Prevention of Chronic Canine Ventricular Tachyarrhythmias with Bretylium Tosylate

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SUMMARY The ability of chronic bretylium tosylate treatment to prevent the induction of ventricular tachycardia was assessed in the conscious dog subjected to serial programmed ventricular stimulation on days 3-6 after acute myocardial infarction. In 34 untreated control dogs, programmed ventricular stimulation produced nonsustained ventricular tachycardia in 11 dogs (32%), sustained ventricular tachycardia in 10 (29%), and ventricular fibrillation in 10 (29%) on the third and fourth day after occlusion and reperfusion of the left anterior descending coronary artery. Bretylium tosylate, 5 mg/kg i.v., was given every 12 hours to a separate group of seven dogs after the induction of ischemic myocardial injury. Programmed ventricular stimulation on the third and fourth days after the induction of myocardial ischemic injury failed to elicit ventricular arrhythmias. Induction of arrhythmias by programmed electrical stimulation could be induced in each of the seven dogs; however, 36 hours after discontinuing bretylium tosylate, two dogs (29%) had non-sustained ventricular tachycardia and five (71%) had sustained ventricular tachycardia. When retested at 60 hours after withdrawal of bretylium tosylate, five (71%) had sustained ventricular tachycardia and two (28%) developed ventricular fibrillation. Readministration of bretylium tosylate (5 mg/kg, i.v.) to four of the five surviving dogs prevented the induction of ventricular arrhythmias in response to programmed ventricular stimulation. The results of these investigations suggest that bretylium tosylate may be effective in preventing the onset of reentrant ventricular rhythms after myocardial ischemic damage, and therefore may be of value in preventing sudden coronary death.

SINCE Leveque's initial report in 1965,1 numerous reports have documented the unique antiarrhythmic property of bretylium. Bretylium raises the electrical threshold for induction of ventricular fibrillation in normal,8 and acutely ischemic canine myocardium, and protects against ventricular fibrillation in dogs that occurs as a result of coronary artery occlusion and reperfusion.8 In man, bretylium is effective in suppressing recurrent ventricular tachycardia and ventricular fibrillation in the setting of acute myocardial infarction.9-11 Spontaneous conversion of ventricular fibrillation to sinus rhythm after bretylium tosylate administration has been observed.10 However, clinical experience with bretylium tosylate in the treatment of ventricular arrhythmias associated with later phases of myocardial infarction is scant.6,11 Therefore, we investigated the effects of bretylium tosylate on ventricular arrhythmias produced in conscious dogs by serial programmed ventricular stimulation 3-6 days after myocardial damage induced by occluding the left anterior descending coronary artery for 90 minutes, followed by reperfusion.

Methods

Animal Preparation

Male mongrel dogs that weighed 12.6-22.2 kg (mean 17.3 ± 2.2 kg) (± sd) were anesthetized with i.v. sodium pentobarbital, 30 mg/kg. An endotracheal tube was inserted and the dogs were ventilated with room air using a Harvard respirator. Arterial Po2, Pco2 and pH were monitored with an Instrumentation Laboratories blood gas analyzer. Tidal volume and rate were adjusted to maintain arterial blood gas values within physiologic limits.

Using an aseptic technique, the left external jugular vein and left common carotid artery were isolated and cannulas inserted. The cannulas were passed subcutaneously to the back of the neck and exited through a small stab wound. A left thoracotomy was performed in the fourth intercostal space. The anterior surface of the heart was exposed and the heart suspended in a pericardial cradle. Using blunt dissection, the left anterior descending coronary artery was isolated from surrounding myocardium just proximal to the first diagonal branch. Coronary artery flow was measured with an electromagnetic flow probe (Carolina Medical Electronics, Inc.). Blunt needles (16-20-gauge) were used to secure a stenosis around the left anterior descending coronary artery. The stenosis diameter was selected so that the maximum hyperemic response to a 10-second occlusion of the left anterior descending coronary artery was reduced by 60% without reducing resting coronary flow. The left anterior descending coronary artery was occluded for 90 minutes using a section of silastic tubing, after which coronary flow was restored through the stenosed vessel.12

A bipolar electrode (1-mm-diameter, silver wire, 3 mm apart) was sewn onto the surface of the left atrial appendage. A second bipolar electrode (25-gauge insulated stainless steel wire, 5 mm long, 2 mm apart) was placed in the interventricular septum through the right ventricular outflow tract. Bipolar composite electrodes were placed on the surface of the left ventricle. A bipolar composite electrode was placed over normal left ventricular myocardium and the second
bipolar composite electrode was placed over ischemic and infarcted left ventricular myocardium. The chest was closed in layers and the electrode wires exited subcutaneously to the back of the neck. The dogs were given 1.2 million units of procaine penicillin G intramuscularly and were allowed to recover from surgery.

**Drug Administration**

Forty-eight hours after myocardial infarction (day 2), bretylium tosylate, 5 mg/kg, was administered to seven dogs as an i.v. infusion given over 10 minutes. The same dose of bretylium was repeated every 12 hours (10 a.m. and 10 p.m.), for a total of four doses given over days 2 and 3. Programmed electrical stimulation was performed on days 3 and 4, 11½ hours after bretylium administration. Programmed electrical stimulation was repeated on days 5 and 6, 36 and 60 hours after the last dose of bretylium. On the sixth day after infarction, bretylium treatment was reinstated and programmed electrical stimulation was repeated 3 hours later. Thirty-four dogs did not receive bretylium and served as controls.

**Programmed Electrical Stimulation**

Programmed electrical stimulation was performed while the dogs were conscious and resting comfortably in a sling. One, two or three ventricular premature complexes (4 msec long, twice diastolic threshold) were introduced into the interventricular septum using a Grass model S88 stimulator and SIU5 stimulus isolation unit. A Tektronix model 565 oscilloscope with type 3A8 operational amplifier was used to trigger the ventricular stimulus from the R-wave of the lead II ECG. A stimulus duration of 4 msec was selected because of its position on the flat section of the stimulus-duration curve of canine ventricular muscle. Shorter pulse durations of 1 or 2 msec have greater threshold values. The data agree with the recent observation that 4 msec is the optimal pulse duration for programmed electrical stimulation.

The programmed electrical stimulation procedure is summarized below: Single premature ventricular stimuli (S₂) at twice diastolic threshold are introduced during normal sinus rhythm at decreasing 10-msec intervals from 350 msec until ventricular refractoriness occurs. Double premature ventricular stimuli at twice diastolic threshold (S₁, S₂) are introduced during normal sinus rhythm at decreasing 10-msec intervals for S₁ stimuli from 350 msec until ventricular refractoriness occurs with S₁S₂ intervals of 200, 180, 170, 160, 150, 145, 140, 135 and 130 msec. Triple premature ventricular stimuli at twice diastolic threshold (S₁, S₂, S₃) are introduced during normal sinus rhythm at decreasing 10-msec intervals for S₂ stimuli from 350 msec until ventricular refractoriness occurs with S₁S₂S₃ intervals as stated above. Programmed electrical stimulation is performed during atrial pacing at rates from sinus rhythm to 210 beats/min (4 msec duration, twice threshold atrial stimuli). Intermittent ventricular pacing (twice diastolic threshold) at rates to 360 beats/min is applied.

The protocol was continued until reproducible sustained ventricular tachycardia was produced or until the entire protocol was performed. To demonstrate the reproducibility of the method of inducing reentrant rhythms, each dog was subjected to three consecutive programmed stimulation regimens on postoperative days 3–8. Therefore, on any given day or subsequent days, sustained ventricular tachycardia was initiated three times, showing the stability of the reentrant mechanism. All bretylium-treated dogs underwent programmed electrical stimulation under the entire protocol listed above. In the event that ventricular tachycardia could not be induced by twice-diastolic-threshold pulses, in the bretylium-treated dogs, the voltage of the premature pulses was increased 2.5 times and programmed electrical stimulation repeated. These methods of programmed electrical stimulation fail to produce ventricular arrhythmias in sham-operated animals.

Arterial blood pressure was measured with a Statham P23DC pressure transducer. The lead II ECG and arterial blood pressure were recorded continuously on a Grass model 7 polygraph. Composite electrograms and a lead II ECG were stored on a FM tape recorder (Lockheed Electronics) and were recorded on an oscillographic recorder (Honeywell model 1858 Visicorder). Composite electrograms were filtered at 15 and 500 Hz. Activation times (Q-EG intervals, the interval between the Q wave of the bipolar composite electrogram) were measured on a Tektronix model 511 storage oscilloscope. The effective refractory period of normal myocardium was measured at twice diastolic threshold while the ventricular rate was maintained constant by atrial pacing (120–162 beats/min).

The dogs were killed with an overdose of sodium pentobarbital, the heart was excised and triphenyltetrazolium (0.5% W/V), a histochemical stain that forms a distinctive red color in the presence of intracellular dehydrogenases, was infused into the left anterior descending coronary artery at the site of coronary occlusion. The histochemical stain demarcates surviving myocardial tissue in the area at risk. Evan's blue (0.5% W/V) was simultaneously infused into the root of the aorta to demarcate the remainder of the ventricular myocardium. The solutions were delivered under equal pressures (100 mm Hg); thus, the method allows for clear delineation of the regions supplied by the respective coronary arteries and eliminates intercommunicating collateral vessels. Non-surviving infarcted and irreversibly injured tissue within the area at risk is easily dissected and its mass determined. Infarct size can then be expressed with respect to the area at risk. A modification of this method has been reported.

**Statistical Methods**

Differences between groups (effective refractory periods and conduction times) were analyzed by an
analysis of variance. Statistical significance was at the $p < 0.05$ level. Data are mean ± sd.

Results

Programmed Ventricular Stimulation, Days 3 and 4

Controls

On days 3 and 4, all dogs were in normal sinus rhythm and were prepared for programmed ventricular stimulation. One, two or three premature ventricular stimuli at twice diastolic threshold were applied to the interventricular septum.

In 10 dogs, ventricular fibrillation was produced within 30 seconds of the application of the premature stimuli. Sustained ventricular tachycardia (cycle length, 167 ± 66 msec) longer than 2 minutes was produced in 10 dogs. Ventricular tachycardia produced by programmed ventricular stimulation was self-terminating (nonsustained) in 11 dogs, with a duration of 13 ± 9 beats and a cycle length of 195 ± 16 msec.

Programmed ventricular stimulation failed to elicit ventricular tachycardia consistently in three dogs. In these three, the mass of infarcted myocardium and the total area at risk of infarction averaged 6.3 ± 1.5 g and 15.2 ± 3.6 g, respectively, and represented a relatively small fraction of left ventricular mass (7.3 ± 1.7% and 17.7 ± 4.2%). Dogs in which programmed ventricular stimulation produced ventricular arrhythmias had larger infarcts and areas at risk of infarction (17.9 ± 3.6 g and 35.2 ± 6.2 g, respectively), which represented a greater proportion of left ventricular mass (20.1 ± 7.0%, 40.1 ± 6.7%).

Bretylium Tosylate Pretreatment

On day 3, programmed ventricular stimulation at twice diastolic threshold failed to elicit ventricular arrhythmias (figs. 1 and 2) in dogs chronically pretreated with bretylium. Programmed ventricular stimulation at five times diastolic threshold produced short periods of ventricular tachycardia that terminated spontaneously in three dogs. Results were similar on day 4. Programmed ventricular stimulation at twice diastolic threshold at ventricular rates from sinus (119 ± 19 beats/min) to 210 ± 24 beats/min failed to produce ventricular arrhythmias in all seven dogs. Programmed ventricular stimulation at five times diastolic threshold produced short, self-terminating ventricular tachycardias in two dogs.

Programmed Ventricular Stimulation, Days 5 and 6 — Withdrawal of Bretylium Tosylate (figs. 1 and 2)

Programmed ventricular stimulation at twice diastolic threshold was performed in the seven dogs treated with bretylium at 36 and 60 hours after withdrawal of this drug. Five dogs developed sustained ventricular tachycardia on day 5 (36 hours after withdrawal of bretylium) and two developed nonsustained ventricular tachycardia. Programmed ventricular stimulation at twice diastolic threshold on day 6 (60 hours after withdrawal of bretylium) produced sustained ventricular tachycardia in five dogs and ventricular fibrillation in two. In four dogs, programmed...
ventricular stimulation on day 7 at twice diastolic threshold produced sustained ventricular tachycardia.

Suppression of Cardiac Arrhythmias by the Reintroduction of Bretylium

On day 6, four of the five surviving dogs were given i.v. bretylium tosylate, 5 mg/kg. Three hours after bretylium tosylate administration, programmed ventricular stimulation at twice diastolic threshold failed to elicit ventricular tachycardia in each of the four dogs (fig. 1).

Effect of Bretylium Tosylate on Ventricular Refractoriness

Myocardial activation times (Q-EG intervals) were measured in normal (14 ± 5 msec) and ischemic (25 ± 7 msec) myocardium. Bretylium tosylate administration failed to alter these values in normal or ischemic myocardium throughout the course of the study. Ventricular refractory periods were significantly higher on days 3 and 4 (160 ± 6 msec and 173 ± 7 msec) than days 5 and 6 (142 ± 11 msec and 138 ± 3 msec) (p < 0.05). Administration of bretylium tosylate on day 6 significantly increased myocardial refractory periods measured 3 hours later (155 ± 3 msec).

Myocardial Infarct Size

In the seven dogs treated with bretylium, infarct mass and area at risk of infarction (20.6 ± 5.2 g, 39.3 ± 4.9 g) representing 22.9 ± 3.6% and 43.4 ± 5.2% of left ventricular mass. These values did not differ significantly from those in control dogs.

Discussion

Current arrhythmia models used to evaluate antiarrhythmic drugs poorly simulate the chronic myocardial ischemic damage and reentrant ventricular tachyarrhythmias associated with sudden coronary death. Ventricular tachycardias present 24–72 hours after coronary artery occlusion rarely proceed to ventricular fibrillation and probably result from enhanced Purkinje fiber automaticity rather than localized reentry of myocardial electrical activity.18 Reentrant cardiac rhythms produced by coronary artery occlusion or reperfusion often terminate in ventricular fibrillation, but poorly simulate the chronic myocardial ischemic damage and continuing electrical instability associated with sudden coronary death.19 Ventricular tachyarrhythmias produced in dogs by programmed ventricular stimulation 3–10 days after myocardial infarction closely resemble those produced in survivors of sudden coronary death. These arrhythmias can be initiated and terminated with premature ventricular stimuli.18–21 Introduction of the ventricular rhythms depends on local fractionation and delayed activation of ventricular myocardium, with continuous diastolic electrical activity present during ventricular tachyarrhythmias.19, 20, 22 More important, the electrical instability is present for several days and can result in ventricular fibrillation. The similarities in the electrophysiology and clinical aspects suggest that programmed ventricular stimulation in dogs after myocardial infarction may be an appropriate model for evaluating the effectiveness of antiarrhythmic drugs for the prevention of sudden coronary death due to ventricular fibrillation.

Bretylium tosylate increases the electrical threshold for induction of ventricular fibrillation in dogs under normal physiologic conditions8, 4 and in the presence of acute myocardial ischemia.6, 7 Bretylium also protects against ventricular fibrillation in dogs that occurs as a result of coronary artery occlusion and reperfusion.3 These results can be extrapolated to man, in whom bretylium is effective in suppressing recurrent ventricular tachycardia and ventricular fibrillation occurring after cardiac surgery or in the presence of acute myocardial infarction.4, 11 Clinical experience and laboratory investigation of the antiarrhythmic action of bretylium in the presence of chronic myocardial ischemic injury has been limited. Bernstein and
Koch-Weser reported six patients who responded favorably to parenteral bretylium and were later maintained favorably on oral bretylium. Three of these patients had coronary artery disease without acute myocardial infarction and three were survivors of acute myocardial infarction. All six had recurrent ventricular tachycardia and/or ventricular fibrillation before parenteral administration of bretylium that occurred upon cessation of bretylium and was suppressed by readministration. Although the clinical results are limited, they are in agreement with the results of our study, which indicate that bretylium tosylate administered in the presence of recurrent underlying electrical instability as a result of chronic myocardial ischemic injury can prevent ventricular tachycardia and ventricular fibrillation in response to programmed electrical stimulation of the heart.

The cardiac electrophysiologic actions of bretylium are complicated by the dual actions of the drug on the sympathetic nervous system and the ventricular myocardium. Initial bretylium administration results in release of norepinephrine from sympathetic nerve terminals, followed by an inhibition of neuronal catecholamine release. Both of these actions have been suggested as mechanisms by which bretylium exerts its antiarrhythmic action. Bretylium administration results in an initial increase in maximum upstroke velocity of phase 0 of the action potential in isolated Purkinje fibers. This action may improve conduction in normal myocardium, but is more likely to improve conduction in injured fibers with initially depressed resting membrane potentials and phase 0 upstroke velocities. Experiments performed in Purkinje fibers from reserpinine-pretreated animals suggest that the enhancement of phase 0 upstroke velocity is a result of catecholamine release. Indeed, catecholamines released by stellate ganglion stimulation will improve conduction in the late myocardial infarction period. In the present study, we could not make precise measurements of activation in discrete areas of myocardium with the composite electrode because of the electrode configuration and the resultant summing of electrical potentials over the left ventricular surface. Thus, our failure to observe a change in myocardial conduction time could be attributed to the recording technique or may actually reflect the action of bretylium. This information, combined with previous experimental data, does not support a generalized depression of myocardial conduction as a mechanism for the antiarrhythmic action of bretylium, because the composite electrode would have permitted us to detect uniform depression of conduction in the ischemically damaged myocardium.

Bretylium tosylate administration produced a significant increase in myocardial refractoriness. On days 3 and 4 after myocardial infarction, bretylium tosylate increased the effective refractory period of normal myocardium to 160 ± 6 msec and 173 ± 7 msec, respectively. After withdrawal of bretylium tosylate, the effective refractory period of normal myocardium decreased to 142 ± 11 msec on day 5 and

138 ± 3 msec on day 6. The decrease in ventricular refractoriness coincided with a return of induced ventricular tachyarrhythmias. Reintroduction of bretylium tosylate resulted in an increase in ventricular refractoriness and suppression of ventricular electrical instability. The most striking direct electrophysiologic effect of bretylium upon ventricular muscle is that of increasing action potential duration and increasing the effective refractory period. The increase in ventricular refractoriness may be the most likely explanation for the ability of bretylium to suppress the induction of ventricular tachyarrhythmias. Although myocardial refractoriness is increased by bretylium, it is not known to what degree differential alterations in refractoriness of various ventricular tissues is involved. A greater increase in action potential duration in Purkinje fibers vs ventricular muscle has been observed with bretylium. This action may be beneficial in preventing access of premature impulses to the damaged myocardium, or reentrance of electrical activity from damaged myocardium to the remainder of the heart. Bretylium may also reduce the disparity of action potential duration and effective refractory periods between normal and damaged myocardium, and may restore an effective ventricular gating mechanism. This action of bretylium has been shown to be effective in preventing reentrant impulses in isolated Purkinje fibers.

Critique of Method

In studies involving programmed electrical stimulation and the study of drug efficacy, the investigators must beware of possible pitfalls. Programmed electrical stimulation must be performed at a wide range of coupling intervals after drug administration to ensure that drug response is not a result of a change in stimulation values necessary to produce ventricular tachyarrhythmias. Similarly, a change in stimulation type to produce the ventricular tachycardia may be important (i.e., double premature stimuli predrug vs triple ventricular stimuli postdrug). In the present study we performed a full range of programmed electrical stimulation studies. Single, double and triple ventricular stimuli during normal sinus rhythm and during atrial pacing, and intermittent rapid ventricular pacing were used to expose ventricular electrical instability in the bretylium-treated dogs. The stimulus strength was increased to five times mid-diastolic threshold to enable earlier premature electrical stimuli to capture the ventricle. Failure of programmed electrical stimulation to produce ventricular arrhythmias in the bretylium-treated dogs cannot be attributed to a failure to test the dogs adequately at more aggressive stimulation values. The full range of coupling intervals (RS1, S2S3, and S3S4) was tested in each dog to ensure that a change in stimulus values was not responsible for the drug response.

A second possible pitfall is the presence of polymorphic ventricular tachyarrhythmias. Polymorphic ventricular tachyarrhythmias other than clinically observed forms are often present in man and may
complicate the interpretation of a drug response.\textsuperscript{28, 29} The canine model used in this study is not marked by the presence of spontaneous ventricular tachycardias. Therefore, suppression of all ventricular tachyarrhythmias produced by programmed electrical stimulation was used as the final end point for drug protection (noninducibility). This may be an important aspect to consider when multiple (triple) premature stimuli are introduced or when rapid ventricular pacing is used, as these variables may increase the incidence of nonclinical ventricular tachycardia and ventricular fibrillation.

Stimulation site location may also play a role in the ability to induce ventricular tachycardia and to suppress the induction of ventricular tachycardia with antiarrhythmic drugs. In the present study, the stimuli were introduced into the interventricular septum approximately 1–1.5 cm from the infarct border. Preliminary work (unpublished) in our laboratory indicates that this site produces the most consistent and successful results. We do not know if stimulation from other sites would have produced different results.

Future studies are needed to evaluate bretylium’s electrophysiologic effects in infarcted and normal myocardium to determine what action of bretylium tosylate is responsible for its antiarrhythmic properties. This need is especially great in regard to its action upon refractoriness and conduction in the ischemic zone.

Bretylium tosylate is a member of the group III antiarrhythmic agents.\textsuperscript{30} The compounds in this class (sotalol, bretylium, amiodarone) increase myocardial refractoriness without significantly depressing myocardial conduction. In light of the success of bretylium tosylate in preventing ventricular fibrillation and ventricular tachycardia in a canine model of sudden coronary death, the group III antiarrhythmic agents deserve further investigation with respect to potential for preventing ventricular fibrillation and sudden coronary death.

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