atrial fibrillation (Fig 7). This is consistent with the smaller increases in atrial effective refractory period produced by sotalol at rapid rates and with the concept that the rate of functional "leading circle" reentry depends on the refractory period not on conduction velocity or wavelength. Both propafenone and procainamide decrease conduction velocity in addition to prolonging refractoriness. Therefore, they need to cause a larger increase in refractoriness than does sotalol to increase the wavelength sufficiently
to stop atrial fibrillation. Consequently, class I agents produce a greater slowing in atrial activation rate before atrial fibrillation termination. The well-known propensity of class I agents, particularly 1c compounds, to accelerate the ventricular response rate to atrial fibrillation55 may therefore be due to slowing in atrial activation during atrial fibrillation because of large increases in atrial effective refractory period, rather than to conduction slowing per se, as is commonly assumed.

Relation to Observations of Drug Action in Other Experimental Atrial Arrhythmias

Although there is little published information about antiarrhythmic drug action in experimental atrial fibrillation, many studies have addressed drug actions in atrial flutter.47-53 Models used have included atrial enlargement due to tricuspid insufficiency,47 atrial injury by intercaval crush,48,52 the use of a Y-shaped right atrial incision,49,50 and sterile pericarditis.51,52 Efficacy against atrial flutter has been demonstrated for procainamide,47,49,51 propafenone,50,52 and sotalol.48,50 Drug doses and concentrations vary, but they are in the same range as in our study, and changes in refractoriness and conduction are similar.

Several studies examined in detail the mechanism of arrhythmia termination. Spinelli and Hoffman50 suggested that failure of the lateral boundaries (ie, short-circuiting of reentry) or reflection underlie the efficacy of sotalol, whereas class I agents produce block in the reentrant pathway. Schools and colleagues51 suggested that procainamide terminates atrial flutter by suppressing conduction to the point of block in a slowly conducting portion of the reentry circuit. Class I drugs did not eliminate the excitable gap, as would have been expected had they increased wavelength beyond the pathlength available.

The nature of the arrhythmia that we studied was quite different from that of the atrial flutter models. Instead of a single, stable circuit with an anatomic-functional basis, cholinergic atrial fibrillation involves multiple unstable reentry circuits in functionally normal hearts. Atrial activation during atrial fibrillation prior to drug administration reflected this mechanism, as previously observed experimentally25,43,44 in keeping with Moe's "multiple wavelet hypothesis."41,42 In contrast to their effects in atrial flutter, class I drugs increased the wavelength in the vagotonic dog, and this increase in wavelength contributed to atrial fibrillation termination by reducing the number of co-existent reentry circuits. On the other hand, it is quite possible that the final extinction of individual macroreentry circuits occurred via mechanisms similar to those previously described in atrial flutter models. For example, the small deflections indicated by arrows in Fig 9, D may indicate alternate local activation impinging on site B1, resulting in termination of reentry by failure of the lateral boundary as suggested by Spinelli and Hoffman.50 Critical depression of conduction by propafenone may have caused the markedly delayed activation at K1 and K2 and arrhythmia termination shown in Fig 10.

Role of Use-Dependent Drug Effects on Refractoriness

We previously found that tachycardia-dependent increases in refractoriness are important in the termination by flecainide of vagal atrial fibrillation25 and now find that propafenone's efficacy involves similar mechanisms. In contrast, sotalol's ability to terminate atrial fibrillation appeared to be limited by reverse use-dependent actions on effective refractory period. Although 2 mg/kg sotalol increased atrial effective refractory period by about 60% at a basic cycle length of 400 ms during vagal stimulation (Fig 4), its effect was reduced by two thirds at a basic cycle length of 200 ms, resulting in small changes in wavelength and limited ability to terminate atrial fibrillation. The small effect of 2 mg/kg sotalol on wavelength at rapid rates, due to reverse use dependence, accounts for the minor effects of low-dose sotalol on activation patterns during atrial fibrillation (Fig 11).

Limited clinical studies of sotalol in the termination of atrial fibrillation have shown relatively low efficacy,57 with the exception of postoperative atrial fibrillation,21 for which β-blockers appear to be particularly effective.54 It is possible, therefore, that sotalol's reverse use-dependent action limits its ability to terminate a very rapid reentrant arrhythmia like atrial fibrillation. The bradycardia-dependent properties of class III drugs have been recognized for a long time,55 and their potential clinical importance has recently been emphasized.56 The limited efficacy of sotalol in terminating cholinergic atrial fibrillation is one of the first experimental demonstrations of the limitation of antiarrhythmic drug efficacy by reverse use-dependent behavior. It should be pointed out that this phenomenon need not limit sotalol's efficacy in preventing atrial fibrillation because atrial fibrillation initiation usually occurs at the slower rates of sinus rhythm.

Study Limitations

Our model has a number of advantages, including the reliability of atrial fibrillation induction, the sustained nature of vagal atrial fibrillation, and the prompt termination of atrial fibrillation when vagal stimulation is stopped. Propafenone and procainamide were effective at doses and concentrations of the same order as those that terminate atrial fibrillation of recent onset in humans.7,9,11 Enhancement of vagal tone may also play an important role in the clinical occurrence of atrial fibrillation.57 Our model fails to reproduce the abnormal electrophysiological substrate58,59 caused by atrial pathology often associated with atrial fibrillation, and may therefore not apply to atrial fibrillation in the setting of structural heart disease. Further observations in experimental atrial fibrillation models involving atrial disease, along with related studies in clinical atrial fibrillation, would be of interest.

The role of vagal tone poses the problem of effects due to antivagal properties. The impact of vagolytic properties was minimized during the assessment of drug effects on effective refractory period, conduction velocity, and atrial fibrillation induction by adjusting vagal stimulation frequency during the maintenance drug infusion to produce the same bradycardic effect as under control conditions. To control for the role of procainamide's vagolytic properties in terminating atrial fibrillation, we increased vagal frequency before procainamide infusion in five dogs, producing a bradycardic action in the presence of drug similar to control conditions. Nonetheless, we cannot completely exclude a contribution to
atrial fibrillation termination of vagalolytic actions that may have been incompletely controlled by adjusting vagal stimulation frequency.

The effects of all drugs on atrial effective refractory period were greater in the presence of vagal stimulation (Fig 4). We previously found a similar interaction for flecainide.25 This interaction between drugs and vagal tone has not, to our knowledge, been reported previously, and its mechanism is unknown. Sodium channel blockade is unlikely to be the sole factor involved because sotalol is devoid of sodium channel–blocking properties at the concentrations studied.60 Recent work indicates that flecainide, propafenone, and disopyramide can inhibit I_KCa in guinea pig atrial myocytes.61 The potential importance of this mechanism bears further investigation, particularly because I_KCa, can be activated in the absence of muscarinic agonists by a membrane-bound nucleoside diphosphate kinase.62

Conclusions

We have shown that sotalol, propafenone, and procainamide are effective in terminating sustained atrial fibrillation in an experimental dog model. This is, to our knowledge, the first comparative assessment of antiarrhythmic drug mechanisms and efficacy in an experimental model of sustained atrial fibrillation. The results suggest that increases in wavelength are central in arrhythmia termination. Rate-dependent drug effects on atrial refractoriness can contribute to (in the case of propafenone) or limit (in the case of sotalol) drug efficacy, depending on whether drug actions on effective refractory period are enhanced or reduced by the rapid rates characteristic of atrial fibrillation.

Acknowledgments

Supported by the Medical Research Council of Canada, Knoll Pharmaceuticals, the Quebec Heart Foundation, and the Fonds de Recherche de l’Institut de Cardiologie de Montréal. S.N. is a Nordic-Fonds de Recherche en Santé du Québec (FRSQ) Senior Research Scholar. M.T. is a Canadian Heart Foundation Research Scholar. G.W.B. is an FRSQ Research Fellow. Z.W. was supported by a Canadian Heart Foundation studentship. The authors thank Emma De Blasio for expert technical assistance and Mary Morello for typing the manuscript.

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Importance of use-dependent effects on refractoriness.

J Wang, G W Bourne, Z Wang, C Villemaire, M Talajic and S Nattel

Circulation. 1993;88:1030-1044
doi: 10.1161/01.CIR.88.3.1030
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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