Suppression of Ventricular Arrhythmias by Propafenone, a New Antiarrhythmic Agent, During Acute Myocardial Infarction in the Conscious Dog

A Comparative Study with Lidocaine

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SUMMARY The responsiveness of ventricular tachycardia (VT) to propafenone, a new antiarrhythmic agent, was evaluated in the conscious dog during acute myocardial infarction (AMI). AMI was produced in the anesthetized closed-chest dogs with an intracoronary catheter system by permanent occlusion in eight dogs and by 2-hour occlusion followed by reperfusion of the left anterior descending coronary artery in eight others. Twenty-four hours after surgery, all dogs in both groups had VT with similar characteristics (rates of 130–220 beats/min) in the conscious, nonsedated state. Administration of propafenone, 4 mg/kg i.v. over 2 minutes, immediately and completely suppressed VT in seven of the permanently occluded and in all eight dogs in the reperfused group. The duration of propafenone-induced normal sinus rhythm (NSR) was inversely related to the rate of VT. Intravenous infusion of propafenone, 0.2 mg/kg/min, after a 4-mg/kg i.v. bolus maintained NSR for the duration of infusion. Propafenone did not change the mean blood pressure. Lidocaine, as much as 5 mg/kg i.v., was ineffective when the VT rate was greater than 160 beats/min and restored NSR only transiently (3–6 minutes) when the VT rate was less than 160 beats/min in either group (p < 0.001 compared with propafenone). Propafenone, unlike lidocaine, significantly (p < 0.05) increased both cathodal and bipolar diastolic excitability threshold and shifted upward the tail portion of the strength-interval relation of the right ventricle. Propafenone had no effect on the effective refractory period of the right ventricle. Plasma propafenone levels during propafenone-induced NSR and myocardial excitability measurements were 3.2 ± 1.6 µg/ml in the reperfused group and 3.0 ± 1.68 µg/ml in the permanently occluded group (mean ± SD) (p > 0.1). We conclude that propafenone is very effective against VT during AMI in the dog, and it may be effective in lidocaine-resistant VT during acute ischemia.

Methods and Materials

Surgical Procedures

Twenty mongrel dogs of either sex that weighed 20–23 kg were premedicated with morphine sulfate (1–1.5 mg/kg i.m.) and then anesthetized with 20% ethyl carbamate (50–100 ml i.v.). A lead II ECG was continuously monitored on a DR16 Electronics for Medicine recorder. AMI was produced with an intracoronary catheter system in two groups of 10 dogs each. This technique produces myocardial infarction in the closed-chest dog without the need for thoracotomy. In 10 dogs, a preformed #8F radiopaque catheter (2.6 mm o.d. and 1.4 mm i.d., 50 cm long) was positioned into the left coronary ostium through the left carotid artery under fluoroscopic control. The catheter tip was shaped to enable it to be positioned easily into the coronary ostium. The coronary vessels were identified radiographically by injecting a small amount of contrast medium (Renografin-76). A flexible guidewire (0.9 mm in diameter) was then advanced through the catheter down the left anterior descending coronary artery (LAD) to the cardiac apex. The catheter was then withdrawn, leaving the guidewire alone within the LAD with a slight curvature on it, indicating the site of the coronary ostium. A wedge-shaped rubber bead 2–3 mm in diameter and 2–3 mm thick was threaded on the guidewire and was advanced with a #6F radiopaque catheter (2 mm o.d. and 0.9 mm i.d.) to 1–2 cm distal to the coronary ostium. A slight lubrication of the rubber bead and the wire greatly facilitated the advancement of the occluding device. Once the rubber bead was positioned within the LAD, the cath-
Figure 1. Structural formula of propafenone.

eter was secured and the guidewire was pulled back, causing the rubber bead to drop off and remain in the lumen of the vessel. (This technique was developed in the laboratory of Dr. William Ganz; see also reference 30). The catheter systems were secured by means of a Tuoy-Borst adapter and were attached to a three-way stopcock. Immediately after inserting the rubber bead, a small amount of contrast medium was injected through the #6F catheter proximal to the occlusive device, and indicated complete arrest of blood flow distal to the rubber bead. This was invariably associated with an increase in the heart rate (40-100%) and the emergence of ST-T abnormalities. Postmortem examination in each dog confirmed the exact site of the rubber beads. These were invariably located within the LAD 1.5-2 cm distal to the coronary ostium. Two dogs died during surgery. The remaining eight dogs are referred to as the permanently occluded group.

In another group of 10 dogs, a preformed #8F radiopaque catheter was placed into the lumen of the left coronary ostium, and an inflatable balloon-tipped catheter (Fogarty, Arterial Embolectomy Catheter, Edwards Laboratories, Inc.) was inserted into the catheter. The tip of the balloon-tipped catheter extended 1.5−2 cm beyond the coronary ostium and into the LAD (i.e., in approximately the same site as the rubber bead in the permanently occluded group). Depending on the size of the LAD, #2F or #3F catheters were used, so the balloons could be inflated to 4 or 5 mm in diameter. The balloon was inflated with the contrast medium so as to completely occlude the LAD. Complete occlusion of the LAD was confirmed by the lack of blood flow distal to the inflated balloon after injecting a small amount of contrast medium proximal to the inflated balloon. As in the permanently occluded group, occlusion caused an acceleration of heart rate (30−100%) and the emergence of ST-T-wave abnormalities. Two hours after complete occlusion of the LAD, the balloon was deflated and blood was left to flow freely through the occluded site. Before reflow, lidocaine (4 mg/kg i.v.) was injected prophylactically in an attempt to minimize the occurrence of ventricular fibrillation. The patency of the artery was confirmed by injecting a small amount of contrast medium into the proximal LAD. Two dogs died after reperfusion. The remaining eight dogs are referred to as the reperfused group.

Two #6F quadripolar electrode catheters (USCI) with an interelectrode distance of 1 cm were inserted under fluoroscopic control through the left jugular vein, one to the right atrium and the other to the right ventricular apex, to record bipolar electrograms (50−500 Hz) or to stimulate the heart. A Tygon catheter (R-363, 3.17 mm o.d. and 1.58 mm i.d.) was inserted through the left carotid artery to the ascending aorta to record aortic blood pressure. All catheters were exteriorized at the neck and were sutured in place. Sterile procedures were used. All dogs in both groups were studied during 20−24-hour (postocclusion) arrhythmic period in the awake, conscious state. Five dogs from each group were also studied 48 hours after occlusion. All dogs had persistent ventricular arrhythmias during this period.

Electrophysiologic Measurements

Diastolic excitability threshold and strength-interval relations were determined in both groups with both bipolar and unipolar cathodal stimulation (the anodal pole was attached to the left groin) using 2-msec rectangular pulses of variable strength (0.1−12 mA). The current was applied by a custom-made, digital, programmable, constant-current source at the right ventricular apex. All measurements were made under control (predrug) conditions and immediately after drug administration. Threshold was defined as the lowest amount of current allowing consistent ventricular depolarization (two to three reproducible trials) applied during late diastole (> 80% of the RR interval). To determine the strength-interval relation, progressively more premature stimuli (Ss) were applied (after the termination of threshold measurement) after eight regularly driven ventricular beats (cycle length S1S2 = 300 msec). The S1S2 interval was shortened by decrements of 5 msec at long coupling intervals (295−180 msec) and by 1−2 msec at shorter coupling intervals, until the ventricle no longer responded to S2. This interval, the ventricular effective refractory period, was first determined using threshold current; then the intensity of S2 was increased by 0.25-mA increments up to 5 mA, followed by 0.5-mA increments up to 12 mA. The S1S2 interval was kept constant at the previously refractory interval until a current intensity was found at which S2 again initiated a ventricular response. Then, at this new, higher current intensity level, the S1S2 interval was shortened by 1−2-msec decrements until S2 again failed to depolarize the ventricle. This procedure was repeated until the current intensity was 12 mA.7,8 The limit of resolution of refractory period measurements using our custom-built digital stimulator was ± 1 msec.

Postmortem Examination

In each dog in the permanently occluded group, the site of the rubber bead in the LAD was located just proximal to the main diagonal branch. In all dogs in both groups, the location of the infarct was confirmed by the triphenyltetrazolium chloride (TTC) staining technique and the size of the infarct measured by planimetric method.9
Drugs Administration

Propafenone hydrochloride (Rytmonorm, Knoll) was dissolved in 5% dextrose at 85°C, at a concentration of 3.5 mg/ml, and was administered intravenously at specified doses over a 2-minute period. Lidocaine (Astra) was administered intravenously at specified doses over 1-minute periods. Drugs were administered to the conscious, nonsedated dogs, while they were lying quietly on a table. Lidocaine was administered 3 hours after propafenone, when ventricular tachycardia similar in rate and morphology to that before propafenone had emerged, eliminating the possibility of any significant “carryover” phenomenon. In three dogs with the fast type of tachycardia studied 48 hours after occlusion, lidocaine was administered before propafenone. In these studies, propafenone was administered 2 hours after lidocaine.

Plasma propafenone levels were measured in 12 dogs (six from each group) at 5, 10, 15, 30 and 60 minutes after a bolus of 4 mg/kg i.v. administered over 2 minutes and at 20, 30 and 40 minutes in four dogs after a bolus of 4 mg/kg i.v. over 2 minutes, followed by a continuous i.v. infusion at a rate of 0.2 mg/kg/min.

Statistical Methods

The data were analyzed by either the analysis of variance test for repeated measurements or Friedman’s two-way analysis of variance. Friedman’s test was used to analyze data only when compared symmetry or normality of the data could not be assumed. Significant effects (p ≤ 0.05) were further analyzed by Newman-Keul’s multiple-range test, with alpha equal to 0.05. Data are presented as mean ± SD.

Results

Permanently Occluded Group

Immediately (1–2 minutes) after the placement of the occluding rubber bead in the lumen of the LAD, the T-wave voltage increased and the ST segment was elevated. Five of the original 10 dogs had premature ventricular depolarizations within the first 30 minutes of occlusion. These then gradually increased in frequency over the first 90 minutes of occlusion. During this period, three dogs developed VF; one was resuscitated with transthoracic electric shock and two died. Twenty-two to 24 hours after occlusion, all eight remaining dogs had frequent periods of ventricular tachycardia at rates of 130–220 beats/min while conscious and unsedated. Two types of ventricular tachycardia were observed during this period (figs. 2 and 3). Three dogs had “slow” ventricular tachycardia (120–160 beats/min), characterized by a uniform QRS morphology, stable rate and with frequent fusion beats (fig. 2). Tachycardia usually began with a ventricular escape that occurred well after the T wave of the preceding beat. In this type of tachycardia, 14 ± 5% of the beats were of sinus origin (mean percentage attained in three dogs by counting 500 consecutive beats in each dog). Five dogs had “rapid” tachycardia (160–220 beats/min) and multiform QRS complexes (fig. 3). The characteristics of these two types of tachycardia were similar to those described in the dog either with the open-chest permanent occlusion of the LAD5 11 or with closed-chest permanent occlusion of the LAD, where occlusion was achieved with intracoronary placement of a thrombus-forming helical copper coil.10

Five dogs, three with rapid and two with slow tachycardia, were also studied 48 hours after permanent occlusion. The arrhythmias during this period were unchanged, except that the rate of the tachycardia was reduced 8–15% for both rapid and slow types.

Reperfused Group

Immediately after the inflation of the balloon, all the ECG changes that occurred in the permanently occluded group also occurred in the reperfused group. Two dogs died after reflow. Transient ST-segment

![image](https://circ.ahajournals.org/doi/figure/10.1161/01.CIR.66.6.1192)
Twenty-two to 24 hours after reperfusion, all eight dogs in the permanently occluded group also occurred. Within 10 minutes of deflation of the balloon, all dogs developed multiformal premature ventricular depolarizations and short periods of ventricular tachycardia at rates of 130–230 beats/min. The frequency of ventricular ectopic activity progressively increased during 4 hours of monitoring after reflow. These observations were similar to those in dogs in which coronary artery occlusion and release were achieved during thoracotomy.8 Twenty-two to 24 hours after reperfusion, all eight surviving dogs had frequent periods of ventricular tachycardia. The tachycardia during this period was similar to that in the permanently occluded group; four dogs had rapid and four slow tachycardia (figs. 2 and 3).

Four dogs in the reperfused group (two with rapid and two with slow tachycardia) had frequent episodes of ventricular tachycardia 48 hours after reperfusion. The pattern and the frequency of these arrhythmias were again remarkably stable, as in the 24-hour arrhythmias seen in five dogs in the permanently occluded group. This allowed us to further evaluate the antiarrhythmic efficacy of both propafenone and lidocaine during the arrhythmic period.

The pattern of ventricular tachycardia in both groups during the 20–24-hour arrhythmic period was remarkably stable and remained unchanged for as long as 6 hours of continuous monitoring. This lack of unpredictable spontaneous variability in the occurrence and frequency of ventricular tachycardia greatly facilitated the evaluation of propafenone’s and lidocaine’s antiarrhythmic efficacy.

Effects of i.v. Propafenone 24 hours After Occlusion

In a preliminary series of experiments, we evaluated the ability of propafenone to modify or terminate the arrhythmias present during the 24-hour arrhythmic period in both groups. We used 1–4 mg/kg i.v., with 1-mg/kg increments administered over 30 seconds (total of 4 mg/kg over a 2-minute period) through a catheter inserted into the left jugular vein. ECGs, bipolar atrial and ventricular electrograms and aortic blood pressure were all continuously recorded before, during and after the administration of propafenone. The percentage of ventricular complexes that resulted from activity of the sinus node and the percentage of ventricular origin were determined. Propafenone, 4 mg/kg, immediately (i.e., by the end of 2 minutes of injection) and completely suppressed ventricular arrhythmias in both groups (figs. 4 and 5). In the permanently occluded dogs, conversion to normal sinus rhythm occurred in 11 out of 13 trials (seven of eight dogs), and in the eight reperfused dogs, it occurred in 13 of 13 trials (eight of eight dogs). The peak effect (100% normal sinus rhythm) appeared within 2–3 minutes after the start of injection and decreased gradually over the next 15–35 minutes (fig. 4). When the tachycardia was slow, 100% conversion to normal sinus rhythm occurred promptly when the cumulative administered dose of propafenone reached 2–3 mg/kg (1–1½-minute injection period). Nevertheless, we completed the injection of all 4 mg/kg of propafenone regardless of conversion of the arrhythmia to normal sinus rhythm. When the tachycardia was rapid, 4 mg/kg were necessary to suppress it completely. Lower doses were ineffective for complete suppression of the tachycardia in both groups with rapid tachycardia.

Conversion of the tachycardia to normal sinus rhythm with propafenone was first preceded by slowing of the rate of tachycardia. This was then followed by a gradual increase in the number of ventricular complexes of atrial origin (usually with 1.5–2.5 mg/kg of propafenone). As the cumulative dose of propafenone reached 4 mg/kg, all of the ventricular complexes were of sinus origin (fig. 4). In one permanently occluded dog with rapid multiformal ventricular tachycardia (230 beats/min), the conversion to normal sinus rhythm was partial; only 50% of the ventricular complexes were of sinus origin.

The duration of propafenone-induced normal sinus rhythm (after 4 mg/kg) was a function of the rate of the tachycardia in both groups. When the tachycardia was slow, this duration was significantly longer than when the tachycardia was faster (12 ± 4.2 minutes vs 37 ± 10 minutes in the reperfused group, p < 0.05, and 11 ± 5 vs 33 ± 12 minutes the permanently occluded
This effect diminished within 2 minutes, all of the ventricular complexes were of sinus origin. This was associated with a decrease in heart rate. However, this effect diminished over the next 60 minutes, and within 2 hours, tachycardia similar to the control state emerged.

group, \( p < 0.05 \). No significant differences were detected in the duration of propafenone-induced normal sinus rhythm between the reperfused and the permanently occluded groups for conversion of either slow or rapid tachycardia.

In each dog in both groups, the conversion of the tachycardia (either slow or rapid) to normal sinus rhythm was associated with a significant decrease in heart rate. In the permanently occluded group, the mean ventricular rate during the tachycardia was 173 ± 36 beats/min; it decreased to 115 ± 20.7 beats/min during the normal sinus rhythm (\( p < 0.01 \)). In the reperfused group, the heart rate decreased from 178.1 ± 35.9 beats/min during the tachycardia to 129 ± 9.4 beats/min during the normal sinus rhythm (\( p < 0.01 \)).

There were no statistically significant differences between the mean rate of the tachycardia in the reperfused and the permanently occluded group, nor were there differences between the mean normal sinus rate induced by propafenone between the two groups. Figure 4 illustrates a representative case in a 24-hour reperfused dog with fast tachycardia (197 beats/min). In all dogs in both groups, propafenone’s antiarrhythmic action completely disappeared within 120–140 minutes after drug administration, and tachycardia similar in rate and morphology to that before drug administration reappeared (fig. 4).

Similar antiarrhythmic effects of propafenone were observed in seven dogs, three in the permanently occluded and four in the reperfused group, during the 48-hour postocclusion arrhythmic period. All seven converted to normal sinus rhythm, four with fast and three with slow tachycardia. The onset and the duration of the suppression of the tachycardia during the 48-hour arrhythmic period were not significantly different from those during the 24-hour arrhythmic period (\( p > 0.1 \)).

The ability of i.v. propafenone to maintain normal sinus rhythm immediately after an initial conversion with a bolus (4 mg/kg) was also studied in seven dogs in the 24-hour arrhythmic periods, four in the reperfused and three in the permanently occluded group. We found that continuous i.v. infusion at 0.2 mg/kg/min maintained normal sinus rhythm for the entire duration of infusion (50–70 minutes). Both fast and slow types of tachycardia were effectively suppressed. Figure 6 is an example from a dog in the permanently occluded group with rapid tachycardia. In these series of experiments, tachycardia was first converted to normal sinus rhythm with a 4-mg/kg bolus of i.v. propafenone; 3 hours later, when tachycardia similar in rate and morphology to that before propafenone administration was established, a second bolus of propafenone, 4 mg/kg i.v., was given, and was immediately followed by a continuous i.v. infusion.

No significant differences in the systolic and diastolic aortic blood pressures were detected in either group during the 24-hour arrhythmic period after either a bolus injection of propafenone or a bolus followed by a continuous i.v. infusion. Furthermore, no statistical differences in these hemodynamic variables were found between the two groups either before or after propafenone. Similarly, no significant changes in these hemodynamic variables occurred in the dogs during the 48-hour arrhythmic period.

Lidocaine

The ability of lidocaine to suppress ventricular tachycardia during the 24-hour arrhythmic period was studied in eight dogs: four in the permanent occlusion group, two with rapid and two with the slow type of
tachycardia, and four in the reperfusion group, two with rapid and two with slow tachycardia. Lidocaine was administered as a bolus, 5 mg/kg i.v. over 1 minute, 3 hours after an initial bolus. At this time, tachycardia similar in morphology and rate to that before propafenone was administered had already been reestablished. Lidocaine did not convert rapid tachycardia to normal sinus rhythm (fig. 3) in any dog. In four dogs, however, 10–18% of the ventricular complexes were of sinus origin, compared with 1–3% during the control period. This “partial” conversion lasted only for 3–5 minutes; thereafter, 97–99% of all ventricular complexes were of ventricular origin. In the four dogs with slow tachycardia, lidocaine completely suppressed the arrhythmia, and all of the ventricular complexes were of sinus origin (fig. 2). The peak effect of lidocaine appeared 1–2 minutes after injection and lasted for 3–6 minutes. (The longer duration was observed with the slow tachycardia.) Within 8–12 minutes, the frequency of ventricular ectopic activity progressively increased and after 15 minutes of lidocaine administration, tachycardia similar in rate and morphology reemerged (fig. 2). Lidocaine’s ability to convert ventricular tachycardia during the 48-hour arrhythmic period was also tested in five dogs (three with the rapid and two with slow tachycardia) in both groups. Results similar to those during the 24-hour arrhythmic period were observed; Lidocaine transiently converted slow tachycardia (for 3–5 minutes) regardless of the type of coronary artery occlusion, and it was ineffective or only partially effective in dogs with rapid tachycardia. In these studies, lidocaine was administered 2 hours before propafenone.

Effects on Diastolic Excitability Threshold and Strength-Interval Relation

Propafenone, 4 mg/kg i.v., significantly increased the diastolic excitability threshold (DET) of the right ventricle for both bipolar and cathodal stimulation in both groups. Five minutes after the administration of propafenone, when normal sinus rhythm was restored, the DET for bipolar stimulation increased from control (i.e., during the period of tachycardia), from 1.38 ± 0.62 to 2.23 ± 0.91 msec (p < 0.05) for bipolar stimulation, and from 0.5 ± 0.1 to 1.9 ± 0.3 msec (p < 0.05) for cathodal stimulation (pooled data for both groups; there were no significant differences between the two groups for either mode of stimulation). Within 50–60 minutes, the DET for both modes of stimulation returned to control values.

Lidocaine, 5 mg/kg i.v., had no significant effect on the DET (measurements made 3 minutes after lidocaine injection) for both cathodal (from 0.6 ± 0.1 to 0.57 ± 0.3 mA) and for bipolar (from 1.38 ± 0.4 to 1.42 ± 0.56 mA) stimulation (p < 0.1 for both comparisons). Figure 7 illustrates the effects of propafenone (4 mg/kg i.v.) on the strength-interval relation for both bipolar and cathodal stimulations. All measurements were made 3 minutes after the termination of propafenone injection in both groups, while the dogs were in normal sinus rhythm. Propafenone had no significant effect on the refractoriness of the right ventricular endocardium in either group for either mode of stimulation (118 ± 10.3 vs 116.7 ± 11.4 msec for bipolar stimulation and 128 ± 11.5 vs 127 ± 14 msec for cathodal stimulation, respectively, p > 0.1) (fig. 7) (pooled data from the two groups, no statistical differences between the two groups for either mode of stimulation before and after propafenone administration).

Propafenone caused a 1–3-mA upward shift in the strength-interval relation curves for both modes of stimulation in all dogs in both groups (fig. 7). This reflected a significant increase in the DET and twice DET induced by propafenone. However, when the current intensities reached 5–7 mA, the curves constructed to describe the strength-interval relations before and after propafenone were superimposable for all
dogs in both groups and for both modes of stimulation (fig. 7).

Lidocaine, 5 mg/kg i.v., had no effect on the strength-interval relation in any dog in either group. The effective refractory period of the right ventricular endocardium was 120.5 ± 7.9 msec before and 118.4 ± 9.5 msec after lidocaine for bipolar stimulation (p > 0.1) and it was 125 ± 9.7 msec before and 127 ± 11.3 msec after lidocaine for cathodal stimulation (p > 0.1). The constructed strength-interval curves before and after lidocaine were superimposable for both modes of stimulation.

Plasma Levels of Propafenone

There were no significant differences between the two groups with respect to peak plasma levels of propafenone attained after an i.v. bolus injection of 4 mg/kg. The time course of log plasma propafenone decay of pooled data of the two groups is shown in figure 7. The mean peak plasma propafenone concentration during conversion of ventricular tachycardia to normal sinus rhythm and during the electrophysiologic measurement was 1.5–4.6 μg/ml (mean 3 ± 1.6 μg/ml).

Sixty minutes after propafenone, when ventricular tachycardia with a rate slower than pre-propafenone rate had emerged and DET and strength-interval relation curves had returned to predrug values, the mean plasma propafenone concentration was 0.57 ± 0.3 μg/ml.

During continuous i.v. infusion of propafenone, 0.2 mg/kg/min, after a bolus of 4 mg/kg i.v., when normal sinus rhythm was maintained for the duration of the infusion period (fig. 5), plasma propafenone levels fluctuated between 1.84 and 5.29 μg/ml (mean 3.8 ± 1.73 μg/ml) (measurements made 20, 30 and 40 minutes after infusion in four dogs). The mean value was obtained 40 minutes after the start of infusion.

Histopathologic Findings

In every dog, myocardial infarct was grossly identified by its yellowish color and was located in the anteroseptal region of the ventricle. The estimated size of the infarct was 32 ± 7% in the permanently occluded group (n = 4) and 36 ± 11% in the reperfused group (n = 4). In each dog, the size of the infarct was estimated in six coronary sections made through the left ventricle. No significant differences were found between the two groups. These findings were similar to our previous observations.9

Discussion

Propafenone completely and rapidly abolished ventricular tachycardia and restored normal sinus rhythm in two models of acute myocardial infarction in the conscious dog. Myocardial infarction was produced in the closed-chest conditions without thoracotomy, and with little surgical intervention, which preserves the neural connections to the heart intact. This may importantly influence the response of the arrhythmic heart to drug interventions.10 We tested the efficacy of propafenone in awake dogs, further eliminating possible artifactual interference of anesthetic agents either with the test drug or with the neural inputs to the heart.

Two types of ventricular arrhythmias were observed in the two models of myocardial infarction: rapid, multiform and slow, unifocal tachycardia. These were similar to our previous observations9 and those of Kus and Sasyniuk.10 Propafenone was equally effective in abolishing both types of arrhythmias in both models, with lower doses sufficient to convert slow tachycardia to normal sinus rhythm. Furthermore, equidoses of propafenone maintained significantly longer periods of normal sinus rhythm in dogs with the slow type of tachycardia than in dogs with the rapid type. No significant differences between the two models could be detected with regard to propafenone’s spectrum of antiarrhythmic efficacy or with respect to its duration of antiarrhythmic action. Propafenone was equally effective against ventricular tachycardia occurring during the 48-hour postinfarction period in both groups.

We found important differences between propafenone and lidocaine with respect to their antiarrhythmic efficacy and electrophysiologic properties. Lidocaine, unlike propafenone, was only effective against the slow, uniform tachycardia, and had significantly shorter duration of antiarrhythmic action, even at doses exceeding that of propafenone. Lidocaine was ineffective against the rapid, multiform tachycardia. The antiarrhythmic and electrophysiologic differences between propafenone and lidocaine could reflect differences in peak plasma concentrations attained by each drug after bolus injections; but this does not seem to be the case. Peak plasma lidocaine levels in the dog after a bolus of 5 mg/kg i.v., the dosage used in the present study, are 5 ± 0.7 μg/ml (mean ± SD),14 levels comparable to or even higher than those achieved by bolus injections of propafenone (4 mg/kg i.v.) observed in the present study. This indicates that for a given plasma concentration, propafenone exerts greater electrophysiologic and antiarrhythmic actions in the dog than comparable therapeutic concentrations of lidocaine.14,27

It is of interest to see that therapeutic plasma propafenone levels comparable to those in the dog were achieved in man,28 and similar antiarrhythmic spectra for both propafenone and lidocaine were also observed in clinical settings of acute myocardial ischemia. Zilcher et al.29 reported that i.v. propafenone, 2 mg/kg, was more effective in suppressing multiform ventricular tachycardia (torsade de pointes) during acute myocardial infarction; suppression occurred in eight of 10 patients (80%), compared with one of 12 patients (8.6%) with lidocaine in equal doses. The onset of suppression of ventricular tachycardia with propafenone was very fast, usually occurring during bolus injections.29 These clinical findings were quite similar to our experimental findings.

Some, if not most, of the ventricular arrhythmias that occur 24 hours after permanent coronary artery occlusion in the dog originate in the subendocardial Purkinje network in the infarcted region.13 Spontaneous diastolic depolarization in these fibers may cause
automatic impulse initiation, resulting in ventricular ectopic beats and ventricular tachycardia. The marked prolongation of the Purkinje fiber action potential duration at this time\textsuperscript{12, 13, 15-17} may also cause reentry.\textsuperscript{13, 17} Thus, ventricular arrhythmias that arise in the subendocardial Purkinje fibers 1 day after permanent occlusion of the LAD may result from either abnormal automaticity or reentry, or possibly both. Twenty-four hours after reperfusion, subendocardial Purkinje fiber action potential duration is not markedly prolonged as in infarcts caused by permanent occlusion,\textsuperscript{12} and no conduction delay or slowing of cardiac impulses occurs in this network either 24 or 48 hours after reperfusion.\textsuperscript{12} Since ventricular arrhythmias that occur 24 or 48 hours after occlusion and reperfusion are indistinguishable from those 24 or 48 hours after permanent occlusion, any role for prolonged action potential duration of Purkinje fibers and subsequent conduction slowing and reentry as a cause of either 24- or 48-hour arrhythmias after permanent occlusion can be questioned.\textsuperscript{12} Thus, propafenone apparently exerts its antiarrhythmic effect by suppressing enhanced automatic activity. A preliminary report by Zeiler et al.\textsuperscript{22} showed that propafenone suppresses abnormal automatic activity of ischemic endocardial Purkinje fibers isolated from canine hearts 24 hours after permanent occlusion of the LAD. We made similar observations.\textsuperscript{21}

Lidocaine also depresses spontaneous diastolic depolarization both in normal canine Purkinje fibers\textsuperscript{18, 19} and in subendocardial Purkinje fibers surviving in the infarcted region in the dog.\textsuperscript{20} This antiautomatonic action of lidocaine may well explain its ability to suppress the slow type of ventricular tachycardia in the present study. Furthermore, the effectiveness of lidocaine (as well as propafenone) in suppressing slow tachycardia is unrelated to a mechanism of overdrive suppression of ventricular (Purkinje) pacemakers caused by acceleration of the sinus rate. The sinus rate after conversion of the slow tachycardia was always significantly slower than the rate of tachycardia with either drug. We do not know why lidocaine did not convert rapid tachycardia to normal sinus rhythm. This may be because of lidocaine’s antiarrhythmic action on Purkinje fibers surviving in infarcted region is not as marked as reported in the studies in normal fibers.\textsuperscript{30} This situation may even be more accentuated in severely depressed fibers in the infarcted zone manifesting enhanced automaticity. Furthermore, lidocaine’s lack of effect on the diastolic excitability threshold may further lessen its antiautomatonic action and therefore make it less effective against ventricular tachycardia in the intact dog.

Finally, the inability of lidocaine to convert rapid tachycardia may result from its rapid distribution into body tissues.\textsuperscript{14} As such, it may be possible that maintenance of peak plasma lidocaine levels in the range of 5 \(\mu\)g/ml (the uppermost therapeutic range\textsuperscript{27}) for extended periods (5 minutes or more) could have converted rapid tachycardia to normal sinus rhythm.

The strength-interval relation describes myocardial excitability throughout the cardiac cycle as a function of the intensity of the stimulus.\textsuperscript{23, 24} In addition to the bipolar mode of stimulation, we also used unipolar cathodal stimulation to avoid the more complex strength-interval relation that characterizes bipolar stimulation.\textsuperscript{23-25} In the present study we could not detect qualitative differences between the two modes of stimulation either before or after drug administration.

In the present study, propafenone, unlike lidocaine, caused a significant increase in the DET of the endocardium of the right ventricular apex, and shifted upward to the tail portion of the strength-interval curve. These effects were seen only while propafenone was exerting its antiarrhythmic action, i.e., during propafenone-induced normal sinus rhythm. Over time, as ventricular ectopic activity started to reemerge, the effects on excitability returned to predrug levels. These effects are quite different from those of lidocaine, and these differences may cause an enhancement of antiarrhythmic activity of propafenone in Purkinje fibers, especially in ischemic fibers that survive in the infarcted region.\textsuperscript{22} These may explain the greater antiarrhythmic efficacy of propafenone over lidocaine against rapid tachycardia.

It may be argued that our technique has been limited to the measurements of excitability characteristics of the normal myocardium, specifically, the right ventricular myocardium, and that the effects of propafenone on the excitability characteristics of the left ventricle, either normal or ischemic, may be different. However, our preliminary studies\textsuperscript{23} and those of Zeiler et al.\textsuperscript{22} indicate that propafenone also depresses myocardial excitability of the left ventricle, and that ischemic left ventricular fibers are even more sensitive to the electrophysiologic effects of propafenone than are normal left ventricular fibers.

Propafenone thus appears to be highly effective against postinfarction ventricular arrhythmias. This drug may be a suitable alternative in lidocaine-resistant ventricular tachycardia during acute myocardial infarction.

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