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Antidysrhythmic actions of meobentine sulfate

The antiarrhythmic efficacy of meobentine sulfate, a bethanidine derivative lacking inhibitory effects on adrenergic neuronal function, was assessed in three canine models. Intranvenous meobentine sulfate, administered in dosages of 5.0, 10,0, and 20.0 mg/kg, produced a dose-related increase in the ventricular fibrillation threshold (VFT) under nonischemic conditions (7.6 ± 1.8 mA vs 37.8 ± 8.6 mA) (20 mg/kg; $p < 0.05$) and during regional myocardial ischemia (5.6 ± 1.5 mA vs 41.8 ± 9.1 mA) (20 mg/kg; $p < 0.05$). The VFT was also increased in the presence of chronic ischemic injury (6.4 ± 1 mA to 31 ± 10 mA) (20 mg/kg; p 0.05). In the conscious dog, 4 days after an anterior myocardial infarction, programmed electrical stimulation (PES) produced nonsustained ventricular tachycardia (VT) in five dogs. After meobentine sulfate administration, eight of nine animals had sustained VT and one animal developed ventricular fibrillation (VF). At a dose of 20 mg/kg, there was prolongation of the cycle length of the VT (169 ± 11 msec to 237 ± 20 msec), prolongation of the QRS duration (58 ± 2.6 msec to 71 ± 3.7 msec), and prolongation of the delay in epicardial activation. There was an enhanced potential after meobentine administration for programmed stimulation to produce ventricular arrhythmias with the introduction of fewer premature impulses. In the third canine model, conscious dogs with a previous anterior myocardial infarction developed VF in response to electrically induced left circumflex coronary artery injury. Meobentine (20 mg/kg) failed to prevent VF in eight of eight dogs. These results suggest that while meobentine sulfate significantly increases the electrical VFT, it does not protect the conscious canine from the induction of ventricular tachyarrhythmias in response to PES, and it does not prevent VF in a conscious canine model of sudden coronary death. The data would suggest that meobentine will not be effective in preventing sudden death in patients with ischemic heart disease. (AM HEART J 107:1117, 1984.)

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Meobentine sulfate is a structural analogue of bethanidine. It has been suggested that this drug has the antidysrhythmic properties of bretylium but does not produce catecholamine release or adrenergic neuron blockade.[1,2] Work by Wastilla et al.[1] and Michelson et al.[3,4] has shown meobentine sulfate to increase the ventricular fibrillation threshold (VFT), thereby suggesting that it might be an effective antifibrillatory agent.

The work done by Gang et al.[5] has suggested that there is a reduction in the VFT in the canine heart after myocardial infarction when ventricular tachycardia (VT) can be induced by programmed stimu-

lation. It has not, however, been demonstrated that all drugs which raise VFT are efficacious in abolishing inducible VT and in preventing the spontaneous development of malignant ventricular arrhythmias. The purpose of this study was to learn more about the antidysrhythmic properties of meobentine sulfate and the relationship between the VFT, the induction of ventricular dysrhythmias with programmed stimulation, and the spontaneous development of lethal ventricular dysrhythmias. Toward this end we examined the actions of meobentine sulfate upon the VFT in the anesthetized dog, upon programmed electrical stimulation (PES) in conscious dogs after myocardial infarction, and upon the spontaneous development of ventricular fibrillation (VF) in a conscious canine model of "sudden coronary death."[6-9]

METHODS

VFT determination: Model I

Animal preparation. Male mongrel dogs, weighing between 10 and 18 kg, were anesthetized with intravenous sodium pentobarbital (30 mg/kg). A cuffed endotracheal tube was inserted and the animals were ventilated with room air by means of a Harvard respirator. The rate and tidal volume were adjusted to maintain arterial pH, P_{CO_2} and P_{O_2} within normal physiologic limits. Arterial pH, P_{CO_2}, and P_{O_2} were measured with an Instrumentation Laboratories blood gas analyzer. The left common carotid artery and left external jugular vein were isolated and cannulated. The arterial pressure was continuously monitored by means of a Statham P23DC pressure transducer. A left thoracotomy was performed in the fourth intercostal space and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was dissected free distal to the second or third diagonal branch and a loose ligature was passed beneath the artery.

Electrode placement. A bipolar clip was placed on the right atrial appendage and the heart rate was controlled with atrial pacing (4 msec duration stimuli, 2 × diastolic threshold). A bipolar plunge electrode (25-gauge stainless steel, 4 mm in length, 2 mm apart) was placed in the left ventricular myocardium in the region perfused by the left circumflex coronary artery. The left ventricular refractory period and the excitation threshold were determined from this electrode. A bipolar electrode consisting of 1 mm diameter silver electrodes embedded 3 mm apart in dental acrylic was sewn onto the right ventricular surface.

Determination of VFT. VFT was determined as previously described.[9] The ventricular rate was maintained constant with atrial pacing while determination of the VFT was performed. Ventricular excitation thresholds (the minimum current necessary to produce a conducted ventricular beat at a stimulus duration of 4 msec delivered 300 msec after the R wave of the lead II ECG), ventricular refractory periods (the longest R to stimulus interval at which a 2 × diastolic threshold stimulus, 4 msec in dura-

tion, failed to produce a conducted ventricular beat), and ventricular activation (the interval between the Q wave and local myocardial activation) were obtained immediately before determination of the VFT. To determine the VFT, trains of 4 msec duration square-wave pulses (60 Hz, 200 msec duration) were delivered to the right ventricle 50 msec after the peak of the R wave. The output of a Grass S-88 stimulator (Grass SIU-5 stimulus isolation and Grass constant current unit) was triggered from the R wave of the lead II ECG by using a Tektronix 565 oscilloscope and type 3A8 operational amplifier. The current intensity was increased in 1.0 mA increments to 10 mA, then in 2 mA increments to 20 mA, and 5 mA increments to 55 mA until VF ensued. Three trials were performed at each current intensity with 8- to 10-beat intervals between trials. The VFT was defined as the current intensity producing VF. Immediately after VF occurred the heart was defibrillated by means of a capacitor-discharge direct-current defibrillator charged to 20 joules.

The VFT was determined under nonischemic conditions and, after a 15-minute recovery period, reassessed during a 2-minute occlusion of the LAD. After a 15-minute recovery period interval, meobentine, 5 mg/kg, was infused intravenously over a 30-minute period. Electrophysiologic testing was repeated 30 minutes later. Additional cumulative doses of 10 and 20 mg/kg were administered in an identical manner and electrophysiologic testing was repeated. VFTs also were determined in the canine, 4 days after myocardial infarction, by means of identical methods. Myocardial infarction was produced as described in the section below.

PES in the conscious dog during the subacute phase of myocardial infarction: Model II

Animal preparation. Male mongrel dogs, weighing 12 to 22 kg, were anesthetized with intravenous sodium pentobarbital, 30 mg/kg. A cuffed endotracheal tube was inserted and the animal ventilated with room air by means of a Harvard respirator. By means of an aseptic technique, the left external jugular vein and left common carotid artery were isolated and cannulas were inserted. The cannulas were passed subcutaneously to the back of the neck and surfaced through a small incision. A left thoracotomy was performed in the fourth intercostal space and the anterior surface of the heart was exposed. The heart was then suspended in a pericardial cradle. Using blunt dissection, the LAD was dissected free at the border of the atrial appendage. A 19-gauge needle with a blunted end was placed parallel to the coronary artery, and a suture was passed around both the coronary artery and the needle. The suture was tied securely and the needle withdrawn, producing a critical stenosis. The artery then was occluded by using a snare formed from a loop of silicone rubber tubing passed through a blunt-ended polyethylene tube. After 2 hours of regional ischemia, blood flow was restored through the stenosed vessel.

Electrode placement. A bipolar electrode was sewn onto the surface of the left atrial appendage. A second bipolar plunge electrode (28-gauge stainless steel, 5 to 7 mm in length) was placed in the right ventricular outflow tract

with the exposed electrode tip placed in the interventricular septum. Bipolar composite electrodes were placed on the epicardial surface of the left ventricle. One bipolar composite electrode was placed over the normal myocardium and the second was placed over the ischemic and infarcted myocardium. Correct placement of the bipolar composite electrodes was confirmed at autopsy. The electrode wires were exteriorized through the chest. The chest incision was closed and the dogs were given ampicillin, 6 mg/kg intramuscularly twice daily, and permitted to recover from anesthesia.

Electrophysiologic studies. Four days after myocardial infarction, the animals were returned to the laboratory. They were conscious and resting comfortably, supported in a sling. Ventricular premature stimuli (4 msec duration square-wave impulses, twice distolic threshold) were applied to the interventricular septum with the use of a Grass S-88 stimulator and SIU-5 stimulus isolation unit. A Tektronix 565 oscilloscope and operational amplifier were used to trigger the stimulus from the R wave of the lead II ECG.

The PES procedure is outlined as follows. (1) Single premature ventricular stimuli (S_2) were introduced during normal sinus rhythm at decreasing 10 msec intervals from 350 msec until ventricular refractoriness occurred. (2) Double premature ventricular stimuli (S_2 and S_3) were introduced during normal sinus rhythm at decreasing 10 msec intervals for S_2 stimuli from 350 msec until ventricular refractoriness occurred with S_2 to S_3 intervals of 200, 180, 170, 160, 150, 140, 135, and 130 msec. (3) Triple premature ventricular stimuli (S_2, S_3, and S_4) were introduced during normal sinus rhythm at decreasing 10 msec intervals for S_2 stimuli until ventricular refractoriness occurred with S_2 to S_3 and S_3 to S_4 intervals as stated previously. (4) Intermittent ventricular pacing (2 × diastolic threshold) at rates to 360 bpm was applied. Previous work has shown that this method of PES fails to produce ventricular dysrhythmias in sham-operated animals without ischemic myocardial injury.[10]

The arterial blood pressure was measured with a Statham P23DC pressure transducer. The lead II ECG and arterial pressure were recorded continuously on a Grass model 7 polygraph. The composite bipolar electrodes and lead II ECG were stored on magnetic tape with the use of a Lockheed FM tape recorder and permanent records were obtained by means of a Honeywell oscillographic recorder. The ventricular refractory period of normal ventricular myocardium was measured at 2 × diastolic threshold (4 msec duration stimulus). After determination of baseline electrophysiologic values and reproduction of sustained or nonsustained VT in triplicate, meobentine sulfate, 5 mg/ kg, was administered intravenously over a 30-minute period. Electrophysiologic testing was repeated 30 minutes later. Additional cumulative doses of meobentine, 10 and 20 mg/kg, were administered in an identical manner and electrophysiologic testing was repeated.

Conscious canine model of sudden coronary death: Model III

Animal preparation. Male mongrel dogs, weighing
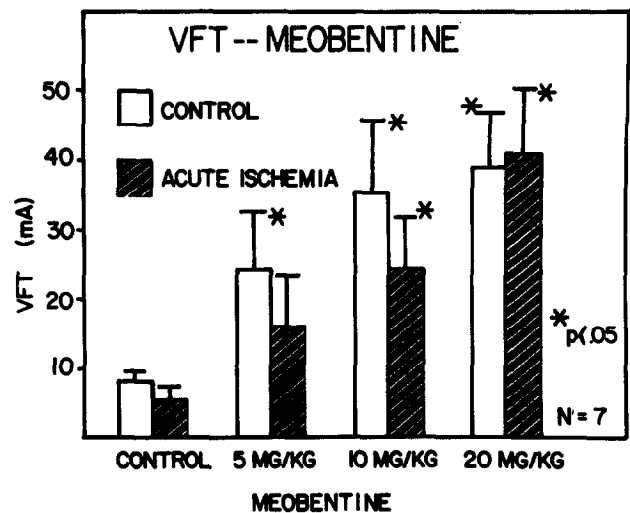
Fig. 1. Ventricular fibrillation threshold *(VFT)* measured under nonischemic conditions and after a 2-minute occlusion of the LAD. Meobentine sulfate resulted in a statistically significant increase in VFT in all dosages except during acute ischemia at the 5 mg/kg dose.

between 13 and 23 kg, were anesthetized with intravenous sodium pentobarbital, 30 mg/kg. A cuffed endotracheal tube was inserted and the animal ventilated with room air by means of a Harvard respirator. Aseptic surgical technique was employed for insertion of cannulas in the jugular vein and carotid artery. A left thoracotomy was performed in the fourth intercostal space and the heart was suspended in a pericardial cradle. Both the LAD and left circumflex coronary arteries were dissected free from the underlying myocardium, the LAD approximately 1 to 1.5 cm from its origin and the circumflex coronary artery approximately 1 cm from its origin. Myocardial infarction within the distribution of the LAD was produced as previously described.

Intracoronary electrode placement. A 30-gauge Teflon-coated silver wire was fashioned with 3 mm of the tip of a 25-gauge hypodermic needle secured on the wire's lead end which served to aid in the penetration of the arterial wall. The wire was inserted through the wall of the left circumflex coronary artery so that approximately 2 to 3 mm of the bare wire-needle-tip assembly was within the vessel lumen and in contact with the intimal surface. The wire was secured to the epicardium with two sutures. The distal end of the silver wire was exteriorized and would subsequently serve to deliver an anodal current of 150 μA to the intimal surface of the left circumflex coronary artery. A silver disk electrode was sutured to the subcutaneous tissue and completed the electrical circuit, which consisted of a 9V nickel-cadmium battery and a 250,000 ohm potentiometer placed in series so as to allow adjustment of the current flow. A bipolar plunge electrode consisting of a 25-gauge insulated stainless steel wire, 4 mm in length and separated by 2 mm, was placed in the ventricular septum adjacent to the right ventricular out-
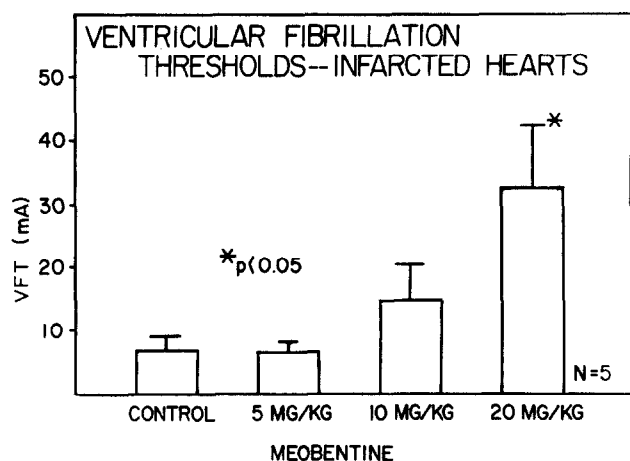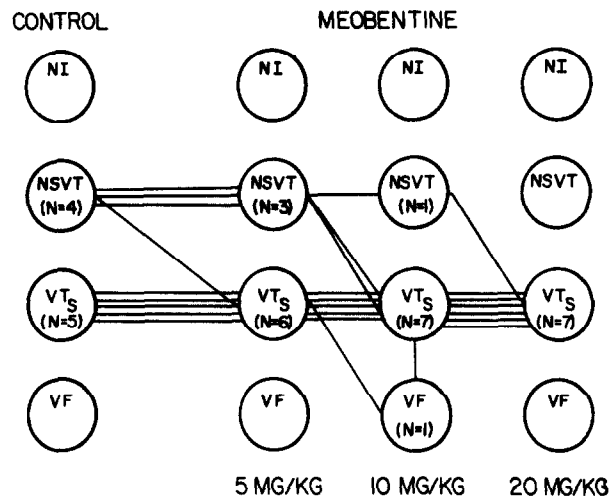
Fig. 2. Ventricular fibrillation threshold *(VFT)* was measured in anesthetized dogs 4 days after myocardial infarction. There was a statistically significant increase in VFT at the 20 mg/kg dose.

Fig. 3. Ventricular tachyarrhythmias induced by PES at increasing dosages of meobentine sulfate. The number of animals having no induced tachyarrhythmias *(NI)*, nonsustained ventricular tachycardia *(NSVT)*, sustained ventricular tachycardia *(VTs)*, and ventricular fibrillation *(VF)* is shown before and after the administration of meobentine. The connecting lines show the responses of individual animals over the course of the experiment.

flow tract. The surgical incision was closed and the animals were given 6 mg/kg of ampicillin intramuscularly and allowed to recover from the surgical procedures.

Experimental procedure. Four days after the thoracotomy, the animals were returned to the laboratory and studied while conscious, unsedated, and resting comfortably in a sling. PES was performed on all animals as described previously. After PES testing was completed, the animals were assigned randomly to one of two groups. One group received meobentine sulfate, 20 mg/kg intravenously administered over a 30-minute period, while the other group received an equal volume of the 0.9% sodium chloride diluent. PES was repeated in the animals which received meobentine sulfate. After completion of programmed stimulation, the animals were placed in a 3 × 6 m isolation room. The lead II ECG was transmitted through telemetry and stored on FM tape for subsequent analysis. The radiotelemetry transmitter, potentiometer, and 9V nickel-cadmium battery were contained in a 10 × 15 × 5 cm box placed securely in a nylon vest, thus allowing the animal freedom of movement. Once adequate baseline recordings were obtained, a continuous direct anodal current of 150 μA was applied to the intimal surface of the left circumflex coronary artery. An observer continuously monitored the transmitted data to detect changes in cardiac rhythm and ST segment shifts.

Myocardial infarct size determinations. The techniques were similar to those previously described.[9] After the animals were killed the heart was excised. In animals in the programmed stimulation study group, cannulas were inserted into the LAD at the point of occlusion and into the root of the aorta. Triphenyltetrazolium chloride (0.5% weight/volume), a histochemical stain which forms a distinctive red color in the presence of intracellular dehydrogenases, was infused directly into the LAD at the site of the previous occlusion. The histochemical stain demarcates surviving myocardium in the area at risk for

infarction. Evans blue dye (0.5% weight/volume) was infused simultaneously into the root of the aorta to demarcate the remaining myocardium. Both solutions were delivered under equal pressure (100 mm Hg) to allow for clear delineation of the region supplied by their respective coronary arteries and to eliminate flow across collateral vessels. Nonsurviving infarcted tissue within the area at risk of infarction is distinguished from surviving tissue by its pale appearance. Infarcted mass and area at risk of infarction were determined gravimetrically.

In the conscious canine model of sudden coronary death, in which VF occurred, the heart was removed and the left circumflex coronary artery carefully dissected and examined for the presence of thrombus. Thrombus mass was determined gravimetrically. The heart was then sectioned into 1 cm rings from apex to base, parallel to the atrioventricular groove. The transverse sections were placed into 0.5% triphenyltetrazolium chloride in 0.01M phosphate buffer (pH 7.4) and infarct size was determined gravimetrically.

Statistics. Data are expressed as the mean ± SEM. Differences within a group were analyzed by one-way analysis of variance. Differences in survival between control and meobentine groups were analyzed with Fisher's exact test. $p < 0.05$ was the criterion for significance.

RESULTS

VFT determinations. Meobentine sulfate dosages of 5.0, 10.0, and 20.0 mg/kg significantly increased VFTs determined in the absence of myocardial ischemia and during acute coronary artery occlusion
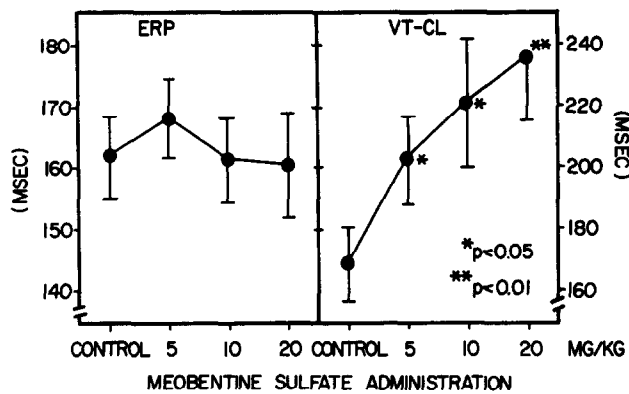
Fig. 4. Effects of increasing dosages of meobentine sulfate on the ventricular effective refractory period *(ERP)* and the cycle length of the ventricular tachycardia *(VT-CL)* measured during PES in the conscious dog during the subacute phase of myocardial infarction. There was a statistically significant increase in the cycle length of the VT at all dosages.

(Fig. 1). There was also an increase in the VFT of animals with previous anterior myocardial infarctions at dosages of 20 mg/kg (Fig. 2). A significant increase in the myocardial conduction time was noted at the 20 mg/kg dose, from a predrug duration of 17.5 ± 1.5 msec to 23.1 ± 1.6 msec; $p < 0.05$. There was no change in the excitation thresholds or in the ventricular effective refractory period.

PES in the conscious dog during subacute phase of myocardial infarction. PES was performed in 10 consecutive dogs 4 days after myocardial infarction. Before the administration of meobentine sulfate, PES produced nonsustained VT in four animals and sustained VT in six animals. After the administration of meobentine sulfate in cumulative dosages of 5, 10, and 20 mg/kg, each of the animals which had displayed nonsustained VT now demonstrated sustained VT. At a dose of 20 mg/kg, all animals tested demonstrated sustained ventricular dysrhythmias (Fig. 3). Slower rates of ventricular pacing and/or fewer premature ventricular impulses were necessary to produce ventricular tachyarrhythmias after the administration of meobentine sulfate.

The cycle length of the VT was prolonged by meobentine sulfate in a dose-related manner; it changed from a predrug mean cycle length of 169 ± 11 msec to 205 ± 17 msec at 5 mg/kg ($p < 0.05$), to 221 ± 22 msec at 10 mg/kg ($p < 0.05$), and to 237 ± 20 msec at 20 mg/kg ($p < 0.01$) (Fig. 4). The QRS duration lengthened in a dose-related manner after meobentine sulfate, with a predrug mean duration of 58 ± 3 msec increasing to 71 ± 4 at a dosage of 20 mg/kg. The prolongation of QRS duration at a
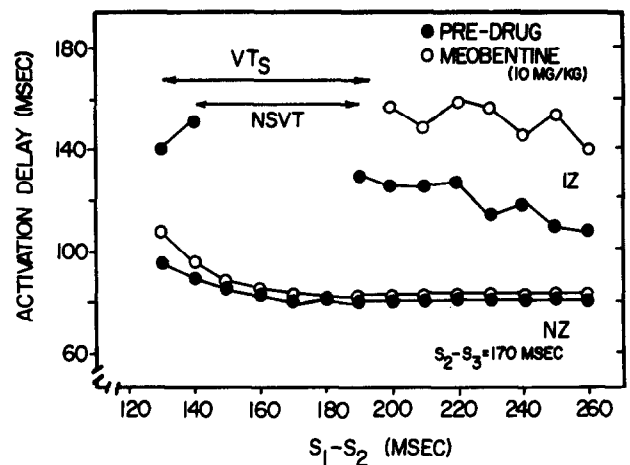
Fig. 5. Electrophysiologic effect of meobentine (10 mg/kg). Before meobentine administration, epicardial activation delays were produced by PES within both normal *(NZ)* and ischemically injured *(IZ)* myocardium. The delay was always greater in the ischemically injured zone. Meobentine administration resulted in prolongation of the epicardial delay in the normal and ischemically injured zone for all S_1S_2 coupling intervals. Prior to the administration of meobentine, an epicardial activation delay of 158 msec, produced with an S_2-S_3 interval of 170 and a S_1S_2 interval of 130 to 140 msec, resulted in the induction of nonsustained ventricular tachycardia *(NSVT)*. After meobentine administration (10 mg/kg) a conduction delay of 160 msec, produced with an S_2-S_3 coupling interval of 170 msec and an S_1-S_2 coupling interval of less than 200 msec, resulted in sustained ventricular tachycardia *(VTs)*.

dosage of 10 and 20 mg/kg reached statistical significance ($p < 0.05$). There was no prolongation in either the PR or QT_c duration at any drug dosage tested.

Bipolar composite electrodes placed over the epicardial surface of the left ventricle in both a normal and ischemically injured region were used to measure epicardial activation delays produced by PES. The delay was always greater in the ischemically injured zone. Meobentine sulfate produced a prolongation of the epicardial activation delay in the normal and to a greater extent in the ischemically injured zone for all S_1S_2 coupling intervals (Fig. 5).

Conscious canine model of sudden coronary death. PES in control animals produced nonsustained VT in five dogs, sustained VT in four dogs, and VF in one dog, three dogs were not inducible. In dogs pretreated with meobentine, PES produced nonsustained VT in three dogs and sustained VT in three dogs; two dogs were not inducible. In the control dogs, ST segment elevation or depression in excess of 0.3 mV developed in all 13 animals at 92 ± 13
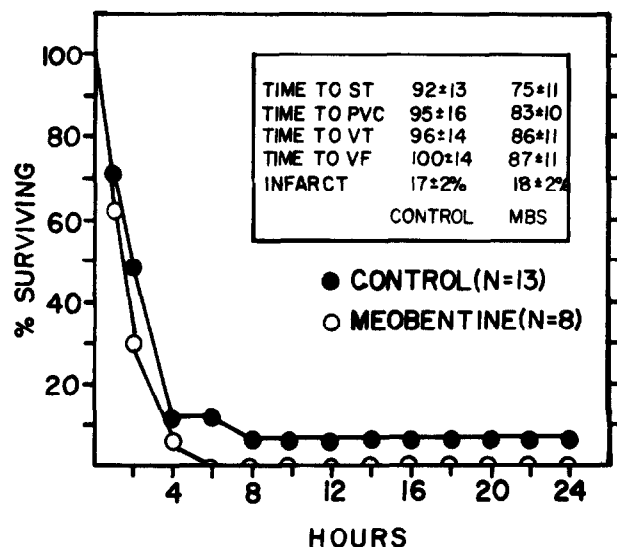
Fig. 6. Survival rate of saline- and meobentine-treated animals after left circumflex intimal injury. Also depicted is the time of ST segment change, time of first ventricular premature beat *(PVC)*, time of onset of ventricular tachycardia *(VT)*, time of development of ventricular fibrillation *(VF)*, and myocardial infarct size in the meobentine-treated and control groups.

minutes after initiation of anodal current flow to the intimal surface of the left circumflex coronary artery. Premature ventricular contractions were manifested at 95 ± 16 minutes followed by VT at 96 ± 14 minutes, with VF developing at 100 ± 14 minutes in 12 of 13 animals. ST segment changes in the meobentine-treated group developed at 75 ± 11 minutes. Premature ventricular beats developed at 83 ± 10 minutes. VT developed at 86 ± 11 minutes and VF developed at 87 ± 11 minutes. Each of the eight dogs in the meobentine-treated group developed VF (Fig. 6).

Myocardial infarct size within the distribution of the LAD was not different between the meobentine-treated (19 ± 2%) and the diluent-treated control group 17 ± 2%). Myocardial infarction as detected by triphenyltetrazolium staining for cellular dehydrogenase activity was not detected within the left circumflex coronary artery distribution of the control or meobentine-treated animals which terminated suddenly as a result of VF.

Hemodynamics. After infusion of meobentine sulfate over 30 minutes at dosages of 5, 10, and 20 mg/kg, we noted no change in heart rate or blood pressure. We did note, however, that the rapid infusion of meobentine sulfate resulted in a transient hypotensive response. In all cases when greater than 20 mg/kg of meobentine was infused, irrevers-

ible hypotension and death resulted, thereby limiting our ability to explore the dose-response relationship any further.

DISCUSSION

Increased VFT. Meobentine sulfate is a structural analogue of bethanidine. It has been suggested that this drug has the antidysrhythmic properties of bretylium because, like bretylium, it increases VFT.[11-14] Wastilla et al.[1] have shown meobentine sulfate to be effective in preventing VF after coronary artery occlusion and release and to significantly increase VFT in dogs at dosages of 20 and 40 mg/kg. Michelson et al.[3, 4] found meobentine sulfate to be effective in preventing VF induced by pacing and programmed stimulation by using anesthetized dogs studied several days after a two-stage LAD occlusion and reperfusion. In this experiment we also found meobentine sulfate to be effective in increasing the VFT under nonischemic conditions, during regional myocardial ischemia, and in the presence of chronic ischemic injury.

There is, however, considerable question as to whether a drug's ability to increase the VFT alone can be used to assess the efficacy of an antiarrhythmic drug.[9, 15-17] Therefore, other animal models which may more closely simulate the conditions leading to sudden coronary death in humans have been employed to assess the potential role of meobentine sulfate.

Canine models of sudden coronary death. It has been shown that patients resuscitated from a cardiac arrest when tested with PES will have reentrant ventricular arrhythmias, which are identical to the spontaneously occurring arrhythmias previously observed.[18-20] Antiarrhythmic drugs, which can suppress the induction of the ventricular tachyarrhythmias in response to PES, have been shown to be successful in preventing the recurrence of the ventricular tachyarrhythmia during chronic therapy.[18, 20] The animal model of PES 3 to 14 days after myocardial infarction has been demonstrated to closely resemble the ventricular tachyarrhythmias produced in patients.[21-24] However, in the use of PES an artificial stimulus is again necessary for induction of ventricular arrhythmias. Recently Patterson et al.,[6] Romson et al.,[7] and Schwartz and Stone[25] have described animal models for the development of VF in a physiologic setting without anesthesia and without being dependent on an external provocative stimulus for the development of VT and/or VF. It was found that if an animal was prepared with a myocardial infarction secondary to occlusion and

reperfusion of the LAD, the addition of an acute thrombotic or occlusive event in the left circumflex coronary artery would result in a high incidence of VF. This was in contrast to the development of VF in only 20% of dogs with an acute thrombotic occlusion of the left circumflex coronary artery but without previous ischemic injury in the region supplied by the LAD. In this model, amiodarone, nadolol, and bretylium have been found to be effective in preventing VF while bethanidine has not proved to be effective.[9, 26-28]

Lack of antiarrhythmic effect. In these two models of the animals, mesobentine sulfate did not appear to be an effective antiarrhythmic agent. In the model of PES in the conscious dog during the subacute phase of myocardial infarction, meobentine sulfate did lengthen the VT cycle length in a dose-dependent manner. It did not, however, result in the prevention of ventricular arrhythmias. In fact, all animals with nonsustained VT induced by programmed stimulation prior to the drug had the development of sustained VT or VF after meobentine. Also, meobentine's administration enabled a less rigorous stimulation protocol to be used in inducing animals to the point of VT. In the conscious canine model of sudden coronary death, meobentine sulfate had no protective effect in any of the eight dogs, each of which died of VF.

Mechanisms of electrophysiologic actions. The mechanism of meobentine's action as an antiarrhythmic agent is largely unknown. Meobentine, unlike the chemically similar compounds bethanidine and bretylium, is known not to be an inhibitor of adrenergic neuronal function.[1, 2] Michelson et al.[3] noted that 4 to 6 days after a two-stage LAD occlusion and reperfusion, the ventricular refractory period increased with meobentine sulfate at a dosage of 20 mg/kg in the normal and ischemic zones but to a greater extent in the ischemic zone. They attributed meobentine's mechanism of action to its differential effect between the normal and ischemically injured myocardium.

In our model of PES the electrophysiologic actions of meobentine closely resembled those of lidocaine and procainamide.[24, 30-32] We noted that increasing dosages of meobentine resulted in an increase in the cycle length of the induced VT and there was an increase in the ease with which VT could be induced with increasing dosages of meobentine. Epicardial conduction delay measured with composite electrodes placed over the ischemically injured and normal zones showed increases in delay in both regions with increasing dosages of meoben-

tine. There was also a statistically significant increase in QRS duration at the 10 and 20 mg/kg dosage, and an increase in myocardial conduction time at the 20 mg/kg dosage.

Conclusions. On the basis of the data from the four animal models, we found that while meobentine has significant effects in raising the VFT, it was ineffective in the conscious canine model of sudden coronary death and in the PES model. In the conscious canine model of sudden coronary death, none of the eight dogs treated with meobentine, 20 mg/kg, was protected from VF. In the PES model, while the induced VT cycle length was prolonged in a dose-related manner, meobentine did not prevent the induction of VT and in fact facilitated its induction. The electrophysiologic actions of meobentine appear to be similar to type 1 antiarrhythmic agents. The drug prolongs the cycle length of inducible VT, prolongs epicardial conduction delay, and increases QRS duration. In many instances, the drug facilitates the induction of inducible VT. The data fail to show that meobentine sulfate has efficacy in preventing ventricular arrhythmias. We therefore feel that meobentine sulfate does not have significant potential as an agent to prevent sudden coronary death secondary to ischemic heart disease in humans.

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